this investigation and to Dr. Fritz. A. Bader and coworkers of Bristol Laboratories for the biological evaluation of some of these compounds. One of the authors (N. C. D.) is thankful to C.S.I.R. Government of India for awarding him a fellowship.

5-Aryl-2-furanacetic Acids

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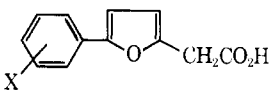
A series of 5-aryl-2-furanacetic acids (Table I), active as antiinflammatory agents as measured by the anti-uv erythema test,[1] have been prepared by the route outlined in Scheme I.

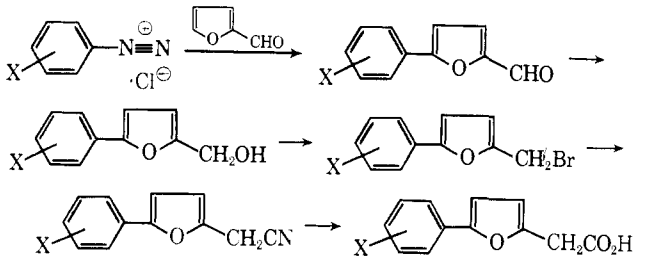
TABLE I
5-ARYL-2-FURANACETIC ACIDS



X	Rel act.[a]	Mp,[b] °C	Recrystn solvent[c]	τ[d]	Formula	Analyses[e]
H	0.9	126–128	B	6.15	$C_{12}H_{10}O_3$	C, H
4-Cl	1.7	147.5–149	A	6.22	$C_{12}H_9ClO_3$	C, H, Cl
3-Cl	0.4	109–110	B	6.20	$C_{12}H_9ClO_3$	C, H, Cl
2-Cl	0.1	98–99.5	A	6.20	$C_{12}H_9ClO_3$	C, H, Cl
4-Br	0.4	162–164	A	6.22	$C_{12}H_9BrO_3$	C, H, Br
4-F	0.2	116–117.5	A	6.23	$C_{12}H_9FO_3$	C, H, F
4-CH_3	0.4	143–144	B	6.23	$C_{13}H_{12}O_3$	C, H
4-CH_3O	0.9	143–145.5	B	6.25	$C_{13}H_{12}O_4$	C, H

[a] Preliminary estimates; phenylbutazone = 1. [b] Melting points were taken on a Thomas–Hoover melting point apparatus in open capillaries and are uncorrected. [c] A = C_6H_6, B = C_6H_{14}-hexane. [d] The τ values are for the $-CH_2-$ grouping and were determined on a Varian A-60 in $CDCl_3$. [e] Analyses for the elements indicated were within $\pm 0.3\%$ of the theoretical values.

SCHEME I



Experimental Section

5-Aryl-2-furfurals.[2]—A mixture of 0.5 mole of the arylamine in H_2O (50 ml) and 135 ml of concentrated HCl was diazotized by the dropwise addition of 36.2 g (0.525 mole) of $NaNO_2$ in 100 ml of H_2O keeping the temperature below 10° by the addition of ice. After stirring at 10° for 10 min, the solution was filtered and added all at once to a solution of 61.5 g (0.64 mole) of furfural in H_2O (200 ml), followed by 23 g of $CuCl_2 \cdot 2H_2O$ in H_2O (100 ml). The mixture was kept at 50–65° for 4 hr, then left standing at room temperature overnight. Volatiles were steam distilled and the black residue was taken up in ether and washed (twice with 5% NaOH, H_2O until neutral). Drying (Na_2SO_4), treatment with charcoal, and removal of the solvent under reduced pressure gave the crude product which could be partially purified by crystallization from EtOH, or by distillation for those compounds which were oils. Yields were in the range of 10–55%.

5-Aryl-2-hydroxymethylfurans.—Reduction of the 5-aryl-2-furfurals with $LiAlH_4$ in 1:1 Et_2O–THF gave the crude products which were converted to the bromo derivatives without further purification.

5-Aryl-2-bromomethylfurans.—A solution of 0.0282 mole of the 5-aryl-2-hydroxymethylfuran in 65 ml of Et_2O was cooled in an ice bath. To this was added dropwise a solution of 2.8 g (0.0103 mole) of PBr_3 in Et_2O (20 ml). After the addition was complete, the mixture was allowed to stir at room temperature for 1 hr. The ether was then decanted and the gummy residue was washed (Et_2O). The combined ether extracts were swirled with cold 50% NaOH, decanted, and dried (solid KOH). The solvent was removed under reduced pressure at *room temperature*. The unstable nature of the bromomethyl compounds necessitate their immediate conversion to the nitriles.

5-Aryl-2-cyanomethylfurans.—The crude 5-aryl-2-bromomethylfuran from 0.0282 mole of the hydroxymethyl compound was dissolved in 50 ml of acetone and treated with 1.5 g (0.03 mole) of NaCN in 10 ml of H_2O and the solution was heated at reflux for 3 hr. Work-up of the dark reaction mixture in the usual manner gave the crude nitrile as a dark, viscous oil.

5-Aryl-2-furanacetic Acids.—The crude nitrile (5 g) in EtOH (100 ml) was treated with 5 g of KOH in 25 ml of H_2O and the resulting solution was heated at reflux for 6 hr. Work-up in the usual manner gave the crude acid as an oil which was chromatographed on silica gel. After elution of some colored material with benzene, the product was eluted with 10% ether in benzene. Recrystallization gave the pure 5-aryl-2-furanacetic acids.

Acknowledgments.—The authors thank Dr. C. V. Winder and associates of these laboratories for the antiinflammatory testing, and Mr. C. E. Childs and coworkers for the microanalyses.

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The Preparation and Pharmacology of Some 11β-Hydroxy-4-methylestratrienes

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Recently we reported that 17α-ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IIIa) and its acetate IIIb showed antiinflammatory properties in the carrageenin-induced foot edema rat assay and that both of these substances also reduced the plasma cholesterol concentration of rats made hypercholesterolemic with propylthiouracil.[1] Earlier, Goldkamp, *et al.*, observed that estra-1,3,5(10)-trien-17-ones and 17α-ethynylestra-1,3,5(10)-trien-17β-ols with a methyl group attached to ring A had a favorable lipodiatic–estrogenic ratio.[2] These findings prompted us to determine whether estratriene derivatives with an oxygen function at C-11, but not in ring A, also possess antiinflammatory and antiatherogenic effects.

11-Oxygenated corticosteroids are systemically active

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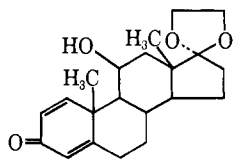
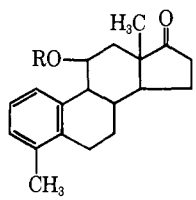
antiinflammatory agents, while steroids lacking the 11-oxygen function are not, although the latter may show potent antiinflammatory activity when injected directly into the inflammatory pouch.[3]

17α-Ethynyl-11β-hydroxy-4-methylestra-1,3,5(10)-trien-17β-ol (IIIc) was synthesized in expectation that the presence of the hydroxyl group at C-11 would either endow or enhance the antiinflammatory activity of the corresponding 11-deoxy compounds. The starting materials for this synthesis was 11β-hydroxyandrosta-1,4-diene-3,17-dione 17-ethylene ketal (I).[4] $LiAlH_4$

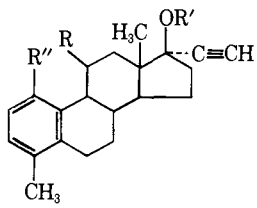


I



IIa, R = H
b, R = CH_3CO

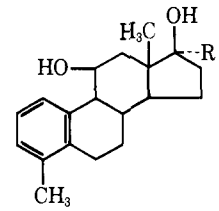
reduction of I followed by treatment with acid gave 11β-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (IIa). This substance had previously been obtained as a by-product from the $LiAlH_4$ reduction of 11β-hydroxyandrosta-1,4-diene-3,17-dione and as the main product from the successive treatment of prednisolone with $LiAlH_4$ and sodium bismuthate.[5] Because of the insolubility of IIa, it was found expedient to acetylate the 11-hydroxyl group before introducing the ethynyl group at C-17. Under the conditions employed for the ethynylation of IIb, partial hydrolysis occurred so that both 17α-ethynyl-11β-hydroxy-4-methylestra-1,3,5(10)-trien-17β-ol (IIIc) and its acetate IIId were obtained from the reaction mixture.



IIIa, R = R′ = H; R″ = CH_3
b, R = H; R′ = CH_3CO; R″ = CH_3
c, R = OH; R′ = R″ = H
d, R = CH_3CO; R′ = R″ = H

At the dose level of 10 mg/kg both ethynyl compounds, IIIc and IIId, lowered the plasma cholesterol concentration of rats made hypercholesterolemic with propylthiouracil,[6] but neither IIIc nor IIId was active in the carrageenin-induced foot edema assay when administered subcutaneously at the screening level of 25 mg/rat (*ca.* 200 mg/kg).[7]

The hydroxy ketone IIa likewise was not active in the foot edema assay, nor was 4-methylestra-1,3,5(10)-triene-11β,17β-diol (IVa), which was prepared according

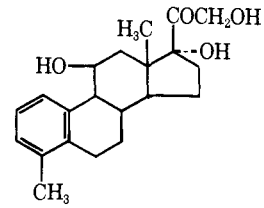


IVa, R = H
b, R = CH_3

to the procedure of Caspi, *et al.*[5] However, 4,17α-dimethylestra-1,3,5(10)-triene-11β,17β-diol (IVb) and the acetate of IIa (*viz.* IIb) were subcutaneously active at 25 mg/rat, and they were also active in the cotton pellet granuloma assay at 20 mg/rat (*ca.* 100 mg/kg) when given orally.[8]

Virtually all of the aforementioned 11-oxygenated 4-methylestratrienes showed significant estrogenic activity, which would preclude their use as lipodiatic agents.[2] Undoubtedly, because of their estrogenic properties, these compounds prevented implantation of fertilized ova in rats.[9] The ED_{50} varied from 140 μg for 11β-acetoxy-4-methylestra-1,3,5(10)-trien-17-one (IIb) to 3600 μg for 4,17α-dimethylestra-1,3,5(10)-triene-11β,17β-diol (IVa).

In view of the antiinflammatory properties displayed by IIb and IVb, 17β-(2-hydroxyacetyl)-4-methylestra-1,3,5(10)-trien-17α-ol (V),[10] which possesses the cortisol



V

side chain, was prepared and tested. This compound was prepared according to a procedure that was an adaptation of one described by Caspi, *et al.*[10] 17β-(2-Hydroxyacetyl)-4-methylestra-1,3,5(10)-trien-17α-ol (V) was orally active in the cotton pellet granuloma assay at 20 mg/rat, but it was inactive in the foot edema assay at the screening level. In order to determine whether V simulates the glucocorticoids in any other biological property, the effect of V on glycogen synthesis was studied. In adrenalectomized rats weighing between 120 and 160 g each,[11] 17β-(2-hydroxyacetyl)-4-methylestra-1,3,5(10)-trien-17α-ol (V) stimulated the synthesis of glycogen in the liver at the subcutaneous doses of 10 and 5 mg/rat. In each case, the response produced was comparable to that elicited by 0.5 mg/rat of cortisone acetate. At 2 mg/rat, however, V was inactive in this assay.[12]

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Experimental Section[13]

11β-Hydroxy-4-methylestra-1,3,5(10)-trien-17-one (IIa).—To a mixture of 3.0 g of $LiAlH_4$ and 250 ml of anhydrous Et_2O, stirred and heated under reflux, was added a mixture of 2.0 g of 11β-hydroxyandrosta-1,4-diene-3,17-dione 17-ethylene ketal (I)[14] in 25 ml of THF. After addition was complete, the addition funnel was rinsed with 10 ml of THF, and the rinse was added to the reaction mixture. The resultant mixture was stirred and heated under reflux for 16 hr. Then it was cooled in an ice bath and successively treated with 20 ml of Me_2CO, 50 ml of H_2O, and 150 ml of 6 *N* HCl. The reaction mixture was distilled under reduced pressure with a minimum of heating to remove the ether. The residue was stirred at room temperature for 1.75 hr. Then it was extracted ($CHCl_3$), and the extract was washed (H_2O), dried (Na_2SO_4), and concentrated to a small volume by distillation under reduced pressure. The residue was diluted with hexane and cooled to 0° to afford 0.78 g of IIa: mp 237.5–243°; λ_{max}^{MeOH} 263–264 mμ (ε 313); λ^{KBr} 2.83, 5.76, 6.29, 13.35 μ. After crystallization from $CHCl_3$–hexane, IIa melted at 235.5–244.5°, $[\alpha]^{25}D$ +204.5° (*c* 1, $CHCl_3$). 11β-Hydroxy-4-methylestra-1,3,5(10)-trien-17-one (IIa) appeared to undergo a change in crystalline form just below its melting point, thus accounting for the broad melting point range [lit.[5] mp 244–246° with change in crystalline structure at 224–226°, $[\alpha]^{25}D$ +95° (dioxane)]. *Anal.* ($C_{19}H_{24}O_2$) C, H. Recrystallization of IIa from DMF raised the melting point to 259–260°, $[\alpha]^{25}D$ +208° (*c* 1, $CHCl_3$).

11β-Acetoxy-4-methylestra-1,3,5(10)-trien-17-one (IIb).—A mixture of 2.85 g of IIIa, 40 ml of pyridine, and 40 ml of Ac_2O was heated on the steam bath for 4 hr after which time it was poured into a mixture of ice and water. The mixture was neutralized with 6 *N* HCl. The resultant solid was collected, washed (H_2O), and dried, mp 197–206.5°. Crystallization from ether afforded 2.66 g of IIb: mp 206.5–208.5°; λ^{KBr} *ca.* 5.73, 6.29, 8.04, 13.45 μ; nmr, 421.5, 357 (quartet, J = 3 cps), 134.5, 110, 63 cps; $[\alpha]^{27}D$ +94° (*c* 1, $CHCl_3$). *Anal.* ($C_{21}H_{26}O_3$) C, H.

11-β-Acetoxy-17α-ethynyl-4-methylestra-1,3,5(10)-trien-17β-ol (IIId).—To a solution of 4.50 g of IIb in 150 ml of THF was added 10.00 g of the lithium acetylide–ethylenediamine complex.[14] While acetylene was bubbled in, the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was treated with 150 ml of H_2O and stirred at room temperature for an additional 1 hour. Then it was acidified with 6 *N* HCl. The acidified mixture was poured into a mixture of ice and water. The yellow gum was collected, washed (H_2O), and dissolved in $CHCl_3$. The solution was dried (Na_2SO_4) and evaporated to dryness to afford a viscous oil. A 4.42-g sample of the oil was chromatographed on 310 g of silica gel. The column was eluted initially with C_6H_6 and then with varying proportions of EtOAc and C_6H_6. Elution of the column with 5% EtOAc in C_6H_6 gave 0.94 g of IIId as a crystalline product. Crystallization from $CHCl_3$–hexane afforded 0.71 g of IIId: mp 201.5–209.5°; λ^{KBr} 2.83, 3.06, 4.72, 5.81, 6.30, 7.92, 7.98, 13.38 μ; $[\alpha]^{26}D$ −19.5° (*c* 1, $CHCl_3$). Another crystallization from the same solvents raised the melting point to 217–219°. Admixed with IIb, IIId melted at 193–199.5°. *Anal.* ($C_{23}H_{28}O_3$) C, H.

17α-Ethynyl-11β-hydroxy-4-methylestra-1,3,5(10)-trien-17β-ol (IIIc).—Continued elution of the aforementioned column with 10% EtOAc in C_6H_6 gave 1.33 g of IIIc as a crystalline substance. Crystallization from ether–hexane afforded 0.87 g of IIIc: mp 186.5–190.5°; λ^{KBr} 2.78, 2.84, 3.08, 4.77, 6.32, 13.37 μ. The melting point was raised to 192–195° on further crystallization from ether, $[\alpha]^{26}D$ +71.0° (*c* 1, $CHCl_3$). *Anal.* ($C_{21}H_{28}O_2$) C, H.

4,17α-Dimethylestra-1,3,5(10)-triene-11β,17β-diol (IVb).—To 40 ml of 3 *M* MeMgBr in Et_2O, stirred at room temperature, was added a solution of 1.10 g of 11β-acetoxy-4-methylestra-1,3,5(10)-trien-17β-one (IIb) in 15 ml of THF. After addition was complete, the addition funnel was rinsed with 20 ml of anhydrous Et_2O, and the rinse was added to the reaction mixture. The reaction mixture was stirred and heated under reflux for 4 hr. Then it was cooled in an ice bath. The reaction mixture was successively treated with H_2O, acidified with 6 *N* HCl, diluted (Et_2O), and shaken. The ether phase was separated, washed (H_2O), dried (Na_2SO_4), and distilled under reduced pressure until a solid appeared. The residue was cooled to 0°. The solid was collected, yield 0.60 g. It was crystallized from ether to afford 0.45 g of IVb: mp 141.5–143.5° with melting and resolidification below 120°; nmr, 421–435.5 (multiplet), 289 (quartet, J = 3 cps), 132.5, 75, 68.5 cps; λ^{KBr} 2.77, 2.88, 6.32, 13.33 μ; $[\alpha]^{24}D$ +120° (*c* 1, $CHCl_3$). *Anal.* ($C_{20}H_{28}O_2$) C, H.

17β-(2-Hydroxyacetyl)-4-methylestra-1,3,5(10)-trien-17α-ol (V).[10]—The procedure of Caspi, *et al.*, was modified. To a mixture of 5.0 g of $LiAlH_4$ and 500 ml of anhydrous Et_2O, stirred and heated under reflux, was added a mixture of 5.0 g of the bismethylenedioxy derivative of prednisolone in 150 ml of THF. After the addition was complete, the addition funnel was rinsed with 50 ml of THF, and the rinse was added to the reaction mixture. The mixture was stirred and heated under reflux for 44 hr, then it was chilled in an ice bath. It was successively and cautiously treated with 20 ml of Me_2CO, 200 ml of H_2O, and 200 ml of 12 *N* HCl. The reaction mixture was distilled under reduced pressure with gentle heating to remove the ether. The residue was stirred at room temperature for 3.5 hr and extracted with $CHCl_3$; the extract was washed (H_2O), dried (Na_2SO_4), and distilled under reduced pressure until a crystalline product appeared. The residue was diluted with hexane and cooled to 0° to afford 1.23 g of V: mp 194–201.5°; λ^{KBr} 2.89, 5.85, 6.31, 13.38 μ. Crystallization from $CHCl_3$–hexane and then from C_6H_6 afforded V as a pale yellow crystalline product: mp 214–217°; $[\alpha]^{24}D$ +118° (*c* 1, $CHCl_3$) [lit.[16] mp 191–193°, $[\alpha]^{25}D$ +112° ($CHCl_3$)]. *Anal.* ($C_{21}H_{28}O_4$) C, H.

Drug Latentiation. The Preparation and Preliminary Pharmacological Evaluation of Some Mephenesin Aryloxyacetates

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Esterification of one or more free hydroxyl groups of a drug is one of the possible means of achieving "latentiation" of the drug itself, *i.e.*, transformation into a derivative from which the active compound is regenerated *in vivo*.[2] The activity of the latentiated drug will depend, among other things, (a) on the rate of absorption, distribution in the tissues, and accumulation on the target area; (b) on the rate of "bioactivation," *i.e.*, *in vivo* hydrolysis to liberate the parent compound.[3] In recent times, attempts have been made to apply some basic concepts of intramolecular catalysis to drug latentiation, by esterifying drugs with acids, whose esters are known to undergo facilitated hydrolysis.[4] On the same ground, other labile drug derivatives such as ethers and amides have been prepared.[5]

Our interest in this field arose from the observation that some aryloxyacetic acids, also known as plant growth regulators, have been found to confer upon esterified drugs enhanced intensity and duration of

(13) Melting points were taken on a Fisher-Johns melting block and are corrected. Nmr spectra were determined in deuteriochloroform on a Varian A-60 spectrometer, and the signals are reported downfield with respect to tetramethylsilane as an internal standard. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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