[Contribution from the Chemical Laboratories of New York University]

CARBOXYMETHYL ETHER OF EPINEPHRINE[1]

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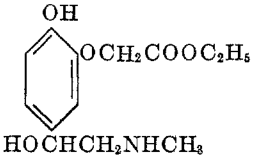
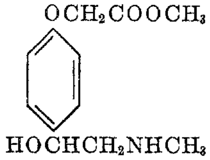
In continuation of work being carried out in this laboratory on sympathomimetic amines (1), the glycollic acid or oxyacetic acid grouping was introduced into epinephrine and synephrine to study the effect on the physiological properties of these compounds. Hydrochlorides of ethyl 5-(β-methylamino-α-hydroxyethyl)-2-hydroxyphenoxyacetate (VII) and methyl 4-(β-methylamino-α-hydroxyethyl)phenoxyacetate (IX) were synthesized. The synthesis started with the aryloxyacetic acid related to catechol or phenol. Steps for the latter are indicated:



VII



IX

$$C_6H_5OCH_2COOH \longrightarrow \text{Ester} \xrightarrow[AlCl_3]{ClCH_2COCl} ClCH_2COC_6H_4OCH_2COOH \longrightarrow \text{Ester}$$

$$\xrightarrow{CH_3NH_2} CH_3NHCH_2COC_6H_4OCH_2COOR \xrightarrow[Pd]{H_2} CH_3NHCH_2CHOHC_6H_4OCH_2COOR$$

The hydrochlorides of ethyl 5-(β-methylamino-α-hydroxyethyl)-2-hydroxyphenoxyacetate (VII) and methyl 4-(β-methylamino-α-hydroxyethyl)phenoxyacetate were pharmacologically tested as to both pressor action and toxicity. The pressor action was determined by the U.S.P. procedure for epinephrine and is reported below as the amount producing the same intensity of pressor action as 0.01 mg. of epinephrine. The toxicity is the dose which, when injected interperitoneally into mice, will kill 50% of the animals.

PHARMACOLOGIC DATA

COMPOUND	PRESSOR ACTION	LD_{50}
Ethyl 5-(β-methylamino-α-hydroxyethyl)-2-hydroxyphenoxyacetate	4.77 mg.	147 mg./kg.
Methyl 4-(β-methylamino-α-hydroxyethyl)phenoxyacetate	17.17 mg.	119 mg./kg.

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[1] Presented before the Division of Medicinal Chemistry at the Atlantic City meeting of the American Chemical Society, September, 1949.

[2] Abstracted from the thesis presented by S. J. Lederer to the faculty of the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, February, 1950.

EXPERIMENTAL

Methyl aryloxyacetates. The respective acid (30 g.) was refluxed for 2 hours with 60 cc. of methanol and 5 cc. of concentrated sulfuric acid. The reaction mixture was cooled to 25° and poured into 250 cc. of an ice-water mixture.

The *methyl o-hydroxyphenoxyacetate* separated as a viscous oil which crystallized slowly on standing at 5°. Recrystallization from ethanol-water gave 30 g. (88%) of white crystals, m.p. 59° (3).

The *methyl phenoxyacetate* did not crystallize and was extracted with 150 cc. of ether. The ether extract was dried over sodium sulfate and the ether was removed on a steam-bath. The residual oil was distilled at 243° (4) to give 30.6 g. of a colorless oil for a 98% yield.

5-Chloroacetyl-2-hydroxyphenoxyacetic acid (I). A mixture of 120 cc. of carbon disulfide, 90 g. of chloroacetyl chloride, and 30 g. of methyl *o*-hydroxyphenoxyacetate was placed in a 500-cc. 3-neck flask equipped with a mercury-sealed stirrer, a reflux condenser with a sodium hydroxide trap, and a powder funnel, and cooled to 10° in an ice-bath. Then 150 g. of anhydrous aluminum chloride was added rapidly with stirring (15–30 minutes). The mixture was kept at 10–15° for 15 minutes and the powder funnel was replaced by a condenser set for distillation. The mixture was heated on a steam-bath to remove the carbon disulfide and the excess chloroacetyl chloride (30–45 minutes). The amber, viscous residue was poured, while hot, into a mixture of 50 cc. of concentrated hydrochloric acid and 300 cc. of ice. The brownish-white solid which precipitated was filtered, washed with 200 cc. of ice-water, and sucked dry on a funnel. This product was recrystallized from hot water with carbon (Darco G-60) until a crystalline compound melting at 173° was obtained. Usually 4–6 recrystallizations were necessary. The yield was 12 g. (30%).

Compound I was esterified by refluxing 12 g. with 20 cc. of ethanol and 2 cc. of concentrated sulfuric acid for one hour. The mixture was cooled to 10° and poured into 80 cc. of ice. The precipitate was filtered off and recrystallized from alcohol-water. The yield of ethyl 5-chloroacetyl-2-hydroxyphenoxyacetate (II) was 10 g. (78%), m.p. 125°.

Then 10 g. of II was dissolved in 20 cc. of benzene and refluxed with 5 cc. of acetyl chloride for 1 hour. The solution was taken to dryness *in vacuo* and the residue was recrystallized from benzene-hexane yielding 10 g. (81%) of ethyl 5-chloroacetyl-2-acetoxyphenoxyacetate (III), m.p. 75°.

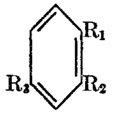
4-(Chloroacetyl)phenoxyacetic acid (IV). Methyl phenoxyacetate (30 g.) and 90 g. of chloroacetyl chloride in 120 cc. of carbon disulfide were reacted with 150 g. of anhydrous aluminum chloride in the same manner as outlined above for the preparation of I. One recrystallization from hot water gave 18 g. (44%) of 4-(chloroacetyl)phenoxyacetic acid (IV) m.p. 155°.

Then 20 g. of IV, 40 cc. of methanol, and 5 cc. of concentrated sulfuric acid were refluxed for 1 hour. The mixture was poured into 150 cc. of ice-water and the oil which separated out crystallized on standing for 48 hours at 5°. Recrystallization from alcohol-water gave 18 g. (85%) of methyl 4-(chloroacetyl) phenoxyacetate (V), m.p. 92°.

Ethyl 5-methylaminoacetyl-2-hydroxyphenoxyacetate (VI). First, 10 g. of III was dissolved in 30 cc. of absolute alcohol and cooled to −40°. Then 30 g. of a 25% solution of anhydrous methylamine in absolute alcohol, also cooled to −40°, was added rapidly. The system was immediately evacuated and placed under an atmosphere of hydrogen. The mixture was shaken at room temperature for 4 days. The temperature was reduced to −30° and the hydrogen was replaced by a stream of carbon dioxide which was passed through until the odor of methylamine had disappeared. The solution was brought to room temperature and concentrated to 10 cc. *in vacuo.* To this residue, which was brownish-black in color, dilute hydrochloric acid was added dropwise until the color had turned to a pale greenish-yellow. A black, tarry precipitate formed and was filtered off. Further addition of acid gave a white precipitate which was purified by reprecipitation from an ammoniacal solution with dilute acid. The yield of VI was 3 g. (25%), m.p. 191°.

TABLE I

PHENOXYACETATE DERIVATIVES



R1	R2	R3	FORMULA	M.P.,[a] °C.	ANALYSES			
					C		H	
					Calc'd	Found	Calc'd	Found
OH	OCH_2COOH	$COCH_2Cl$	$C_{10}H_9ClO_5$	173	49.06	49.05	3.72	3.72
OH	$OCH_2COOC_2H_5$	$COCH_2Cl$	$C_{12}H_{13}ClO_5$	125	52.70	52.66	4.75	4.68
$OCOCH_3$	$OCH_2COOC_2H_5$	$COCH_2Cl$	$C_{14}H_{15}ClO_6$	75	53.22	53.10	4.74	4.73
OCH_2COOH	H	$COCH_2Cl$	$C_{10}H_9ClO_4$	155	52.25	52.13	3.94	3.91
OCH_2COOCH_3	H	$COCH_2Cl$	$C_{11}H_{11}ClO_4$	92	54.13	53.99	4.51	4.44
							N	
OH	$OCH_2COOC_2H_5$	$COCH_2NHCH_3$	$C_{13}H_{17}NO_5$	191			5.39	5.25
OH	$OCH_2COOC_2H_5$	$CHOHCH_2NHCH_3 \cdot HCl$	$C_{13}H_{20}ClNO_6$	160			4.53	4.55
OCH_2COOCH_3	H	$COCH_2NHCH_3$	$C_{12}H_{15}NO_4$	181			5.82	5.53
OCH_2COOCH_3	H	$CHOHCH_2NHCH_3 \cdot HCl$	$C_{12}H_{17}NO_4$	196			5.76	5.76
			$C_{12}H_{18}ClNO_4$	150			5.06	5.13

[a] The thermometer readings are all uncorrected.

Methyl 4-(methylaminoacetyl)phenoxyacetate (VIII). Compound V (18 g.) was dissolved in 45 cc. of absolute alcohol and the temperature was lowered to −5°. Then 45 g. of a 25% solution of anhydrous methylamine in alcohol was added rapidly. The mixture was evacuated and an atmosphere of hydrogen was introduced. The reaction was carried out by shaking for 24 hours at room temperature. The excess methylamine was replaced by carbon dioxide as outlined in the preparation of VI and the solution was concentrated *in vacuo* to 20 cc. The addition of several drops of dilute hydrochloric acid to the green solution gave a copious black precipitate which was filtered off and rejected. Acid was added dropwise until the color turned to a pale yellow and the addition of one more drop of acid gave a white precipitate which was purified by reprecipitation from ammonia with hydrochloric acid. The yield of VIII was 7 g. (40%), m.p. 181°.

Ethyl 5-(β-methylamino-α-hydroxyethyl)-2-hydroxyphenoxyacetate (VII). Three grams of VI was suspended in 10 cc. of 95% ethanol and dissolved by the addition of the theoretical quantity of concentrated hydrochloric acid. Then 0.7 g. of freshly prepared palladium catalyst (2) was added and the solution was shaken for 6 hours under hydrogen (45 p.s.i.) at which time the theoretical uptake of hydrogen was noted. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 15 cc. of anhydrous ethanol and crystallized by the addition of 15 cc. of anhydrous ether. The yield of ethyl 5-(β-methylamino-α-hydroxyethyl)-2-hydroxyphenoxyacetate hydrochloride was 2.8 g. (96%), m.p. 160°.

Methyl 4-(β-methylamino-α-hydroxyethyl)phenoxyacetate (IX). Compound VIII (6 g.) was dissolved in 20 cc. of 95% ethanol by the addition of the theoretical quantity of concentrated hydrochloric acid. Reduction under the same conditions as outlined for VII gave 6 g. (100%) of methyl 4-(β-methylamino-α-hydroxyethyl)phenoxyacetate hydrochloride m.p. 150°.

The hydrochloride (4 g.) was dissolved in 15 cc. of distilled water and the free amine was precipitated with dilute ammonia in 2.8 g. yield (77%), m.p. 196°.

SUMMARY

1. Ethyl 5-(β-methylamino-α-hydroxyethyl-2-(hydroxyphenoxyacetate hydrochloride and methyl 4-(β-methylamino-α-hydroxyethyl)phenoxyacetate hydrochloride were prepared.

2. Both showed some pressor activity but only 1/477th and 1/1771th that of epinephrine.

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REFERENCES

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