[Chem. Pharm. Bull. 12 (2) 196 ~ 203] UDC 577.176.511.5

27. Hidehiko Kaneko, Masahisa Hashimoto, and Akio Kobayashi : The Synthesis of 2- and 4-Alkoxymethylestrogens.

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Our interest in 2-substituted ring A aromatized steroids was aroused by the report[1] that the introduction of alkyl groups into C-2 position of steroid hormones in certain instances affected considerably its biological activity. The authors have synthesized a number of 2- and 4-alkoxymethylestrogens in connection with our studies of the effects of substituents at C-2 or C-4 on the estrogenic activity and the serum cholesterol lowering activity of estrogens. This article describes in detail some of the exprimental procedures employed in synthesizing the compounds reported in an earliar communication.[2]

Recently Patton[3] reported that the Mannich reaction of estrone occurred exclusively at the C-2 position of the steroid molecule. The author was unsuccessful in isolating the other possible mono-substituted isomers (C-4 and C-16). In our hand the reaction product resulted in essentially under the same condition was found by thin layer chromatography to be of two basic steroids contaminated with a trace of unchanged material. Chromatography on silica gel resulted in complete separation of the two isomers of Mannich base. First elution with benzene afforded a small amount of 4-dimethylaminomethylestrone (IIa) which was purified by recrystallization from ethanol, and further elution with benzene and benzene-ether (2:1) gave the 2-isomer (Ia) as the major product. The ratio of the isomers was 1:15. The nuclear magnetic resonance spectrum[*2] of IIa supported the assignment for a 4-substitution in which the aromatic *o*-hydrogen atoms are spin-spin coupled (J=8.8) while in the other isomer (Ia) the *p*-hydrogen atoms were not spin-spin coupled, and the OH protons appeared at 0.27 τ and $-0.08\,\tau$ respectively as in the Table I. The cryptophenolic character of IIa was exhibited by the fact that it could not be etherified with an alkylating agent as in the 2-isomer.[3] The infrared spectrum also failed to show any absorption in the 3μ region characteristic of the phenolic OH group.

Compound (IIa) afforded 4-methylestrone[4] on reduction with Raney nickel, which subsequently was reduced with sodium borohydride to give 4-methylestradiol[4] (IIIb).

As the nucleophilic displacement of quarternary salts of 2- and 4-dimethylaminomethylestrogens provides a potentially valuable route for the preparation of 2- and 4-substituted estrogens hitherto unknown or prepared with difficulty, we investigated a number of reactions involving the displacement of alkoxide anion.

Treatment of the methiodide of Ia with methanolic alkali readily formed 2-methoxymethylestrone (Va) which displayed benzene ring proton absorption as two singlets in the nuclear magnetic resonance spectrum, while 4-methoxymethylestrone (VIa) prepared

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[*2] Nuclear magnetic resonance spectra were measured at 60 Mc./sec. for deuterochloroform solution and calibrated against internal tetramethylsilane. Chemical shifts are given in τ-values and coupling constants (J) in c.p.s.

1) *a*) H.J. Ringold, E. Bartres, O. Halpern, E. Nechoechea: J. Am. Chem. Soc., **81**, 427 (1959); *b*) R. Mauli, H.J. Ringold, C. Djerassi : *Ibid.*, **82**, 5494 (1960).

2) H. Kaneko, M. Hashimoto, Y. Mitta, K. Kawase : This Bulletin, **11**, 264 (1963).

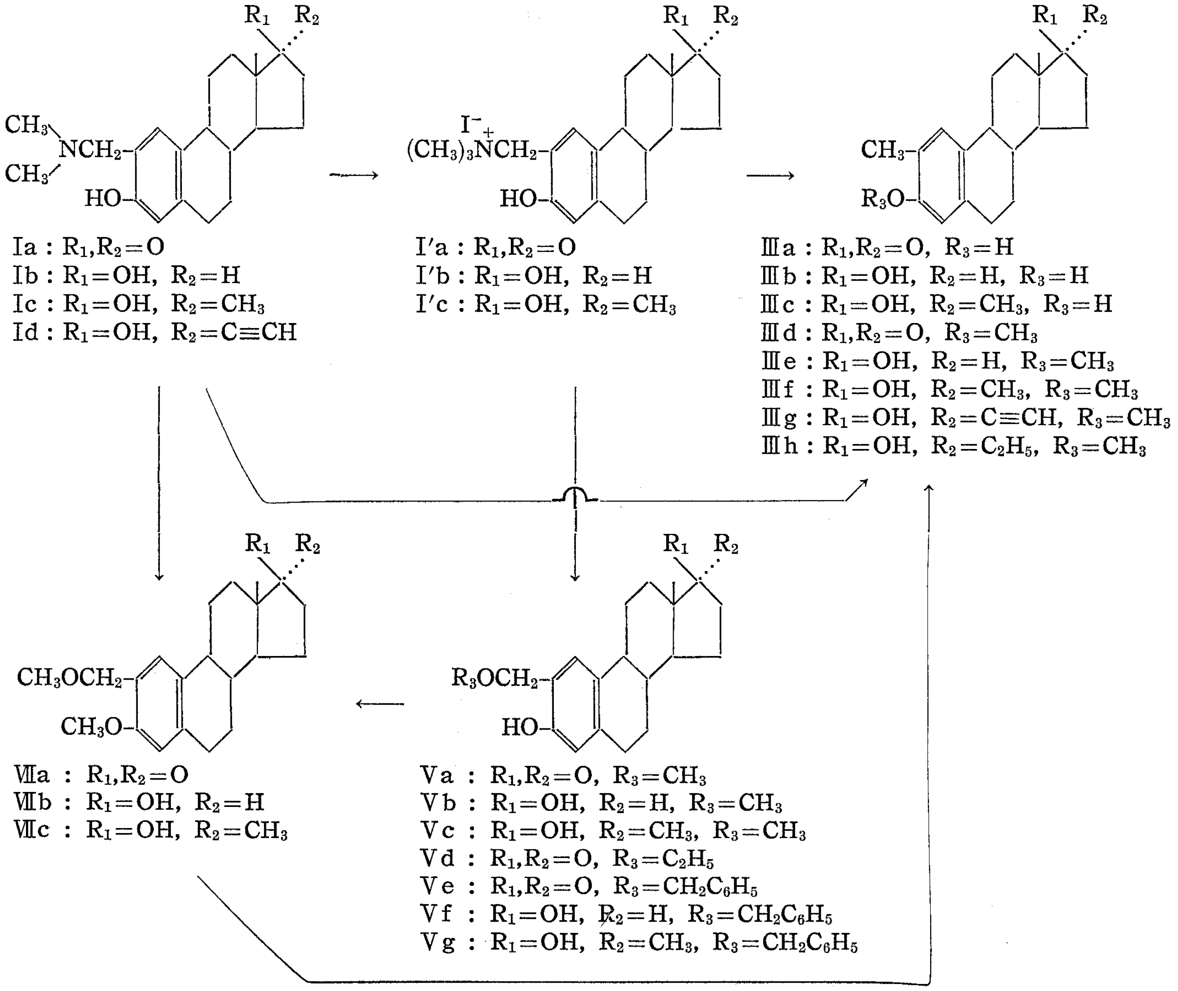
3) T.L. Patton : J. Org. Chem., **25**, 2148 (1960).

4) 4-Methylestrone and 4-methylestradiol were identified from the comparison of IR spectra, melting points and optical rotations reported by D.H. Peterson, L.M. Reineke, H.C. Murray and O.K. Sebek : Chem. & Ind. (London), **1960**, 1301.

in the similar manner from the methiodide of IIa displayed two adjacent proton benzene ring absorption of two asymmetric doublets characteristic of an AB system with spin-spin coupling. Table I lists the principal absorption bands and proton assignments for the phenols (Ia, IIa, Va, and VIa).

Table I. Peaks in the Nuclear Magnetic Resonance Spectra of Substituted Estrogens*2

Compounds	Chemical Shift (τ)							
	C_3-OH	C_{13}-CH_3	$N(CH_3)_2$	-OCH_3	C_2-CH_2- or C_4-CH_2-	C_1-H, C_4-H	C_1-H, C_2-H	C_{17}-βOH
2-Dimethylaminomethyl-estrone (Ia)	0.27	9.08	7.68	—	6.4	3.12, 3.41	—	—
4-Dimethylaminomethyl-estrone (IIa)	−0.08	9.08	7.65	—	6.39	—	two doublets (J=8.8)	—
2-Methoxymethyl-estrone (Va)	2.84	9.10	—	6.59	5.39	3.09, 3.40	—	—
4-Methoxymethyl-estradiol (VIb)	2.15	9.23	—	6.54	5.29	—	two doublets (J=9.1)	8.46


Ia : $R_1,R_2=O$
Ib : $R_1=OH$, $R_2=H$
Ic : $R_1=OH$, $R_2=CH_3$
Id : $R_1=OH$, $R_2=C{\equiv}CH$

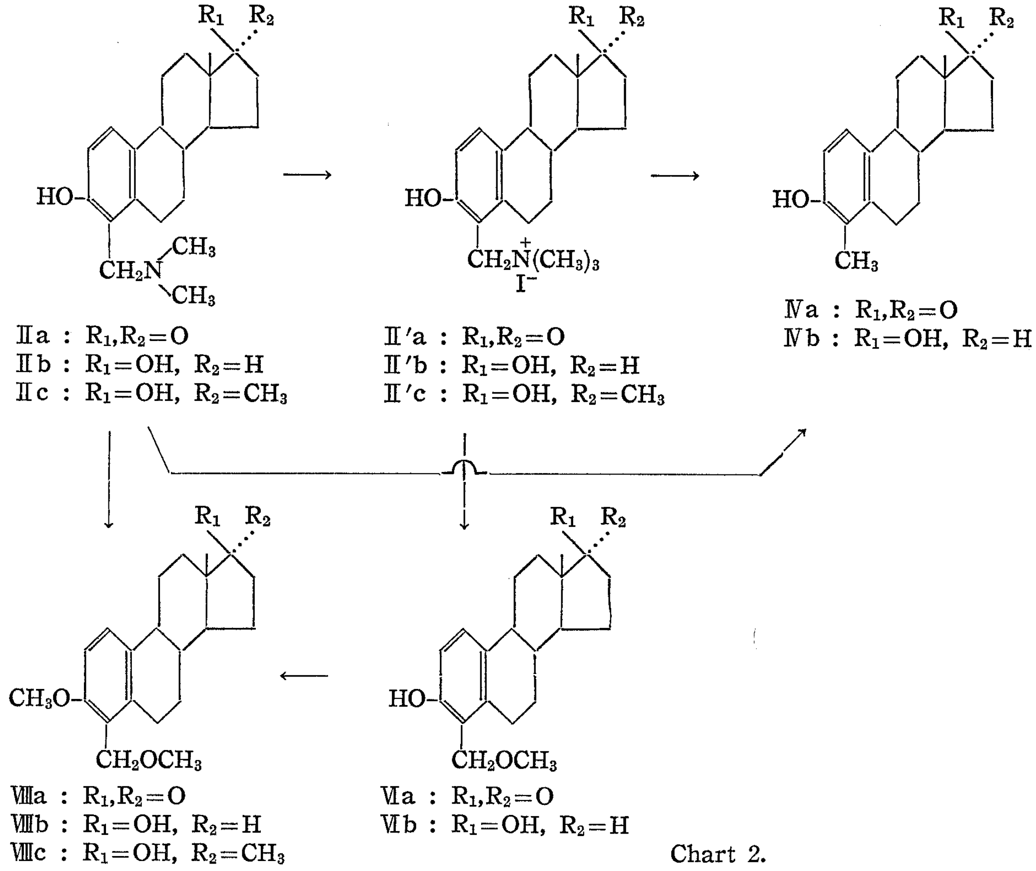
I'a : $R_1,R_2=O$
I'b : $R_1=OH$, $R_2=H$
I'c : $R_1=OH$, $R_2=CH_3$

IIIa : $R_1,R_2=O$, $R_3=H$
IIIb : $R_1=OH$, $R_2=H$, $R_3=H$
IIIc : $R_1=OH$, $R_2=CH_3$, $R_3=H$
IIId : $R_1,R_2=O$, $R_3=CH_3$
IIIe : $R_1=OH$, $R_2=H$, $R_3=CH_3$
IIIf : $R_1=OH$, $R_2=CH_3$, $R_3=CH_3$
IIIg : $R_1=OH$, $R_2=C{\equiv}CH$, $R_3=CH_3$
IIIh : $R_1=OH$, $R_2=C_2H_5$, $R_3=CH_3$

VIIa : $R_1,R_2=O$
VIIb : $R_1=OH$, $R_2=H$
VIIc : $R_1=OH$, $R_2=CH_3$

Va : $R_1,R_2=O$, $R_3=CH_3$
Vb : $R_1=OH$, $R_2=H$, $R_3=CH_3$
Vc : $R_1=OH$, $R_2=CH_3$, $R_3=CH_3$
Vd : $R_1,R_2=O$, $R_3=C_2H_5$
Ve : $R_1,R_2=O$, $R_3=CH_2C_6H_5$
Vf : $R_1=OH$, $R_2=H$, $R_3=CH_2C_6H_5$
Vg : $R_1=OH$, $R_2=CH_3$, $R_3=CH_2C_6H_5$

Chart 1.



IIa : $R_1,R_2=O$
IIb : $R_1=OH, R_2=H$
IIc : $R_1=OH, R_2=CH_3$

II′a : $R_1,R_2=O$
II′b : $R_1=OH, R_2=H$
II′c : $R_1=OH, R_2=CH_3$

IVa : $R_1,R_2=O$
IVb : $R_1=OH, R_2=H$

VIIIa : $R_1,R_2=O$
VIIIb : $R_1=OH, R_2=H$
VIIIc : $R_1=OH, R_2=CH_3$

VIa : $R_1,R_2=O$
VIb : $R_1=OH, R_2=H$

Chart 2.

The same procedure afforded the corresponding 2- and 4-alkoxymethylestrones (Va, Vd, Ve, and VIa), 2- and 4-alkoxymethylestradiols (Vb, Vf, and VIb) respectively.

Methiodide of Ia was readily reduced with sodium borohydride to give 2-methylestradiol (IIIb) in good yield, which proved to be identical with an authentic sample prepared by another route[3,5] *via* 2-methylestrone.

Although the two isomeric Mannich bases could not be etherified under usual methylating conditions at room temperature, 2- and 4-dimethylaminomethylestrone (Ia and IIa) when treated with dimethylsulfate in boiling methanolic alkali, yielded the corresponding methylated products (VIIa and VIIIa) respectively. Both of those products were found to be devoid of nitrogen and analyzed well for a compound of empirical formula $C_{21}H_{28}O_3$, having a carbonyl group at C-17 and two methoxyl groups, one of which masked the phenolic hydroxyl group at C-3 since their ultraviolet spectra did not show any bathochromic shift in an alkaline medium. Thus these compounds were position isomers, and the one originating from Ia assigned the 3-methyl ether of 2-methoxymethylestrone structure (VIIa), and the other arising from IIa accorded the 3-methyl ether of 4-methoxymethylestrone (VIIIa) formulation. In the same manner compounds (VIIb, c and VIIIb, c) were also synthesized from Ib, c and IIb, c respectively. Compounds (VIIa and VIIIa) were also prepared from 2- and 4-methoxymethyl estrone (Va and VIb) with dimethylsulfate. The reduction of VIIa with lithium-ammonium chloride in liquid ammonia afforded the 3-methyl ether of 2-methylestradiol (IIIe). The course of the formation of compounds VIIa or VIIIa from the Mannich bases of estrone appears to be analogous to that of the amine exchange reaction of a Mannich base[6] ($R'CH_2N^+R_3+:B \longrightarrow R'CH_2B+:NR_3$). It is assumed that methylation of Ia or IIa led initially to the

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5) J. Iriarte, H. J. Ringold: Tetrahedron, 3,28 (1958).
6) H. R. Snyder, J. H. Brewster: J. Am. Chem. Soc., **70**, 4230 (1948).

TABLE Ⅱ.

Compounds	$[\alpha]_D$ a)	IRcm^{-1} (region)					UV λ_{max}^{EtOH}	
		$\nu_{C=C}$			δ_{C-H}		mμ	ε
		1600	1580	1500	810 b)	880 c)		
2-Dimethylaminomethylestrone (Ia)	+158°	1625	1585	1502	—	882	286	3100
4-Dimethylaminomethylestrone (Ⅱa)	+137°	1596	—	1480	813	—	284	2300
2-Methylestrone (Ⅲa)	+198°	1623	1600	1511	—	881	283	2600
4-Methylestrone (Ⅳa)	+147°*	1591	—	1493	812	—	284	1850
2-Methoxymethylestrone (Ⅴa)	+143°	1627	1573	1499	—	883	285	2900
2-Ethoxymethylestrone (Ⅴd)	+152°	1630	1583	1504	—	890	286	2800
2-Benzyloxymethylestrone (Ⅴe)	+116°	1620	1574	1504	—	891	286	3200
4-Methoxymethylestrone (Ⅵa)	+134°	1599	—	1491	815	—	284	2700
2-Dimethylaminomethylestradiol (Ib)	+ 83°*	1622	1585	1503	—	871 885 890	285	3000
4-Dimethylaminomethylestradiol (Ⅱb)	+ 52°	1599	—	1477	821	—	286	2150
2-Methylestradiol (Ⅲb)	+ 87°	1620	1589	1505	—	880	285	2400
4-Methylestradiol (Ⅳb)	+ 57°	1592	—	1494	814	—	284	1550
2-Methoxymethylestradiol (Ⅴb)	+ 93°*	1618	1576w	1505	—	885	285	2900
2-Benzyloxymethylestradiol (Ⅴf)	+ 65°*	1619	1592	1505	—	870	285	3100
4-Methoxymethylestradiol (Ⅵb)	+ 70°	1590	—	1487	811	891	285	2600
2-Dimethylaminomethyl-17α-methylestradiol (Ic)	+ 57°*	1621	1584	1503	—	887	286	2900
4-Dimethylaminomethyl-17α-methylestradiol (Ⅱc)	+ 22°	1597	—	1480	812	—	286	2100
2,17α-Dimethylestradiol (Ⅲc)	+ 57°*	1621	1591	1512	—	881	285	2900
2-Methoxymethyl-17α-methylestradiol (Ⅴc)	+ 53°*	1619	1589w	1505	—	886	286	2800
2-Benzyloxymethyl-17α-methylestradiol (Ⅴg)	+ 52°*	1623	1580	1501	—	885 897	286	3200
2-Dimethylaminomethyl-17α-ethynylestradiol (Id)	+ 3°	1618	1586	1500	—	889	286	3000
2-Methylestrone 3-methyl ether (Ⅲd)	+151°	—	—	—	—	—	282 287	2810 2810
2-Methoxymethylestrone 3-methyl ether (Ⅶa)	+146°	1615	1580	1505	—	895	282 287	2740 2680
4-Methoxymethylestrone 3-methyl ether (Ⅷa)	+135°*	1585	—	1485	810	—	282 287	2480 2430
2-Methylestradiol 3-methyl ether (Ⅲe)	+ 74°	—	—	—	—	—	284	2600
2-Methoxymethylestradiol 3-methyl ether (Ⅶb)	+ 75°	1615	1578	1504	—	898	282 286	2620 2580
4-Methoxymethylestradiol 3-methyl ether (Ⅷb)	+ 81°*	1595	1582	1495	808	886	282 286	2430 2400
2,17α-Dimethylestradiol 3-methyl ether (Ⅲf)	+ 68°	1615	1578	1507	—	881	284	2800
2-Methoxymethyl-17α-methylestradiol 3-methyl ether (Ⅶc)	+ 49°	1618	1580	1503	—	892	287	2800
4-Methoxymethyl-17α-methylestradiol 3-methyl ether (Ⅷc)	—	1597	1587	1485	807	—	282 286	2400 2300
2-Methyl-17α-ethynylestradiol 3-methyl ether (Ⅲg)	+ 45°*	1618	1580	1508	—	886	282 286	2710 2660
2-Methyl-17α-ethylestradiol 3-methyl ether (Ⅲh)	+ 7°*	1613	1579	1505	—	882	282 286	2640 2560

a) Optical rotation were measured in dioxane solution (* in $CHCl_3$ solution).
b) Out of plane vibrations of two adjacent ring hydrogens.
c) Out of plane vibrations of two isolated ring hydrogens.

formation of the quarternary salt, from which a methylene quinone as an intermediate is liberated by the alkali. The resulting intermediate is attacked by a nucleophilic alkoxide anion followed by simultaneous methylation to form the compound (Ⅶa or Ⅷb).

Recently, Holton[7,8] has made use of the aromatic C=C stretching and C–H deformation vibrational bands of the infrared absorption spectra to differentiate between the two C-alkylestrogens at C-2 and C-4. This observation can also be applied to our new steroids. In the case of 2-substituted estrogens the three principal peaks attributed to the C=C stretching vibrational modes occur in the 1600~1620 cm^{-1}, 1580 cm^{-1}, and 1500~1510 cm^{-1} region, while the 4-substituted estrogens with only two peaks appear in the 1585~1600 cm^{-1} and 1480~1500 cm^{-1} region. The band at about 1580 cm^{-1} was not discernible. On the other hand, the 2-substituted estrogens with only isolated 1,4 ring hydrogens possesses a band in the 880~890 cm^{-1} region; while the 4-substituted estrogens with two adjacent ring hydrogens show a band at about 810~820 cm^{-1}. The assigned structure for 2- and 4-substituted estrogens are found to be in good agreement with the observations of Holton as shown in Table Ⅱ.

In our compounds as was found for the corresponding 2- and 4-alkylestradiols,[7] the intensity of the ultraviolet maximum of the substituted estrogens clearly distinguished between the 2- and 4-isomers. In general, the 2-alkoxy and 2-dimethylaminomethylestrones showed increased intensities as compared with estrone, and the 4-alkoxymethyl- and 4-dimethylaminomethylestradiols showed reduced intensities. Finally, it is seen in Table Ⅱ that the optical rotations of 2- and 4-substituted estrones are much more positive than those of the corresponding estradiols. Thus, it can be stated that the presence of a carbonyl group at C-17 contributes a positive effect on the optical rotation of the steroids.

This series of compounds including the 2- and 4-alkoxymethylestradiols and the methyl ethers was tested for estrogenic uterotrophic activity using immature female mice and for lipid-shifting effects in the castrated male rats and intacts with triton-induced hyperlipemia. It was found that the introduction of alkoxymethyl groups at C-2 or C-4 in A-ring aromatized steroids produced an extreme decrease in estrogenic activity of the parent steroids, whereas the lipid-shifting activity was increased as compared with the parent steroids and natural estrogens. Of the tested compounds, 2-methoxymethyl-17α-methylestradiol 3-methyl ether (Ⅶc) was found to be most highly active in lowering the serum and hepatic cholesterol level in experimental by induced hypercholesterolemia in rats and rabbits. Detailed biological results of the steroids will be reported elsewhere.

Experimental[*3]

2- and 4-Dimethylaminomethylestrone (Ia and IIa)——The Mannich reaction of estrone (10 g.) was carried out by the method reported by Patton.[3] The resulting crude product (12.5 g.) was chromatographed on silica gel. Recrystallization of the first benzene eluate from EtOH gave 0.65 g. (5%) of 4-dimethylaminomethylestrone (Ⅱa), m.p. 218~223°, $[\alpha]_D^{32}$ +137°(c=0.89). *Anal.* Calcd. for $C_{21}H_{29}O_2N$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.31; H, 8.54; N, 3.99.

Further elution with benzene and benzene–Et_2O (2:1) followed by crystallization from EtOH gave 9.3 g. (77%) of 2-isomer (Ia), m.p. 177~179°, $[\alpha]_D^{30}$ +158°(c=0.92). *Anal.* Calcd. for $C_{21}H_{29}O_2N$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.84; H, 8.95; N, 4.06.

2- and 4-Dimethylaminomethylestradiol (Ib and IIb)——a) To a solution of estradiol (3.0 g.) in benzene (60 ml.) and EtOH (40 ml.) were added N,N,N′,N′-tetramethylmethylenediamine (2.3 g.) and paraformaldehyde (0.36 g.). After refluxing for 17 hr., reaction mixture was treated in the same manner

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[*3] Melting points were taken on a Kofler block and were uncorrected. Optical rotations were measured in dioxane solution, unless specified otherwise.

7) P.G. Holton: J. Org. Chem., **27**, 357 (1962).

8) T.L. Patton: Chem. & Ind. (London), **1960**, 1567.

as reported for the Ia. Residue (3.5 g.) was chromatographed on silica gel. The eluate with 20% petr. ether in benzene afforded 140 mg. (4%) of Ⅱb, m.p. 195～201°, $[\alpha]_{\mathrm{D}}^{30}$ +52° (c=1.02). *Anal.* Calcd. for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found : C, 76.60; H, 9.35; N, 4.03.

Further elution with benzene afforded 2.6 g. (72%) of Ib, m.p. 156～157°, $[\alpha]_{\mathrm{D}}^{20}$ +83° (c=0.23, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found : C, 76.68; H, 9.43; N, 3.94.

b) To a solution of Ia (980 mg.) or Ⅱa in MeOH (20 ml.) was added 0.5 g. of $NaBH_4$ portionwise and allowed to stand at room temperature overnight. The product was isolated in the usual way and recrystallization from Et_2O gave 0.9 g. (91%) of Ib or Ⅱb. The products in (a) were identical with the samples prepared in (b) confirmed by comparison of IR spectrum and mixture melting point determination.

2-Dimethylaminomethyl-17α-methylestradiol (Ic)——A solution of Ia (2.5 g.) in anhydrous benzene (60 ml.) was added dropwise with stirring to methylmagnesium iodide solution prepared from Mg-ribbon (1 g.) and CH_3I (6 g.) in anhyd. Et_2O (40 ml.), and refluxed gently for 4 hr. After decomposition of the reaction mixture with 10% NH_4Cl (60 ml.), the benzene layer was separated and aqueous layer was extracted with benzene. The combined benzene extracts gave 1.8 g. of crude product which was recrystallized from MeOH to give 0.93 g. (48%) of Ic, m.p. 172～174°, $[\alpha]_{\mathrm{D}}^{24}$ +57° (c=1.10, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{33}O_2N$: C, 76.92; H, 9.68; N, 4.08. Found : C, 77.21; H, 9.51; N, 3.89.

4-Dimethylaminomethyl-17α-methylestradiol (IIc)——The analogous reaction of Ⅱa (0.98 g.) as in Ic and recrystallization from MeOH gave Ⅱc (0.62 g., 60%), m.p. 160～166°, $[\alpha]_{\mathrm{D}}^{28}$ +22° (c=0.42). *Anal.* Calcd. for $C_{22}H_{33}O_2N$: C, 76.92; H, 9.68; N, 4.08. Found : C, 76.71; H, 9.52; N, 3.91.

2-Dimethylaminomethyl-17α-ethynylestradiol (Id)——To a solution of potassium *tert*-amylate prepared from K (3 g.) in *tert*-amylalcohol (60 ml.) was added 80 ml. of anhyd. Et_2O on ice bath and the air was displaced by N_2 stream. After a slow stream of dry acetylene was passed through the solution for 30 min. on ice bath, 3 g. of Ia was added. The addition of acetylene gas was continued for 4.5 hr. at 0°. After treating with NH_4Cl aq. solution, the reaction mixture was evaporated *in vacuo* to give 3.3 g. of oily product which was chromatographed on neutral Al_2O_3. Fractions eluted with 0～40% $CHCl_3$ in Et_2O afforded 1.8 g. of crude crystal. Repeated recrystallizations from Me_2CO and hexane gave 1.4 g. of pure Id, m.p. 161～165°. $[\alpha]_{\mathrm{D}}^{28}$ +3° (c=0.98). *Anal.* Calcd. for $C_{23}H_{31}O_2N$: C, 78.14; H, 8.84; N, 3.96. Found : C, 78.53; H, 8.84; N, 3.81.

2-Dimethylaminomethylestrone Methiodide (I′a)——To a solution of Ia (2.0 g.) in anhyd. Et_2O (200 ml.) was added 10 ml. of CH_3I. The mixture was allowed to stand at room temperature overnight. The crystalline precipitate was collected, washed with dry Et_2O and recrystallized from anhyd. Me_2CO to give 2.3 g. (85%) of Ia, m.p. 229～231° (decomp.).

Methiodides of 2-dimethylaminomethylestradiol, 2-dimethylaminomethyl-17α-methylestradiol, 4-dimethylaminomethylestrone and 4-dimethylaminomethyl-17α-methylestradiol, (I′b), (I′c), (Ⅱ′a), and (Ⅱ′c) were prepared in analogous manner described above. I′b : m.p. 212～215°, I′c : m.p. 217～219° (decomp.).

2-Methylestradiol (IIIb)——To a solution of I′a (940 mg.) in abs. EtOH (45 ml.) was added $NaBH_4$ (1 g.) and heated at reflux temperature for 3 hr. Reaction mixture was concentrated *in vacuo*, added H_2O and extracted with Et_2O to give 600 mg. of crude product. Recrystallizatios from EtOH gave 440 mg. (80%) of Ⅲb, m.p. 185～187°, $[\alpha]_{\mathrm{D}}^{28}$ +87° (c=0.75). The product was identical with an authentic specimen3) inferred from comparison of IR spectrum and mixture melting point determination.

2,17α-Dimethylestradiol (IIIc)——A solution of I′c (485 mg.) in abs. EtOH (25 ml.) was treated with $NaBH_4$ (500 mg.) at reflux temperature to give 270 mg. of solid, which was recrystallized from MeOH giving 220 mg. (70%) of Ⅲc, m.p. 204～207°, $[\alpha]_{\mathrm{D}}^{25}$ +57° (c=1.02, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found : C, 80.06; H, 9.68.

Reduction of Ic with Raney Ni gave an identical specimen with Ⅲc by comparison of IR spectrum.

4-Methylestrone (IVa)——A solution of Ⅱa (500 mg.) in EtOH (80 ml.) and Raney Ni (5 g.) was treated in the conventional way to give 300 mg. of product. Recrystallization from MeOH afforded 180 mg. of crystalline product, which was chromatographed on silica gel. Elution with 40% $CHCl_3$ in benzene afforded 80 mg. of crude crystal, melted at 228～231°. Recrystallization from EtOH gave 50 mg. of Ⅳa, m.p. 241～243°, $[\alpha]_{\mathrm{D}}^{25}$ +147° (c=0.38, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.02; H, 8.47.

4-Methylestradiol (IVb)——Reduction of Ⅱa (0.42 g.) with $NaBH_4$ gave oily product, Ⅱb, which was further treated with Raney Ni in EtOH to give 0.30 g. of crystalline product. Recrystallization from EtOH gave 260 mg. of Ⅳb, m.p. 218～223°, $[\alpha]_{\mathrm{D}}^{20}$ +57° (c=1.89). *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found : C, 79.49; H, 8.91.

2-Methylestrone 3-Methyl Ether (IIId)——2-Methylestrone was converted to 2-methylestrone 3-methyl ether with Me_2SO_4 at room temperature. Recrystallization from EtOH gave an analytical specimen which melted at 152～154°, $[\alpha]_{\mathrm{D}}^{30}$ +151° (c=0.93). *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; MeO, 10.40. Found : C, 80.34; H, 8.73; MeO, 10.02.

2-Methylestradiol 3-Methyl Ether (IIIe)——a) By the same procedure described above, the specimen recrystallized from cyclohexane melted at 138～139°, $[\alpha]_D^{26}$ +74°(c=0.95). *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.38. Found : C, 79.90; H, 9.33.

b) To a stirred solution of VIIa(1.0 g.) in anhyd. Et_2O and liquid NH_4OH(600 ml.) was added Li metal (3.0 g.) in small pieces over a period of 45 min. After stirring for 1 hr., 36 ml. of abs. EtOH was added dropwise over a period of 20 min. After evaporation of NH_3, the reaction mixture was decomposed with H_2O (100 ml.) and extracted with benzene. Benzene extract was treated in the usual way to give 1.0 g. of oily residue, which on addition of MeOH gave 200 mg. of crystal. The crystal was recrystallized from benzene-cyclohexane to give 100 mg. (11%) of 2-methyl-3-methoxyestra-2,5(10)-dien-17β-ol, m.p. 280～287°, $[\alpha]_D^{26}$ +97°(c=0.70). The MeOH soluble fraction was chromatographed on neutral Al_2O_3. Eluate with 30% petr. ether in benzene was recrystallized from cyclohexane to give 300 mg. (33%) of IIIe, m.p. 138～139°. The product obtained in (b) was identical with the sample prepared in (a) (IR spectrum and mixture melting point determination).

2,17α-Dimethylestradiol Methyl Ether (IIIf)——Methylation of IIIc with Me_2SO_4 and recrystallization from hexane gave IIIf, m.p. 142～143°, $[\alpha]_D^{23}$ +68°(c=1.01). *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found : C, 80.23; H, 9.35.

2-Methyl-17α-ethynylestradiol 3-Methyl Ether (IIIg)——Ethynylation of IIId (1.0 g.) in the similar way described for Id, gave 0.9 g. of crude product, which was chromatographed on silica gel. Fractions eluted with 10% Et_2O in benzene was evaporated and recrystallization of the residue from hexane gave 90 mg. (8%) of IIIg, m.p. 124～126°, $[\alpha]_D^{28}$ +45°(c=1.05, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found : C, 81.24; H, 8.76.

2-Methyl-17α-ethylestradiol 3-Methyl Ether (IIIh)——A suspension of activated 5% Pd-C (40 mg.) in a solution of IIIg (320 mg.) in dioxane (30 ml.) was shaked in an atmosphere of H_2, absorbing one equivalent of gas in 15 min. The solution was filtered and concentrated *in vacuo* to give 300 mg. of crystalline product. Recrystallization from MeOH afforded 250 mg. (76%) of IIIh, m.p. 131～132°, $[\alpha]_D^{28}$ +7°(c=0.99, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 80.44; H, 9.83. Found : C, 80.22; H, 9.99.

2-Methoxymethylestrone (Va)——A solution of I′a (1.6 g.) and KOH (3.2 g.) in MeOH (32 ml.) was heated at reflux temperature for 3 hr. The reaction mixture was concentrated to one fourth, diluted with H_2O, acidified with conc. HCl and extracted with Et_2O. The ethereal extract was treated in the usual way to give 0.9 g. of crude product, which was chromatographed on silica gel. Elution with 5% Et_2O in benzene afforded 830 mg. (80%) of Va. Recrystallization from EtOH gave 750 mg. of pure crystal, m.p. 158～160°. $[\alpha]_D^{30}$ +143°(c=1.04). *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; MeO, 9.87. Found : C, 76.49; H, 8.22; MeO, 9.79.

Solvolysis of I′b, I′c, and II′a were carried out in the same way as in Va with KOH and MeOH, and afforded Vb, Vc, and VIa respectively. Their physical constants and analytical values were as follows : a) 2-Methoxymethylestradiol (Vb) : m.p. 181～182.5°, $[\alpha]_D^{20}$ +93°(c=1.07, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found : C, 75.92; H, 8.88.

b) 2-Methoxymethyl-17α-methylestradiol (Vc) : m.p. 157～158°, $[\alpha]_D^{20}$ +53°(c=1.02, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; MeO, 9.37. Found : C, 76.00; H, 8.87, MeO, 9.27.

c) 4-Methoxymethylestrone (VIa) : m.p. 163～165°, $[\alpha]_D^{30}$ +134°(c=1.34). *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; MeO, 9.87. Found : C, 76.17; H, 8.36; MeO, 9.77.

4-Methoxymethylestradiol (VIb)——Reduction of VIa with $NaBH_4$ gave crystalline product. Recrystallization from MeOH to yield 95 mg. of VIb, m.p. 195～201°(decomp.), $[\alpha]_D^{30}$ +70°(c=1.03). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; MeO, 9.81. Found : C, 75.87; H, 9.08; MeO, 9.92.

2-Ethoxymethylestrone (Vd)——A solution of 1.41 g. of I′a and KOH (2.8 g.) in EtOH (30 ml.) was treated in the analogous way to give 900 mg. of crude product, which was chromatographed on silica gel. Elution with 5% Et_2O in benzene afforded 540 mg. of crystalline product, which was recrystallized from EtOH to give 480 mg. (49%) of Vd, m.p. 109.5～111.5°, $[\alpha]_D^{30}$ +152°(c=1.07). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; EtO, 13.72. Found : C, 76.62; H, 8.58; EtO, 13.49.

2-Benzyloxymethylestrone (Ve)——To a solution of I′a (1 g.) in benzylalcohol (20 ml.) was added a solution of KOH (2 g.) in benzylalcohol (20 ml.). The mixture was heated on oil bath at 110° with stirring for 3 hr. The reaction mixture was diluted with H_2O, acidified with conc. HCl, and extracted with Et_2O. The ethereal extract was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to yield 1 g. of crude product. The product was chromatographed on silica gel and elution with 3% Et_2O in benzene gave crystalline product, which was recrystallized from Et_2O to give 510 mg. (60%) of Ve, m.p. 115.5～117°, $[\alpha]_D^{22}$ +116°(c=1.16, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{30}O_3$: C, 79.96; H, 7.74. Found : C, 79.84; H, 7.76.

Solvolysis of I′b and I′c were carried out in the same manner as in Ve with KOH and benzylalcohol and afforded Vf and Vg, recrystallized from benzene. Their physical constants and analytical values were as follows : a) 2-Benzyloxymethylestradiol (Vf) : m.p. 176.5～178.5°, $[\alpha]_D^{22}$ +65°(c=0.88, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found : C, 79.54; H, 8.40.

b) 2-Benzyloxymethyl-17α-methylestradiol (Vg.) : m.p. 146～149°, $[\alpha]_D^{22}$ +52° (c=0.50, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{34}O_3$: C, 79.76; H, 8.43. Found : C, 79.71; H, 8.22.

2-Methoxymethylestrone 3-Methyl Ether (VIIa)——To a solution of Ia (2 g.) in MeOH (70 ml.) and 17% KOH aq. solution (22 ml.) was added Me_2SO_4 (5.5 ml.) dropwise over a period of 30 min. while stirring at reflux temperature. An additional 14 ml. of 17% KOH solution was then added followed by dropwise addition of 3 ml. of Me_2SO_4 over a 20 min. period. After keeping at the same condition for 5 hr. the reaction mixture was diluted with H_2O, extracted with AcOEt. The extract was treated in the usual way to give 1.95 g. of crude product, which was chromatographed on neutral Al_2O_3. Elution with 20% Et_2O in benzene gave 720 mg. of residue, which was recrystallized from MeOH to give 650 mg. of VIIa, m.p. 124~126°, $[\alpha]^{24}_{D}$ +146° (c=1.09). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; MeO, 18.89. Found : C, 77.17; H, 8.56; MeO, 18.79.

Methylation of 2-methoxymethylestrone (Va) with Me_2SO_4 in the conventional manner at room temperature afforded 2-methoxymethylestrone 3-methyl ether in good yield, which was identical (IR spectrum and mixture melting point determination) with a specimen obtained above.

Methylations of Ib, Ic, IIa, IIb, and IIc were carried out in the same manner as in VIIa and afforded VIIb, VIIc, VIIIa, VIIIb, and VIIIc respectively. Their physical constants and analytical values were as follows : a) 2-Methoxymethylestradiol 3-methyl ether (VIIb) : m.p. 94~95°, $[\alpha]^{29}_{D}$ +75° (c=0.98). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found : C, 76.30; H, 9.06.

b) 2-Methoxymethyl-17α-methylestradiol 3-methyl ether (VIIc) : m.p. 134~136°, $[\alpha]^{32}_{D}$ +49° (c=1.03). *Anal.*Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found : C, 76.40; H, 9.15.

c) 4-Methoxymethylestrone 3-methyl ether (VIIIa) : m.p. 152.5~153.7°, $[\alpha]^{24}_{D}$ +135° (c=1.10, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; MeO, 18.90. Found : C, 76.76; H, 8.43; MeO, 18.62.

d) 4-Methoxymethylestradiol 3-methyl ether (VIIIb) : 168~170°, $[\alpha]^{24}_{D}$ +81° (c=0.75, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; MeO, 18.78. Found : C, 76.53; H, 8.83; MeO, 18.85.

e) 4-Methoxymethyl-17α-methylestradiol 3-methyl ether (VIIIc) : m.p. 134~136°. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found : C, 76.39; H, 9.10.

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Summary

2-Dimethylaminomethylestrone (Ia) and the 4-isomer (IIa) were obtained from the Mannich product of estrone. Methiodides of I'a-c and II'a-c were treated with alcoholic alkali to give 2- and 4-alkoxymethylestrogens in good yields. Methylation in the usual manner of I and II failed, but reaction of I and II with dimethylsulfate in a boiling methanolic alkali gave the 3-methyl ethers of 2- and 4-methoxymethylestrogens, respectively. The structural assignments of the isomers were discussed based on nuclear magnetic resonance, infrared and ultraviolet spectra.

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