to **1** (or **3**) produces an approximately equal amount of the undesired (and difficultly separable) side-chain diastereomer, and (ii) the overall yield for the conversion of i to **1** (or **3**) is, in all four cases, ≤5%. (c) K. L. Mikolajczak, C. R. Smith, Jr., D. Weisleder, T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Lett.*, 283 (1974); (d) S.-W. Li and J.-Y. Dai, *Hua Hsueh Hsueh Pao*, **33**, 75 (1975) [*Chem. Abstr.*, **84**, 150812q (1976)]; W.-K. Huang, Y.-L. Li, and S.-F. Pan, *K'o Hsueh T'ung Pao*, **21**, 178 (1976) [*Chem. Abstr.*, **85**, 63208 (1976)]; (e) Institute of Pharmacology, *ibid.*, **20**, 437 (1975); **21**, 509, 512 (1976) [*Chem. Abstr.*, **86**, 171690e (1977)]; (f) K. L. Mikolajczak and C. R. Smith, Jr., Abstracts of the 175th American Chemical Society National Meeting, March 1978, Anaheim, Abstract MEDI 023.

(11) The selection of **5** as the precursor to the side chain was influenced by the following considerations: (a) the limiting substrate in the preparation of **1** will be, almost certainly, **4**; consequently the side-chain synthon should be as fully elaborated as possible and require a minimum of further transformations once attached to **4**; (b) generation of the chiral center in the acyl moiety should precede esterification to cephalotaxine in order to avoid diastereomeric difficulties;[10b] (c) the acyl synthon should be sufficiently stable to survive the relatively vigorous conditions (vide infra) required to acylate **4**.

We submit that previous unsuccessful attempts[10a] to prepare **1** and **3** are a consequence of (a) steric hindrance (in both **4** and the acylating agents) and (b) the suspected instability of activated derivatives of the appropriate fully elaborated half acids corresponding to the natural esters of **4**. The absence in the literature of physical or spectral characterizations of any activated side-chain synthons[10a] would appear to support the latter hypothesis.

It was envisaged that constraining the two alkyl substituents in the acyl group into a lactone ring would not only reduce steric hindrance problems but also attenuate the potential for destructive intramolecular interactions between the various functional groups in putative side-chain precursors.

(12) The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

(13) As anticipated from the studies of R. Huisgen and H. Ott [*Tetrahedron*, **6**, 253 (1959)], cleavage of the acyl linkage to cephalotaxine is less facile than methanolysis of the lactone ring in **6**. The olefinic double bond in cephalotaxine has been shown[2d] to be highly resistant to catalytic hydrogenation.

(14) J. Monnin, *Helv. Chim. Acta*, **39**, 1721 (1956).

(15) The procedure described in the Experimental Section for the obtention of pure **10a** from the mixture of **9a** and **9b** was developed by Professor R. J. Parry and Dr. Richard Dufresne at Brandeis University and is a distinct improvement over methods previously used by us. In particular, recrystallization of the sodium salt of **10a** provides material of higher purity than can be obtained by recrystallization of the acid itself. We thank Professor Parry for advising us of this procedure.

(16) Cursory attempts to enhance the regioselectivity of the reaction between isoprene and **6** by employing Lewis acid catalysis ($AlCl_3$) were unfruitful (unpublished results of T. R. Kelly and B. K. Prazak). The possibility of preparing **12** directly by Diels–Alder reaction of isoprene with $CH_2{=}CH(OCH_2Ph)COOCH_2Ph$ (ii) was not investigated (nor was ii prepared) because it was anticipated [S. M. McElvain, H. I. Anthes, and S. H. Shapiro, *J. Am. Chem. Soc.*, **64**, 2525 (1942)] that ii would undergo a Claisen rearrangement in preference to cycloaddition.

(17) M. Freifelder, "Practical Catalytic Hydrogenation", Wiley, New York, N.Y., 1971, p 429.

(18) While it remains to be determined whether the absolute configuration of (−)-**10a** corresponds to that found in **1**, since both enantiomers of ephedrine are available, resolution of **10a** with the other enantiomer of ephedrine will, if necessary, provide (+)-**10a**. At present the yield of the resolution is approximately 20% of theory. Efforts to improve the resolution step are in progress.

(19) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

6-Aminoalkyl Catechol Estrogens: Models of Steroidal Biogenic Amines[1]

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Reaction of 2,3-dibenzyloxy-17β-acetoxyestra-1,3,5(10)-trien-6-one (IIc) with trimethylsilyl cyanide gave as the sole product the 6β-cyano-6α-(trimethylsilyloxy) derivative IIIa. Subsequent reductive elaboration of IIIa afforded 6β-(aminomethyl)estra-1,3,5(10)-triene-2,3,6α,17β-tetrol (IIIe) which combines the structural features of the centrally active catechol estrogens and the biogenic catecholamines. The synthesis of the related 6α- and 6β-(2-acetaminoethyl)estra-1,3,5(10)-triene-2,3,17β-triol triacetates (VIe and VIf) was attained via Wittig reaction of the 6-ketone IIc with diethyl cyanomethylphosphonate and subsequent reduction.

The catechol estrogens (2,3-dihydroxyestrogens) have been identified as the major metabolites of estradiol in man and other species.[3,4] The principal site of their formation is in the liver but the presence of this biotransformation has also been demonstrated in the CNS[5,6] where the concentration of the catecholestrogens has been reported to be disproportionately high.[7] The formation and presence of the catechol estrogens within CNS assumes particular significance because of the unusual nature of their biological activity. The major catechol estrogen, 2-hydroxyestrone (Ia), is unique among the estrogens in that it exhibits central[8,9] but not peripheral hormonal activity[10] and hence its in situ biosynthesis in the brain may have important physiological consequences. The neuroendocrine action of the catechol estrogens could be mediated by their competitive inhibition of the O-methylation of the biogenic catecholamines by catechol-*O*-methyl transferase,[11] or possibly by other interactions with catecholaminergic mechanisms. These as well as other considerations suggested that compounds which combine the structural features of the catechol estrogens and of the catecholamines may exhibit novel pharmacological properties. Additional interest in such compounds derives from their structural relationship to morphine and related opiates which would imply a potential for analgetic activity in these substances. Because of the inherent symmetry of the 2,3-dihydroxyestrogen structure the desired catechol ethylamine feature could be generated by the insertion of an amino group at carbons 7, 8, and 11, or of an aminomethyl group at positions 6 and 9. Because of relative accessibility and because of the opportunity for greater structural versatility in an amino group located on a primary carbon, we elected to construct the structures initially by the introduction of the 6-aminomethyl group at the C-6 position.

Functionalization of the 6-keto intermediate which is readily accessible via benzylic oxidation of a suitably protected catechol estrogen represented a convenient route to these compounds. Reaction of 2,3,17β-trihydroxyestra-1,3,5(10)-triene triacetate (Ib) with chromic anhydride in acetic acid[12] yielded the corresponding 6-keto derivative IIa in over 30% yield. Attempts to obtain a cyanohydrin from the C-6 ketone in IIa by conventional procedures failed to yield any product. Similarly, an attempt to generate the cyanohydrin by the reaction of the intermediate tosylhydrazone with potassium cyanide in ethanol provided only the regenerated ketone IIa. Modification of the phenolic protection groups was then sought in the hope of affecting the reactivity of the benzylic ketone. Hydrolysis of the acetates at C-2 and C-3 and their replacement by benzyl ethers was accomplished at the same

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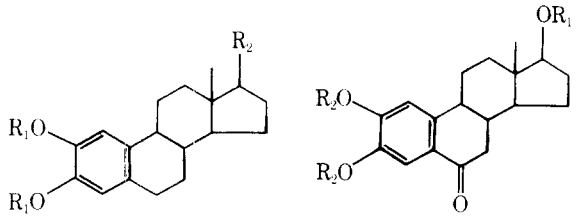
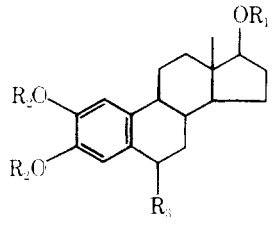
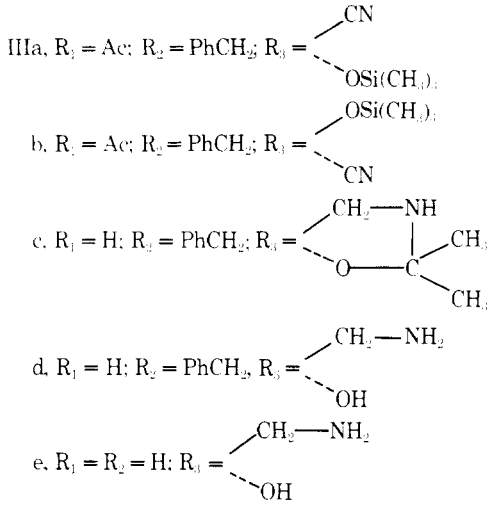
time through the use of benzyl chloride in potassium carbonate and generated the dibenzyl ether IIb which was converted to the 17-acetate IIc. This derivative, however, also failed to provide the cyanohydrin under the conditions previously employed. The resistance of the C-6 ketone to cyanohydrin formation was finally overcome through the use of trimethylsilyl cyanide as the reagent[13] which provides for more favorable energy requirements for the reaction. Reacting the dibenzyl ether IIc with a large excess of trimethylsilyl cyanide in the presence of zinc iodide as a catalyst yielded the cyanohydrin silyl ether derivative IIIa, in virtually quantitative yield. Only one of the two possible isomeric cyano derivatives was obtained, although under somewhat more drastic conditions the formation of the isomeric cyano compound IIIb was also detected. This material was, however, unstable and rapidly decomposed to regenerate the starting ketone. The orientation of the cyano and trimethylsilyl ether groups in IIIa was assigned as β and α respectively on the basis of steric considerations. Analysis by NMR of epimeric 6-hydroxy[14] and 6-methyl[15] substituents of estradiol has provided evidence that ring B in these compounds is in the half-chair form and that therefore the α and β orientation are quasi-equatorical and quasi-axial, respectively. In the case of IIIa, the far bulkier trimethylsilyloxy group would therefore be predictably more stable in the α orientation in which interaction with axial 8β hydrogen is absent. The isolated stable isomer would therefore be the 6β-cyano 6α-silyl ether IIIa, and the unstable product IIIb has the reverse orientation insofar as these groups are concerned. The validity of this assigned stereochemistry in IIIa and IIIb was securely confirmed on the basis of the sequence described later in this report.



Ia, R_1 = H; R_2 = O
b, R_1 = Ac; R_2 = OAc

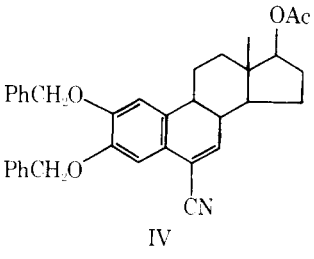
IIa, R_1 = R_2 = Ac
b, R_1 = H; R_2 = $PhCH_2$
c, R_1 = Ac; R_2 = $PhCH_2$



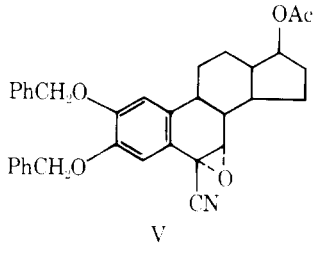


Reduction of the cyanohydrin silyl ether IIIa with diborane proved to be less than satisfactory in producing the desired alkylamine, but the use of lithium aluminum hydride followed by extraction with acetone provided the 6-oxazolidine adduct IIIc[16] in excellent yield. Treatment of the oxazolidine IIIc with dilute acetic acid readily yielded the aminomethyl alcohol IIId. Removal of the benzylic ethers was then accomplished with hydrogen over palladium to give the desired 6β-(aminomethyl)estra-1,3,5(10)-triene-2,3,6α,17β-tetrol (IIIe) which was isolated as the hydrochloride salt.

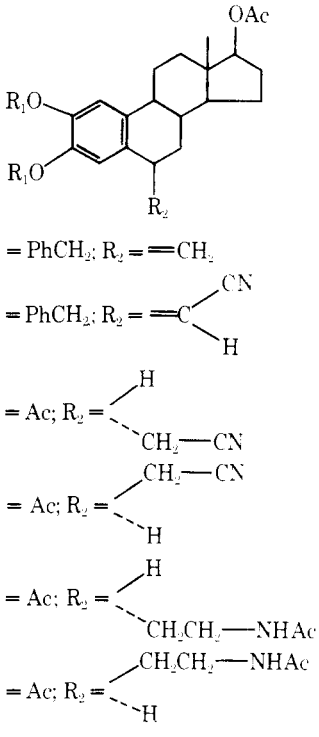
Because of the inability to obtain a NMR spectrum of the unstable cyanohydrin silyl ether IIIb, the spectral evidence for the correctness of the assigned configurations at C-6 in IIIa was inconclusive. The validity of the assignment was therefore established by the following scheme. Treatment of IIIa with phosphorus oxychloride caused the elimination of the silyl ether and yielded the 6-cyano-6-ene product IV. Epoxidation



IV



V



of the latter with *m*-chloroperbenzic acid gave as the sole isolated product the 6α,7α-epoxide V. The α orientation of the epoxide in V followed from its NMR spectrum in which the 7β proton appeared as a doublet at δ 4.50 with a coupling constant of 1.2 Hz. Such a coupling constant is only consistent with an interaction of 7β and 8β protons with a dihedral angle of 80° and is in agreement with the coupling constants of 1.5 and 1.0 Hz previously observed for $J_{7,8}$ in other steroid 6α,7α-epoxides.[17,18] Reduction of the 6β-cyano 6α,7α-epoxide V with lithium aluminum hydride provided an oxazolidine which was identical in all respects with that obtained by the reduction of the cyanohydrin silyl ether IIIa, thus establishing the orientation of the C-6 substituents in IIIa and in the products IIIc, IIId, and IIIe derived from it.

The possibility of arriving at the 6-aminoalkyl compounds via an alternative route involving Wittig reaction of the 6-ketone was also explored. Although the 6-methylene derivative VIa could be obtained in moderate yield by the conventional Wittig process, hydroboration and aminolysis of the 6-methylene group failed to yield the requisite 6-aminomethyl derivative. Other modifications of the Wittig reaction designed to introduce a 1-carbon functionally at C-6 capable of being transformed to a aminomethyl group also failed and attention was then directed to the introduction of an aminoethyl side chain at C-6. Such structures would provide information on the impact of the extension of the 6-aminoalkyl side chain on the pharmacology of these new compounds.

Reaction of IIa with diethylcyanomethylphosphorane[19,20] gave as the sole product a substance whose spectral and analytical data conformed to the 6-cyanomethylene derivative VIe in which the cyano group is trans to the aromatic ring. This trans structure is assigned to the compound because of the absence of a deshielding effect on the C-4 hydrogen which appears at 7.25 in VId and at 7.06 in the 6-methylenecyano compound VIb. It would be expected that the closer proximity of the cyano group to the C-4 hydrogen in the cis form would have produced a more pronounced downfield shift. Reduction of the C-6 double bond in VIb with hydrogen over palladium proceeded with concomitant loss of the benzyl ethers and gave the isomeric 6α- and 6β-cyanomethyl derivatives VIc and VId isolated as the triacetates. The orientation of the C-6 substituents in these compounds was tenatively assigned on the basis of their C-18 methyl chemical shifts. The α-cyanomethyl derivative VIc exhibited a C-18 methyl singlet at δ 0.82, while the β-cyanomethyl VId exhibited a slight downfield shift to δ 0.85 reflecting the greater proximity of the deshielding cyano group in this structure. In addition the reduction of VIb gave the 6β and 6α products in a 4:1 ratio which is consistent with the expected preference for hydrogen addition from the α side. Reduction of the cyano group in VIc and VIa was accomplished with diborane and the isomeric aminoethyl compounds were isolated as the acetates VIe and VIf, the chemical shifts of the 18 methyls at 0.78 and 0.82 respectively reflecting the α and β orientations of the C-6 substituents.

The derivatives of the catechol estrogens described in this communication whose structures combine features of the centrally active steroids and of the biogenic catecholamines are presently undergoing pharmacological evaluation.

Experimental Section[21]

2,3,17β-Triacetoxyestra-1,3,5(10)-trien-6-one (Ib). To a solution of 1.32 g of 2,3,17β-triacetoxyestra-1,3,5(10)-trien-6-one (IIa) in 4 mL of acetic acid a solution of 0.94 g of chromic oxide in 0.76 mL of water and 5.6 mL of acetic acid was added. The mixture was allowed to stand for 24 h at room temperature at which time 1.3 mL of ethanol was added to reduce the excess chromic acid. The reaction was then diluted with water, extracted with ether which was then washed with saturated sodium biocarbonate solution and water, dried over anhydrous sodium sulfate, and evaporated. The residue was subjected to separation with the Girard's T reagent, with the crude ketonic fraction being reacetylated with acetic anhydride in pyridine. The usual workup yielded 420 mg of 2,3,17β-triacetoxyestra-1,3,5(10)-trien-6-one: mp 188–190 °C obtained as prisms from ethanol; IR (KBr) ν_{max} cm^{-1} 1697, 1747, 1777 (C=O); NMR ($CDCl_3$ solution) δ 0.82 (3 H, s, 18-CH_3), 2.07 (3 H, s, 17β-$COCH_3$), 2.29 (6 H, s, 2- and 3-$COCH_3$), 4.69 (1 H, t, 17α-H), 7.26 (1 H, s, 1-H), 7.88 (1 H, s, 4-H). Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.09; H, 6.54.

2,3-Di(benzyloxy)-17β-hydroxyestra-1,2,5(10)-trien-6-one (IIb). To a solution of IIa (1 g) in absolute ethanol (400 mL) were added anhydrous potassium carbonate (4 g) and benzyl chloride (4 mL) and the mixture was refluxed for 9 h. The reaction mixture was taken to dryness under reduced pressure and the residue was extracted with chloroform. The extract, after evaporation, was dissolved in 30 mL of ethyl acetate–cyclohexane (1:1) and chromatographed on silica gel (150 g). Elution with ethyl acetate–cyclohexane (1:1) and recrystallization from ethanol gave IIb (0.5 g) as colorless needles: mp 163–165 °C; IR (KBr) ν_{max} cm^{-1} 1655 (C=O), 3450 (OH); NMR ($CDCl_3$ solution) δ 0.78 (3 H, s, 18-CH_3), 3.69 (1 H, t, 17α-H), 5.18 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 5.20 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 6.90 (1 H, s, 1-H), 7.66 (1 H, s, 4-H). Anal. Calcd for $C_{32}H_{34}O_4$: C, 79.64; H, 7.10. Found: C, 79.56; H, 7.10.

2,3-Di(benzyloxy)-17β-acetoxyestra-1,3,5(10)-trien-6-one (IIc). Acetylation of IIa (500 mg) in the usual manner with pyridine–acetic anhydride and recrystallization from ethanol gave IIc (400 mg) as colorless needles: mp 134–135 °C; IR (KBr) ν_{max} cm^{-1} 1678, 1735 (C=O); NMR ($CDCl_3$ solution) δ 0.80 (3 H, s, 18-CH_3), 2.02 (3 H, s, 17β-$COCH_3$), 4.78 (1 H, t, 17α-H), 5.23 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 5.27 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 6.96 (1 H, s, 1-H), 7.71 (1 H, s, 4-H). Anal. Calcd for $C_{34}H_{36}O_5$: C, 77.83; H, 6.92. Found: C, 77.90; H, 6.95.

2,3-Di(benzyloxy)-6α-(trimethylsilyloxy)-6β-cyanoestra-1,3,5(10)-trien-17β-ol Acetate (IIIa). Method A. IIc (500 mg) was added to a stirred solution of trimethylsilyl cyanide (2 mL) containing a catalytic amount of zinc iodide at room temperature. White crystals separated out within a few minutes and the mixture was then allowed to stand under a nitrogen atmosphere for 10 min to complete the reaction. The crystals were filted and washed with cold ethanol. Recrystallization from ethanol gave IIIa (550 mg) as colorless needles: mp 166–168 °C; IR (KBr) ν_{max} cm^{-1} 1742 (C=O); NMR ($CDCl_3$ solution) δ 0.15 (9 H, s, 6α-$Si(CH_3)_3$), 0.86 (3 H, s, 18-CH_3), 2.07 (3 H, s, 17β-$COCH_3$), 5.10 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 5.12 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 6.78 (1 H, s, 1-H), 7.12 (1 H, s, 4-H). Anal. Calcd for $C_{38}H_{45}O_5NSi$: C, 73.16; H, 7.27; N, 2.46. Found: C, 73.15; H, 7.28; N, 2.43.

Method B. A mixture of IIc (300 mg) and trimethysilyl cyanide (0.3 mL) containing a catalytic amount of zinc iodide in dry benzene (5 mL) was heated at 50 °C for 8 h under nitrogen. After evaporation of the solvent the crude product was submitted to preparative TLC using ethyl acetate–cyclohexane (3:7) as developing solvent. In addition to the product IIIa a slightly less polar component was also present which was presumed to be the epimeric cyanohydrin silyl ether IIIb. Elution of the appropriate regions and recrystallization from ethanol gave IIIa (150 mg) but all of IIIb was found to have been converted by the workup procedure to the starting material IIc (23 mg).

2,3-Di(benzyloxy)-6,6-(2',2',-dimethyloxazolidino)estra-1,3,5(10)-trien-17β-ol (IIIc). To a stirred suspension of lithium aluminum hydride (700 mg) in anhydrous ether (60 mL) a solution of IIIa (600 mg) in dry benzene (20 mL) was added dropwise at 0 °C. The mixture was stirred for 1 h and then refluxed for 2 h. After cooling in an ice bath, water (20 mL) was added dropwise and the solvent was evaporated under reduced pressure, followed by the addition of 10% sodium hydroxide solution (20 mL). The precipitate formed was collected by filtration, washed with water, dried, and extracted with acetone in a Soxhlet for 24 h. After the evaporation of the solvent the residual oil was crystallized from aqueous methanol. Recrystallization from the same solvent gave IIIc (382 mg) as colorless needles: mp 102–104 °C; NMR ($CDCl_3$ solution) δ 0.78 (3 H, s 18-CH_3), 1.40 (3 H, s, 2'-CH_3), 1.43 (3 H, s, 2'-CH_3), 2.99 (2 H, d, 4'-$NHCH_2$), 3.68 (1 H, t, 17α-H), 5.10 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 5.12 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 6.78 (1 H, s, 1-H), 6.89 (1 H, s, 4-H). Anal. Calcd for $C_{36}H_{43}O_4N{\cdot}H_2O$: C, 75.65; H, 7.88; N, 2.45. Found: C, 75.48; H, 7.92; N, 2.45.

2,3-Di(benzyloxy)-6β-(aminomethyl)estra-1,3,5(10)-triene-6α,17β-diol (IIId). A solution of IIIc (300 mg) in glacial acetic acid (1.5 mL) was made alkaline with 10% sodium hydroxide solution. The precipitate formed was collected by filtration and washed well with water. Recrystallization from methanol–water gave IIId (287 mg) as colorless fine needles. IIId (100 mg) was also obtained directly from IIIa (500 mg) by extraction of the crude lithium aluminum hydride reduction product with methanol–chloroform (1:1): mp 130–132 °C; NMR ($CDCl_3$ solution) δ 0.88 (3 H, s, 18-CH_3), 3.71 (1 H, t, 17α-H), 5.15 (4 H, s, 2- and 3-$OCH_2C_6H_5$), 6.88 (1 H, s, 1-H). Anal. Calcd for $C_{33}H_{39}O_4N$: C, 77.16; H, 7.63; N, 2.73. Found: C, 77.40; H, 7.35; N, 2.61.

6β-(Aminomethyl estra-1,3,5(10)-triene-2,3,6α,17β-tetrol Hydrochloride (IIIe). A solution of IIId (8.4 mg) in anhydrous ethanol (15 mL) was stirred with palladium-on-calcium carbonate (90 mg) under hydrogen for 48 h at room temperature. After removal of the catalyst by filtration, dry hydrogen chloride gas was bubbled through the ethanol filtrate under ice cooling to form the amine hydrochloride salt. The ethanol solution was concentrated under reduced pressure and addition of dry ether gave IIIe (30 mg) as an amorphous solid. Purification of IIIe was carried out by reprecipitation with ethanol–ether: mp 200 °C dec; IR (KBr) ν_{max} cm^{-1} 3000–3400 (OH and $-N^+H_3$); NMR (Me_2SO-d_6 solution) δ 0.68 (3 H, s,

18-CH_3), 6.65 (1 H, s, 1-H or 4-H), 6.70 (1 H, s, 1-H or 4-H), 7.92 (1 H, s, 2-OH or 3-OH), 8.17 (1 H, s, 2-OH or 3-OH). Anal. Calcd for $C_{19}H_{28}O_4NCl$: C, 61.69; H, 7.63; N, 3.79. Found: C, 61.86; H, 7.38; N, 3.58.

6-Cyano-2,3-di(benzyloxy)-estra-1,3,5(10),6-tetraen-17β-ol Acetate (IV). A mixture of IIIa (500 mg) and phosphorus oxychloride (2 mL) in pyridine (8 mL) was heated at 50–55 °C for 50 h with stirring. After evaporation of the solvent, ice water was added to the residue and the precipitate was collected by filtration. Recrystallization from ethanol gave IV (305 mg) as colorless silky needles: mp 120–122 °C; IR (KBr) ν_{max} cm^{-1} 1735 (C=O), 2220 (CN); NMR ($CDCl_3$ solution) δ 0.81 (3 H, s, 18-CH_3), 2.04 (3 H, s, 17β-$COCH_3$), 4.72 (1 H, t, 17α-H), 5.13 (4 H, s, 2- and 3-$OCH_2C_6H_5$), 6.60 (1 H, broad s, 7-H), 6.83 (1 H, s, 1-H), 7.05 (1 H, s, 4-H).

6β-Cyano-2,3-di(benzyloxy)-6α,7α-epoxyestra-1,3(10)-trien-17β-ol Acetate (V). A mixture of IV (200 mg) and *m*-chloroperbenzoic acid (85%, 200 mg) in chloroform (7 mL) was allowed to stand at room temperature for 72 h. The reaction was then diluted with ether and washed with 5% $Na_2S_2O_3$ solution, 5% $NaHCO_3$ solution, and water. The organic phase was evaporated and the oily residue was submitted to preparative TLC on silica gel using ethyl acetate–cyclohexane (3:7) as the developing solvent. Elution of the appropriate region and recrystallization from MeOH·H_2O gave V (60 mg): mp 85–88 °C; NMR ($CDCl_3$ solution) δ 0.80 (3 H, s, 18-CH_3), 2.02 (3 H, s, 17β-$COCH_3$), 4.50 (1 H, d, 7β-H), 4.68 (1 H, t, 17α-H), 5.14 (4 H, s, 2- and 3-$OCH_2C_6H_5$), 6.88 (1 H, s, 1-H).

Reduction of V (40 mg) with lithium aluminum hydride under the same conditions as employed in the reduction of IIIa gave 12 mg of IIIc, mp 102–104 °C, which was identical in all respects with the material obtained from the reduction of IIIa.

2,3-Di(benzyloxy)-17β-hydroxy-6-methyleneestra-1,3,5-triene Acetate (VIa). Sodium hydride (5.4 mmol as a 50% dispersion in oil) was washed with several portions of petroleum ether. The flask was then equipped with rubber stoppers and the system was flushed with nitrogen. Dimethyl sulfoxide (1 mL) was then introduced and the mixture was heated at 75 °C for 45 min. To the dark green solution 1.93 g of methyltriphenylphosphonium bromide in 3.5 mL of dimethyl sulfoxide was added. After stirring for 15 min, 140 mg of IIb in 1 mL of dimethyl sulfoxide was added and the reaction was stirred at 60–65 °C for 23 h at which time it was diluted with 75 mL of ice cold water and extracted with chloroform. After purification by preparative thin-layer chromatography on silica gel the product was crystallized from ethanol to give 60 mg of VIa, mp 114–116 °C, the infrared spectrum of which showed the absence of a carbonyl group: NMR ($CDCl_3$ solution) δ 0.73 (3 H, s, 18 CH_3), 4.91 (2 H, q, 6′, CH_2), 5.10 (4 H, s, 2- and 3-$OCH_2C_6H_5$), 6.90 (1 H, s, 1-H), 7.25 (1 H, s, 4-H).

2,3-Di(benzyloxy)-6-cyanomethylene-17β-hydroxyestra-1,3,5(10)-triene Acetate (VIb). Sodium hydride (300 mg, 50% mineral oil dispersion) was washed three times with light petroleum ether to remove the mineral oil. After removal of the last trace of petroleum ether the system was connected to a source of dry nitrogen and tetrahydrofuran (5 mL) was introduced via syringe. To this suspension was added dropwise diethyl cyanomethylphosphonate (700 mg) in tetrahydrofuran (5 mL) with stirring at 0 °C. After stirring for ca. 30 min, IIb (300 mg) in tetrahydrofuran (2 mL) was added to the suspension and the mixture was stirred at room temperature for 40 h. The reaction mixture was then concentrated to a small volume, poured into water (30 mL), and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. After the usual workup the crude product was submitted to preparative TLC using ethyl acetate–cyclohexane (1:1) as developing solvent. Elution of the region corresponding to the spot gave an oily product. Acetylation of the material in the usual manner with pyridine–acetic anhydride and recrystallization from ethanol gave VIb (170 mg) as colorless plates: mp 153–155 °C; IR (KBr) ν_{max} cm^{-1} 1733 (C=O), 2202 (C≡N); NMR ($CDCl_3$ solution) δ 0.85 (3 H, s, 18-CH_3), 2.05 (3 H, s, 17β-$COCH_3$), 4.70 (1 H, t, 17α-H), 5.15 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 5.17 (2 H, s, 2- or 3-$OCH_2C_6H_5$), 5.43 (1 H, s, 6′-CHCN), 6.88 (1 H, s, 1-H), 7.06 (1 H, s, 4-H). Anal. Calcd for $C_{36}H_{37}O_4N$: C, 78.94; H, 6.81; N, 2.55. Found: C, 78.72; H, 6.68; N, 2.67.

6α- (VIc) and 6β-Cyanomethylestra-1,3,5(10)-triene-2,3,17β-triol Triacetate (VId). A solution of VIb (160 mg) in ethyl acetate (30 mL) was stirred with palladium-on-calcium carbonate (200 mg) under a stream of hydrogen at room temperature for 48 h. After the usual workup the product was acetylated with pyridine–acetic anhydride and submitted to preparative TLC using ethyl acetate–cyclohexane (1:1) as developing solvent. Elution of the adsorbent corresponding to the spots gave VIc (82 mg) and VId (18 mg). The analytical samples of VIc and VId were recrystallized from acetone–petroleum ether. VIc: mp 180–182 °C; IR (KBr) ν_{max} cm^{-1} 1738, 1778 (C=O), 2250 (C≡N); NMR ($CDCl_3$ solution) δ 0.82 (3 H, s, 18-CH_3), 2.05 (3 H, s, 17β-$COCH_3$), 2.26 (6 H, s, 2- and 3-$COCH_3$), 2.65 (2 H, d, 6-CH_2CN), 4.66 (1 H, t, 17α-H), 7.00 (1 H, s, 4-H), 7.09 (1 H, s, 1-H). Anal. Calcd for $C_{26}H_{31}O_6N$: C, 68.85; H, 6.88; N, 3.08. Found: C, 68.25; H, 6.77; N, 3.24. VId: mp 195–198 °C; IR (KBr) ν_{max} cm^{-1} 1728, 1778 (C=O), 2244 (C≡N); NMR ($CDCl_3$ solution) δ 0.85 (3 H, s, 18-CH_3), 2.04 (3 H, s, 17β-$COCH_3$), 2.25 (6 H, s, 2- and 3-$COCH_3$), 2.66 (2 H, d, 6-CH_2CN), 4.64 (1 H, t, 17α-H), 6.95 (1 H, s, 4-H), 7.10 (1 H, s, 1-H). Anal. Calcd for $C_{26}H_{31}O_6N$: C, 68.85; H, 6.88; N, 3.08. Found: C, 68.84; H, 6.85; N, 3.08.

6α-(2-Acetaminoethyl)estra-1,3,5(10)-triene-2,3,17β-triol Triacetate (VIe). Diborane was generated by adding a solution of sodium borohydride (280 mg) in diglyme (4.9 mL) to a stirred solution of boron trifluoride etherate (1.7 mL) in dyglyme (4 mL) as described. The diborane gas was passed into a solution of VIc (70 mg) in anhydrous tetrahydrofuran (4 mL) for 40 min with a slow stream of nitrogen. After standing for 1.5 h at room temperature ethanol was added cautiously to destroy excess diborane. The solvents were evaporated under reduced pressure and the residue was acetylated in the usual manner with pyridine–acetic anhydride. After the usual workup the crude product was purified by preparative TLC using ethyl acetate–cyclohexane (7:3) as the developing solvent to give VIe (24 mg) as a colorless amorphous substance: mp 100–104 °C; IR (KBr) ν_{max} cm^{-1} 1545 (amide II, C=O), 1655 (amide I, C=O), 1734, 1770 (C=O), 3340 (NH); NMR ($CDCl_3$ solution) δ 0.78 (3 H, s, 18-CH_3), 1.85 (3 H, s, 6α-$CH_2CH_2NHCOCH_3$), 2.02 (3 H, s, 17β-$COCH_3$), 2.22 (6 H, s, 2- and 3-$COCH_3$), 3.0–3.6 (4 H, m, 6α-$CH_2CH_2NHCOCH_3$), 4.65 (1 H, t, 17α-H), 5.60 (1 H, broad t, 6α-$CH_2CH_2NHCOCH_3$), 7.01 (2 H, s, 1-H and 4-H). Anal. Calcd for $C_{28}H_{37}O_7N$: C, 67.31; H, 7.47; N, 2.80. Found: C, 67.94; H, 7.20; N, 2.35.

6β-(2-Acetaminoethyl)estra-1,3,5(10)-triene-2,3,17β-triol Triacetate (VIf) was prepared from VId (33 mg) in the same manner used in the preparation of VIe. The substance exhibited mp 89–94 °C; IR (KBr) ν_{max} cm^{-1} 1540 (amide II, C=O), 1650 (amide I, C=O), 1726, 1766 (C=O), 3300 (NH); NMR ($CDCl_3$ solution) δ 0.85 (3 H, s, 18-CH_3), 1.89 (3 H, s, 6β-$CH_2CH_2NHCOCH_3$), 2.02 (3 H, s, 17β-$COCH_3$), 2.22 (6 H, s, 2- and 3-$COCH_3$), 3.1–3.6 (4 H, m, 6β-$CH_2CH_2NHCOCH_3$), 4.67 (1 H, t, 17α-H), 6.05 (1 H, broad t, 6β-$CH_2CH_2NHCOCH_3$), 6.87 (1 H, s, 4-H), 6.99 (1 H, s, 1-H). Anal. Calcd for $C_{28}H_{37}O_7N$: C, 67.31; H, 7.48; N, 2.80. Found: C, 66.98; H, 7.52; N, 2.40.

Registry No.—Ib, 7291-56-7; IIa, 68129-02-2; IIb, 68129-03-3; IIc, 68129-04-4; IIIa, 68129-05-5; IIIb, 68129-06-6; IIIc, 68129-07-7; IIId, 68129-08-8; IIIe·HCl, 68129-09-9; IV, 68129-10-2; V, 68129-11-3; VIa, 68129-12-4; VIb, 68129-13-5; VIc, 68129-14-6; VId, 68129-15-7; VIe, 68129-16-8; VIf, 68129-17-9; 2,3-dibenzyloxy-6-cyanomethylene-17β-hydroxyestra-1,3,5(10)-triene, 68129-18-0; 6α-cyanomethyl-2,3-dibenzyloxyestra-1,3,5(10)-trien-17β-ol acetate, 68129-19-1; 6β-cyanomethyl-2,3-dibenzyloxyestra-1,3,5(10)-trien-17β-ol acetate, 68129-20-4; 6α-(2-aminoethyl)estra-1,3,5(10)-triene-2,3,17β-triol triacetate, 68129-21-5; trimethylsilyl cyanide, 7677-24-9; methyltriphenylphosphonium bromide, 1779-49-3; diethyl cyanomethylphosphonate, 2537-48-6.

References and Notes

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Prostaglandins and Congeners. 21.[1] Synthesis of Some Cyclohexyl Analogues (11a-Homoprostaglandins)

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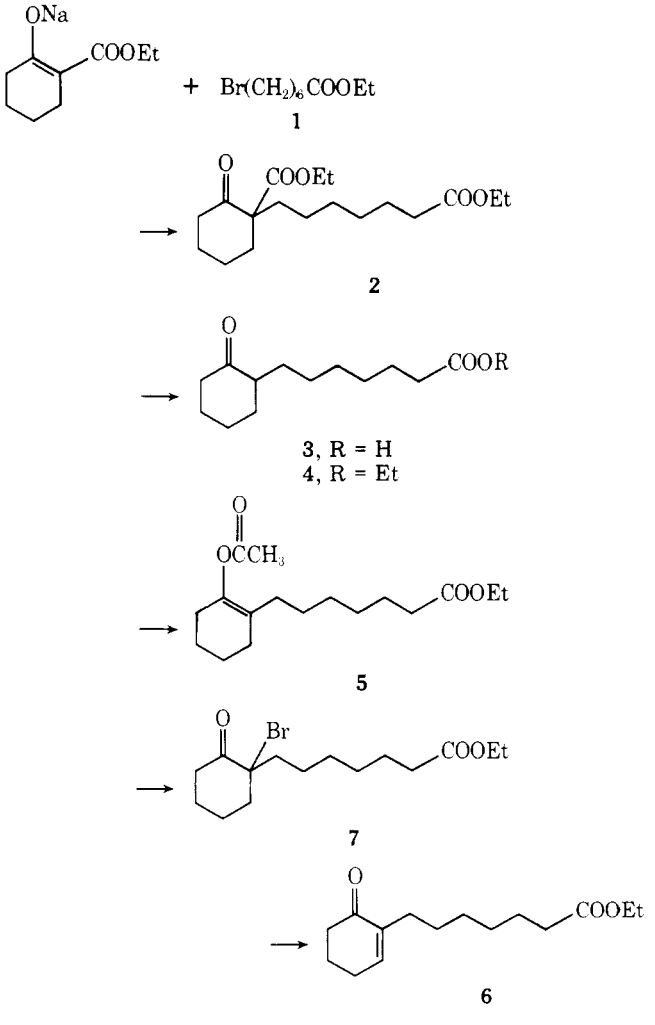
Several six-membered ring analogues of prostaglandin E_1 have been prepared. The compounds were all synthesized via conjugate addition of organometallic reagents to cyclohexenone **6**. A cyclohexenone analogue (**28**) of PGA_1 was prepared by a high-yield multistep net dehydrogenation of a cyclohexanone precursor (**18**). The PGA_1 analogue **28** was partially hydrated to the PGE_1 analogue **30** in aqueous base.

As part of an ongoing prostaglandin analogue synthesis program we wish to report the preparation of certain 11a-homoprostaglandins wherein the cyclopentanone ring has been replaced by the cyclohexanone ring.[2] Of particular interest was the preparation of 11a-homo-PGA_1, since this compound would not be expected to undergo the facile enzymatic or physiological medium-mediated biologically inactivating isomerization presumably characteristic of the PGA series. Thus the 11a-homo series provides a good approach to "frozen PGA" compounds.[3]

The synthetic scheme regularly utilized in our laboratories for prostaglandin synthesis is based upon the conjugate addition of a lithium 1-alkenylalanate[4] or lithium 1-alkenylcuprate reagent to an appropriate cyclopentenone. Accordingly, our first synthetic goal in the present study was the preparation of cyclohexenone **6**. All of the prostaglandin congeners reported herein are derived from this intermediate, which was prepared as follows.

The sodium enolate of commercially available 2-carbethoxycyclohexanone was alkylated with bromo ester **1** in DMF at 50 °C to give crude product **2**, which underwent hydrolysis, decarboxylation, and reesterification to ester **4** in ca. 50% overall yield. For the introduction of the required unsaturation the general method of Bedoukian,[5] which entails bromination of an enol acetate, was used to regiospecifically place bromine in the 2 position of the cyclohexanone ring. Other studies have shown that enolacetylation of 2-substituted cyclohexanones under equilibrating conditions results in predominant formation of the more substituted olefinic product.[6] Thus, reaction of **4** with refluxing acetic anhydride in the presence of PTSA with removal of acetic acid by distillation gave in 93% yield the desired enol acetate **5**, which on treatment with bromine in HOAc–pyridine[7] afforded crude bromo ketone **7**. The final step, dehydrobromination to the required cyclohexenone **6**, was accomplished with lithium bromide–lithium carbonate in hot DMF (82% overall yield from **5**).[8]



For the preparation of 11,15-dideoxyprostaglandins, of interest as specific prostaglandin antagonists,[9] the conjugate addition of lithium trialkyl-*trans*-1-alkenylalanates to cyclopentenones has been a particularly useful procedure.[10] Reaction of alanates **8** and **9** with cyclohexenone **6** by this method gave the desired conjugate addition products **10** and **11**, which were saponified to the corresponding acids **12** and **13**.

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