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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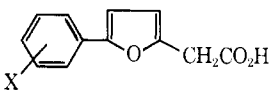
Received January 20, 1968

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.

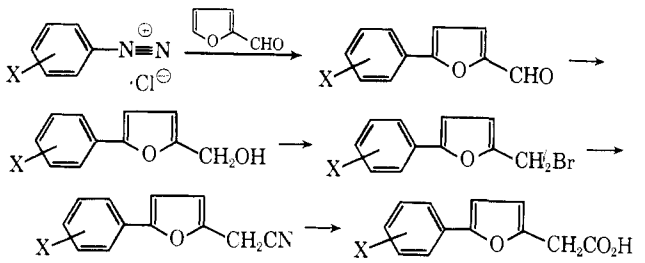
TABLE I
5-ARYL-2-FURANACETIC ACIDS



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_6–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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Received January 25, 1968

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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