α,β-Unsaturated Ketone Derivatives of Aryloxyacetic Acids, a New Class of Diuretics

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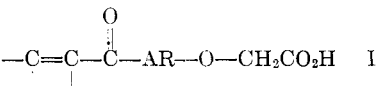
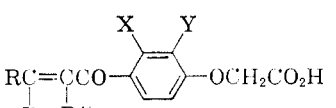
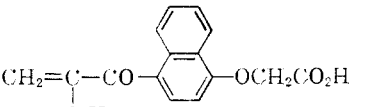
The thiazide-type[1] of sulfonamide diuretics offered the first useful departure from the mercurial agents. The clinical success as well as the shortcomings of the many drugs of this class has stimulated an intensive search for improved agents. This search has extended to new chemical classes of diuretics. More recent efforts in our laboratory have been directed toward compounds that are neither mercurials nor sulfonamides. One such class of compounds that exhibits a high order of activity in laboratory animals and in man is α,β-unsaturated ketone derivatives of aryloxyacetic acids of the general structure I.



I

Structural variations at many points in I have resulted in quantitative and qualitative changes in activity. Typical of the more potent compounds are these:





V

II, R, R′, Y = H; R″ = C_2H_5; X = Cl
III, R, R′ = H; R″ = C_2H_5; X, Y = Cl
IV, R, R′ = H; R″ = C_2H_5; X, Y = CH_3
VI, R = H; R′ = CH_3; R″ = C_2H_5; X, Y = Cl

These compounds are highly active in the dog when administered orally, intravenously or intramuscularly.[2] They are inactive in the rat by all routes of administration. In the dog, the excretion of

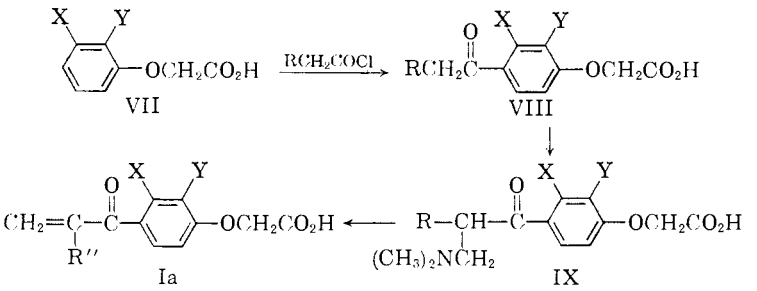
(1) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957); *cf. Ann. N. Y. Acad. Sci.*, **71** (4), 321 (1958).

sodium and chloride is increased by approximately equivalent amounts. In contrast to the thiazides, but similar to the mercurials, these compounds greatly increase the volume of urine. The results of preliminary studies indicate that several of these compounds have an order of activity, on a dose basis, comparable to chlorothiazide and hydrochlorothiazide. However, with higher doses of these compounds, it is possible to achieve a sodium chloride excretion several-fold that possible with the thiazides. This pronounced effect on sodium chloride excretion is accompanied by only a slight increase in the potassium excretion. Thus the activity of these compounds is qualitatively and quantitatively different from the thiazides and suggests a unique mode of action.

The structure I evolved from a search for biologically active compounds that react selectively with functionally important sulfhydryl groups. All of the compounds with a significant diuretic activity also show a high order of reactivity *in vitro* toward representative sulfhydryl-containing compounds.

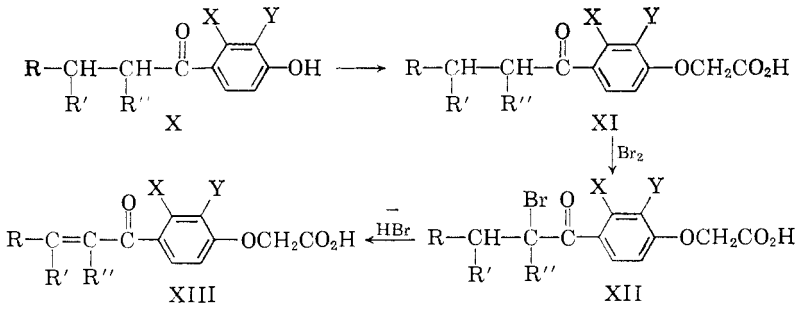
For maximum biological activity, one position in the aromatic nucleus *ortho* to the unsaturated ketone function must be substituted. Halogen and methyl groups are outstandingly effective. 2,3-Disubstitution further enhances activity but additional substitution may adversely affect activity.

For those compounds having a terminal methylene group (II–V), the following syntheses were generally successful.[3] VIII was prepared by the Friedel–Crafts reaction between the appropriate aryloxyacetic acid (VII) and acid halide. The Mannich reaction on this product yielded IX as the hydrochloride and on treatment with base this gave Ia.



(2) We are indebted to Dr. John E. Baer and his associates for the biological results. For methods see Karl H. Beyer, John E. Baer, *et al.*, *Proc. Soc. Exptl. Biol. Med.*, **100**, 442 (1959); *Ann. N. Y. Acad. Sci.*, **71**, 363 (1958).

(3) The structure of all of the products and intermediates was supported by appropriate analyses and physical data including ultraviolet, infrared, and n.m.r. spectra.



For the preparation of compounds where the unsaturation is not in the terminal position, the acylphenoxyacetic acids (XI) were brominated and the resulting α-bromoketones (XII) were then dehydrobrominated to give compounds of the type XIII of which VI is an example. The required acyl compounds (XI), where the acyl group is highly branched or where X and Y are both halogen, were most satisfactorily prepared from the acylphenol (X). The synthesis of X is achieved *via* the Friedel-Crafts reaction of the appropriately substituted anisole and acyl halide followed by cleavage of the resulting ether.

TABLE I

Compound	M.p. (corr.), °C.	M.p., °C., of intermediates VIII	IX·HCl	X	XI	XII
II	109–111	89–90	127–129	...	...	...
III	121–122	110.5–111.5	164–167	...	...	...
IV	83.5–84.5	87.5–89.5	182.5–183.5	...	...	...
V	106–109	137–139	176–178	...	...	...
VI	124.5–125.5	...	...	85–86	144.5–145.5	152–153