## AMIDES AND HYDRAZIDES OF OXALIC ACID

## XIX. SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMINOALKYL-SUBSTITUTED AMIDES OF OXANILIC ACIDS

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It was previously established [1, 2] that aminoalkyl-substituted amides of alkoxy- and carboxyoxanilic acids possess hypotensive activity.

In this work the synthesis of aminoalkyl-substituted amides of oxanilic acids was accomplished and their biological activities were studied:



The initial arylides of aminobenzoic acid (I) were prepared by known methods [3,4]. Reaction of I with the acid chloride of monoethyl oxalate (II) in absolute pyridine gave up to 90% yield of the arylides of N-ethyloxalylaminobenzoic acids (III). Disubstituted amides of N-ethyloxalylanthranilic acid (VIII) were prepared by the reaction of secondary amines (VII) with ethoxalylanthranil (VI):



The structure of compound VIII was proved by an alternative synthesis of the morpholide of Nethyloxalylanthranilic acid (VIIIa, X = 0) which was prepared by reaction of the acid chloride II with the morpholide of anthranilic acid (IX, X = 0).

Compounds III (Table 1) are crystalline substances whose ester groups are easily hydrolyzed with aqueous alkali. Their reaction with the diamines (IV) yielded up to 90% of the aminoalkyl-substituted amides of oxanilic acids (V, Table 2). These are crystalline compounds of basic character the salts and halid alkylates of which are readily soluble in water.

Pharmacological tests<sup>\*</sup> showed that the salts and halide alkylates of the amides Va-Vj fairly sharply but momentarily reduce arterial pressure (AP). The methyl iodide of Vg and the hydrochlorides of Ve, Vg and Vh in 1 -3 mg /kg doses reduce AP 70 and 50%, respectively, in 15 sec. With the aim of prolonging the activity, the cationic part of the molecule was made larger: instead of the methy iodide of Vd, the benzyl chloride was prepared. The latter in strength and duration of activity surpassed aminophylline (in 5 mg/kg dose it reduced AP by 80 mm for 10 min, while aminophylline reduced AP by 34 mm for 2-5 min) and deserves further study.

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Compound	Position of RNHCO	RNHCO	Yield (in %)	mp (in °C), solvent for crystalliza- tion - eth- anol	Found N (in %)	Empirical formula	Calculated N (in %)
IIIa IIIb IIIc IIId IIIe VIIIa VIIIa	34222222	$C_{4}H_{4}NHCO$ $C_{4}H_{6}NHCO$ 2-CiC <sub>6</sub> H <sub>4</sub> NHCO 2-BrC <sub>6</sub> H <sub>4</sub> NHCO 2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> NHCO 0 (CH <sub>2</sub> ) <sub>4</sub> NCO (CH <sub>2</sub> ) <sub>5</sub> NCO	66,3 90,4 68,2 78,0 56,4 79,4 69,4	1678 2113 1534* 1523 1734 1657 901	8,83 9,07 7,93 7,05 8,71 9,31 9,35	$\begin{array}{c} C_{12}H_{16}N_{2}O_{4}\\ C_{12}H_{16}N_{2}O_{4}\\ C_{12}H_{16}CIN_{2}O_{4}\\ C_{12}H_{16}BIN_{2}O_{4}\\ C_{18}H_{18}N_{2}O_{4}\\ C_{18}H_{18}N_{2}O_{4}\\ C_{16}H_{18}N_{2}O_{5}\\ C_{16}H_{20}N_{2}O_{4}\\ \end{array}$	8,99 8,99 8,08 7,16 8,59 9,14 9,21

TABLE 1. Aryl(heteryl)amides on N-Ethyloxalylaminobenzoic Acids

\*From acetone.

TABLE 2. Aminoalkyl-Substituted Amides of Oxanilic Acids

Compound Position of	RNHCO	RNHCO	n	NR2	Yield (in %)	mp (in °C)	Found N (in %)	Empirical formula	Calculated N (in %)	Hydro- chlo- <u>ride</u> mp	Methyl iodide (in °C)
Va Vb Vc Vd Vf Vf Vf Vf Vf Vf Vj	2 3 4 2	C <sub>8</sub> H <sub>5</sub> NHCO 2-CH <sub>2</sub> C <sub>8</sub> H <sub>4</sub> NHCO 2-BrC <sub>8</sub> H <sub>4</sub> NHCO 2-CH <sub>3</sub> C <sub>8</sub> H <sub>4</sub> NHCO 2-CH <sub>3</sub> C <sub>8</sub> H <sub>4</sub> NHCO 2-CH <sub>3</sub> C <sub>9</sub> H <sub>4</sub> NHCO O (CH <sub>2</sub> ) <sub>5</sub> NCO	$2^{3}_{2}^{2}_{2}$	N (CH <sub>3</sub> ) <sub>2</sub> N (C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N (CH <sub>3</sub> ) <sub>4</sub> O N (CH <sub>3</sub> ) <sub>2</sub> N (CH <sub>3</sub> ) <sub>2</sub>	91,6 90,2 89,0 62,2 98,0 93,3 87,0 84,5 84,6 62,2	200-2 (from ethanol) 228 (from dimethylformamide) 270 (from dimethylformamide) 186-7 (from ethanol) 205-6 (from dimethylformamide) 196-7 (from dimethylformamide) 153-4 (from ethanol) 166-7 (from ethanol) 189-90 (from acetone)	15,85 15,93 15,97 15,31 14,63 13,07 14,32 12,36 16,31 10,97	$\begin{array}{c} C_{19}H_{22}N_4O_3\\ C_{19}H_{22}N_4O_3\\ C_{19}H_{22}N_4O_3\\ C_{20}H_{24}N_4O_3\\ C_{19}H_{21}CIN_4O_3\\ C_{19}H_{21}BIN_4O_3\\ C_{22}H_{28}N_4O_3\\ C_{22}H_{28}N_4O_4\\ C_{17}H_{24}N_4O_4\\ C_{25}H_{34}N_4O_6S^{\dagger} \end{array}$	$15,79 \\ 15,79 \\ 15,79 \\ 15,20 \\ 14,41 \\ 12,92 \\ 14,11 \\ 12,13 \\ 16,10 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,80 \\ 10,8$	$\begin{array}{r} 221\\ 177\\ 212\\ 155\\ 216-7\\ 216-7\\ 192-3\\ 153\\ 170\\ -\end{array}$	

\*Benzyl chloride, mp 230°C (decomp.). \*Methyl benzenesulfonate.

## EXPERIMENTAL

<u>Morpholide of Anthranilic Acid (IX, X = O)</u>. This was prepared by reduction of the morpholide of 2nitrobenzoic acid with iron filings in acetic acid. Yield was 47.3%, mp 72°C. Found %: N 13.71.  $C_{11}H_{14}N_2O_2$ . Calculated %: N 13.59.

Morpholide of N-Ethyloxalylanthranilic Acid (VIIIa, X = O). A. To a solution of 2.8 g of IX in 5 ml of absolute pyridine was added 1.8 g of II; the mixture was heated to 60°C, cooled, diluted with 20 ml of water, and acidified with hydrochloric acid (1:1). The precipitate was filtered off and crystallized. Yield was 2.4 g (57.8%).

B. To a suspension of 6.5 g of VI in 6 ml of dimethylformamide was added 2.6 g of VII (X = O). The mixture warmed up and VI dissolved. It was then boiled for 30 min, cooled, and diluted with 30 ml of water. The oil which separated quickly crystallized and was filtered off. Yield was 7.3 g.

A mixed sample of both products showed no melting point depression.

 $\frac{\gamma$ -Morpholinopropylamide of 2-o-Toluidinooxanilic Acid (Vh). A mixture of 3.85 g IIIe and 1.87 g (10% excess) of  $\gamma$ -morpholinopropylamide in 10 ml of dimethylformamide was heated for 20 min on a water bath; it was then left at room temperature for 3 h,diluted with 10 ml of water, the precipitate filtered off and crystallized. Yield was 3.3 g. The amides Va – Vg, Vi and Vj were prepared analogously.

The Hydrochloride was prepared by mixing together alcoholic solutions of Vh and hydrogen chloride.

The Methylammonium Iodide was prepared by allowing an acetone solution of Vh to stand with excess methyl iodide.

The Benzylammonium Chloride of Vd. A mixture of 3.36 g of Vd and 1.38 g of benzyl chloride in 10 ml of ethanol was heated to the disappearance of the alkali reaction (about 2 h). The mixture was cooled; the precipitate was filtered off and crystallized from ethanol. Yield was 4.1 g (94.8%). Found %: N 13.44.  $C_{27}H_{31}ClN_4O_3$ . Calculated %: N 13.21.

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