Notes

The Preparation and Pharmacology of Some 1,4-Dimethylestratrienes

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The purpose of correlating structure with activity is to delineate the structural feature of a molecule which is essential for a specific pharmacological activity. Hopefully, such a study would lead to compounds, which can be prepared from readily available starting materials, having only the desired activity.[1]

In a recent publication, Goldkamp, *et al.*,[2] reported that removal of the hydroxyl group of estrone reduces both the lipid-shifting and estrogenic effects of this substance. Because the estrogenic effect is reduced to a greater extent, a desirable separation of the two effects is achieved in the product, estra-1,3,5(10)-trien-17-one. When a methyl group is introduced into the 4 position of estra-1,3,5(10)-trien-17-one, there is approximately a tenfold increase in the separation of the lipid shifting and estrogenic effects. Thus, the lipodiatic–estrogenic ratio[2] of estra-1,3,5(10)-trien-17-one is 13 and that of 4-methylestra-1,3,5(10)-trien-17-one is 150. Estrone, the standard, was arbitrarily assigned a value of 1. A similar pattern was observed when the same molecular transformations were applied to 17α-ethynylestradiol, which has a lipodiatic–estrogenic ratio of 0.1.

In order to determine whether the introduction of an additional methyl group would further enhance the desired separation of activities, we undertook the synthesis of 1,4-dimethylestra-1,3,5(10)-trien-17-one (III) and 17α-ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IVa). It was hoped that the additional methyl group at C-1 would produce an enhancement of the lipodiatic–estrogenic ratio by increasing the lipid-shifting effect.

This hope, however, was not realized. Both the ketone III and the ethynylcarbinol IVa failed to lower the plasma cholesterol–phospholipid ratio of the cholesterol-fed cockerels.[2] Hence, our results indicate that a methyl group at C-1 reduces the lipodiatic activity of estra-1,3,5(10)-trien-17-one just as does a methyl group at either of the three other positions on the aromatic ring.[2] Furthermore, it appears likely that the lipid-shifting effect produced by one methyl group augments that produced by another methyl group.

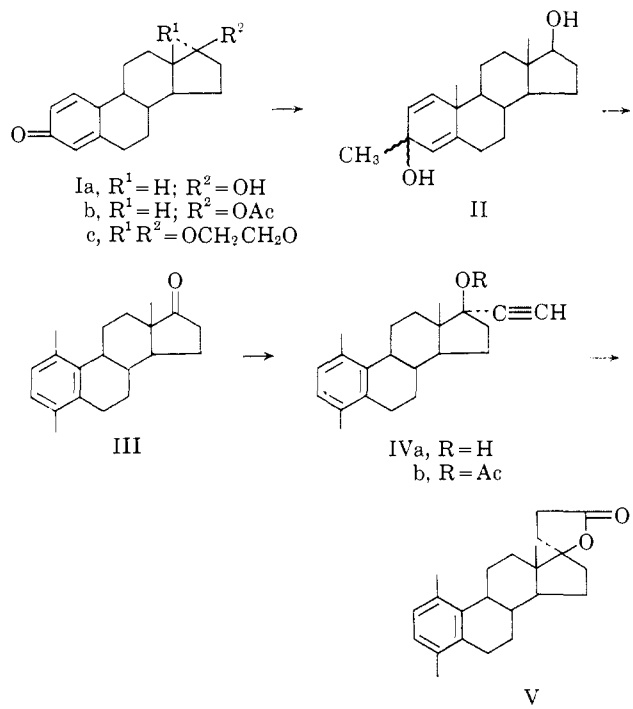
Although 17α-ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IVa) does not produce the desired lipodiatic effect, IVa and its acetate IVb were found to reduce the plasma cholesterol concentration of rats made hypercholesterolemic with propylthiouracil. 17α-Ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IVa) also shows slight progestational activity (about 5% the activity of progesterone) in the Clauberg assay. Both IVa and IVb exhibit antiinflammatory properties in the carrageenin-induced foot edema rat assay at the subcutaneous dose level of 25 mg/rat. However, only the acetate IVb is active in the cotton wad granuloma rat assay. It is active at the 5-mg/rat level when administered orally.

The spirolactone V was prepared in the hope that it would have antimineralocorticoid activity,[1a] but it was found to be inactive in blocking the effect of deoxycorticosterone acetate in the saline-loaded adrenalectomized rats.

The 1,2,3,4-tetrasubstituted benzene system of the 1,4-dimethylestratrienes was derived from a dienol–benzene rearrangement of the Grignard product obtained from 17β-hydroxyandrosta-1,4-dien-3-one (Ia) or its acetate Ib.[3]

Treatment of either Ia or Ib with methylmagnesium bromide affords the dienol II (Scheme I). In an acidic

SCHEME I



medium, II dehydrates and rearranges to give 1,4-dimethylestra-1,3,5(10)-trien-17β-ol.[3a] The latter on oxidation yields the corresponding ketone III.[4] Alternatively, 1,4-dimethylestra-1,3,5(10)-trien-17-one (III) is obtained by treating androsta-1,4-diene-3,17-dione 17-ethylene ketal (Ic) with the Grignard reagent and then dehydrating and rearranging the resultant product with dilute hydrochloric acid.[5]

(1) (a) L. J. Chinn, H. L. Dryden, Jr., and R. R. Burtner, *J. Org. Chem.*, **26**, 3910 (1961); (b) L. J. Chinn, *ibid.*, **27**, 1741 (1962).

(2) A. H. Goldkamp, W. M. Hoehn, R. A. Mikulec, E. F. Nutting, and D. L. Cook, *J. Med. Chem.*, **8**, 409 (1965).

(3) (a) H. Dannenberg and H.-G. Neumann, *Ann.*, **646**, 148 (1961); (b) L. J. Chinn, *J. Org. Chem.*, **27**, 2703 (1962).

(4) C. Burgess, D. Burn, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, A. P. Leftwick, J. S. Mills, and V. Petrow, *J. Chem. Soc.*, 4995 (1962).

(5) H. L. Dryden, Jr., G. M. Webber, and J. J. Wieczorek, *J. Am. Chem. Soc.*, **86**, 742 (1964).

The ketone III is converted into 17α-ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IVa) with either potassium acetylide or the lithium acetylide–ethylenediamine complex. When heated with acetic anhydride and pyridine, IVa gives the acetate IVb, while successive carboxylation and hydrogenation[1a] transform IVa into the spirolactone, 3-(17β-hydroxy-1,4-dimethylestra-1,3,5(10)-trien-17α-yl)propionic acid lactone (V).

Experimental Section[6]

1,4-Dimethylestra-1,3,5(10)-trien-17-one (III).[4]—To a stirred solution of 20 ml of 3 *M* methylmagnesium bromide in diethyl ether and 200 ml of anhydrous ether was added a mixture of 10 g of androsta-1,4-diene-3,17-dione 17-ethylene ketal[7] in 700 ml of anhydrous ether. The reaction mixture was stirred and heated under reflux for 2.5 hr. Then it was cooled in an ice bath and decomposed with a saturated solution of NH_4Cl. The ether phase was separated, washed successively with water and a saturated solution of NaCl, dried (Na_2SO_4), and distilled to dryness under reduced pressure to afford a viscous oil. The oil was treated with a solution of 9 ml of 6 *N* HCl in 90 ml of 95% ethanol. The mixture was stirred at room temperature for 0.5 hr. Then it was diluted with water and extracted with ether. The ether extract was separated and worked up as previously described. The resultant viscous oil was chromatographed on 700 g of silica gel. Elution of the column with benzene gave 3.3 g of a colorless crystalline product, which melted at 126–127° after crystallization from ether–pentane (lit.[4] 126–128°). It proved identical with an authentic sample of IV prepared by the CrO_3 oxidation[4] of 1,4-dimethylestra-1,3,5(10)-trien-17β-ol (III)[3a] obtained from either 17β-hydroxyandrosta-1,4-dien-3-one (Ia) or its acetate (Ib).

17α-Ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IVa). **A.**—Acetylene was passed for 1 hr into a solution of 15 g of potassium *t*-butoxide in 200 ml of *t*-butyl alcohol and 100 ml of toluene, stirred, and maintained in an ice bath. A solution of 1.6 g of III in 40 ml of toluene was then added as acetylene was still being passed into the solution. After 4 hr, passage of acetylene was stopped. The reaction mixture was stirred for an additional 12 hr during which time it was permitted to warm to room temperature. The reaction mixture was then diluted with a large volume of a saturated solution of NH_4Cl. The organic phase was separated, washed with water, and distilled to dryness under reduced pressure. The residue was chromatographed on 80 g of silica gel. Elution with 2% ethyl acetate in benzene gave Va, which was crystallized from ether–pentane, mp 170.5–172°, yield 0.31 g. The melting point was raised to 174–174.5° on recrystallization from ether–pentane; λ^{KBr} 3425, 3311, 3289, 801 cm^{-1}.

Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.87; H, 9.22.

B.—A mixture of 1.36 g of III, 2.7 g of lithium acetylide–ethylenediamine,[8] and 100 ml of tetrahydrofuran (freshly distilled from methylmagnesium bromide) was stirred at room temperature for 2 hr. The reaction mixture was decomposed with a dilute solution of NH_4Cl and then extracted with ether. The ether extract was washed successively with water and a saturated solution of NaCl, dried (Na_2SO_4), and distilled to dryness under reduced pressure to afford a viscous orange-red oil. The oil was chromatographed on 150 g of silica gel. Elution with benzene, followed by crystallization of the solid product from ether–pentane, afforded 0.54 g of IVa, mp 171–171.5°, which was identical with that obtained by procedure A. From the mother liquor an additional 0.12 g of IVa, mp 164.5–167.5°, was obtained.

17α-Ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol Acetate (IVb).—A solution of 0.78 g of IVa, 6 ml of pyridine, and 8 ml of acetic anhydride was maintained at 95° for 18 hr after which time it was concentrated to about 2 ml by distillation under reduced pressure. The residue was diluted with ice water and extracted with ether. The ether extract was washed successively with a 5% solution of $NaHCO_3$ and water, dried (Na_2SO_4), and distilled to dryness under reduced pressure. The residual viscous oil was chromatographed on 80 g of silica gel. Elution with benzene gave a colorless viscous oil. This was evaporatively distilled at 180° (0.1 mm) to afford IVb as a colorless amorphous product, λ^{KBr} 3311, 2119, 1761, 1592, 1250, 1241, 1229, 896 cm^{-1}. Thin layer chromatography indicated that the product was homogeneous.

Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 82.17; H, 8.65.

3-(17β-Hydroxy-1,4-dimethylestra-1,3,5(10)-trien-17α-yl)propionic Acid Lactone (V).—To a stirred solution of 15 ml of 3 *M* methylmagnesium bromide in diethyl ether and 25 ml of tetrahydrofuran (THF) was added over a period of 10 min a solution of 2.4 g of IVa in 30 ml of THF. The reaction mixture was distilled to remove the diethyl ether. Then it was stirred and heated under reflux under N_2 for 15 hr. The cooled reaction mixture was stirred for an additional 22 hr while CO_2 was continuously passed into it. An ice-cold, dilute solution of H_2SO_4 was added. The resultant solid was collected, washed well with water, and dried, mp 105–110°. A solution of the solid (2.7 g) and 0.83 g of triethylamine in 100 ml of 95% ethanol was hydrogenated over 0.3 g of 5% Pd–C at room temperature and atmospheric pressure. After the calculated amount of hydrogen was absorbed, hydrogenation was stopped. The filtered solution was distilled to dryness under reduced pressure. The residue was triturated with dilute HCl to afford a colorless crystalline product. The product was collected, washed well with water, and dried. Crystallization from methanol–water gave 1.65 g of V; mp 200–202.5°; λ^{KBr} 1792, 1595, 804 cm^{-1}; $[\alpha]^{20}D$ +8.9° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.74; H, 8.85.

(6) Melting points were taken on a Fisher-Johns melting block and are corrected.

(7) M. J. Gentles, J. B. Moss, H. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, **80**, 3702 (1958).

(8) O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963); *ibid.*, **29**, 1872 (1964).

Synthesis and Pharmacological Evaluation of α-Substituted 1-Naphthylacetic Acids

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Continuing our investigation on the pharmacological properties of α,α-disubstituted 1-naphthylacetonitriles and 1-naphthylacetamides,[1] we have prepared 21 α-substituted 1-naphthylacetic acids for pharmacological screening, including studies of acute toxicity and antiinflammatory, antipyretic, analgesic, diuretic, choleretic, and hypoglycemic action, as well as the *in vitro* antibacterial and antifungal activities.

The monosubstituted acids were prepared by hydrolysis of the nitriles with dilute sulfuric acid (see Experimental Section, methods A and B). This procedure failed to give the disubstituted acids, only the corresponding amides being obtained as previously reported.[1b] However, these acids were easily prepared by reaction of the amides with isoamyl nitrite in glacial acetic acid, in the presence of HCl (method C), as described for α-alkyl-substituted 1-naphthylacetic acids.[2] All the acids were isolated and identified as the hydrochlorides (Table I).

The results of the pharmacological screening are reported in Table II. Compared with the corresponding

(1) (a) S. Casadio, G. Pala, E. Crescenzi, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **8**, 589 (1965); (b) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **8**, 594 (1965); (c) G. Pala, S. Casadio, T. Bruzzese, E. Crescenzi, and E. Marazzi-Uberti, *ibid.*, **8**, 698 (1965).

(2) S. Casadio, G. Pala, T. Bruzzese, and E. Marazzi-Uberti, *Farmaco* (Pavia), *Ed. Sci.*, **17**, 797 (1962).