AMIDES AND HYDRAZIDES OF OXALIC ACID.

XVII. BASIC AMIDES OF CARBALKOXY-OXANILIC ACIDS

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The synthesis of basic amides of carbalkoxy-oxanilic acids, their hydrochlorides and alkyl halide complexes, has been carried out as a development from previous investigations [1,2]. Starting amino-carboxylic acid esters (I) were obtained by known methods [3]. By the interaction of the latter with monoethyl oxalyl chloride, the ethyl esters of carbalkoxy-oxanilic acids (II; Table 1) were formed in 67-97% yield.

ACOOR — ACOOR — ACOOR — ACOOR — NHCOCONH(CH₂)₂ NR'₂

$$(I) \qquad (II) \qquad (III) \qquad (III)$$

Electrophilic properties of the ester groups in esters (II) are more strongly expressed by the eth-oxalyl residue (pKa C_6H_5 NHCOCOOH 1.92 [4]) than by the group bound to the benzene ring (pKa $NH_2C_6H_4$ -COOH 4.74-4.95 [5]). Consequently reaction with N,N-dialkylethylenediamine takes place with the former group, with the formation of N,N-dialkylaminoethylamides of carbalkoxy-oxanilic acids (III; Table 2). These are crystalline substances, basic in character, which readily form highly crystalline and water soluble hydrochlorides and alkyl halide complexes.

Since the biological activity of the salts of basic amides and esters is linked with the presence of an intramolecular ion-dipole interaction [6], it seemed of interest to extend this concept to the salts of amides (III) as well. The IR absorption spectra in the region of the amide CO group stretching vibration in amide (III, $R = CH_3$, $R' = C_2H_5$, A = nothing), its hydrochloride and methiodide (1692, 1708; 1693, 1708; 1693, 1708 cm⁻¹ respectively) indicate the absence of any interaction between the ammonium cation and carbonyl in both the ester and amide group.

Pharmacological investigations showed that the hydrochloride and alkohalide salts of amides (III) possess weak cholinolytic and hypotensive activity*.

Posi – tion of ACOOR	A	R	Yield (in %)	Mp (in °C; recrystalli- zation sol- vent, etha- nol)	Found N (in %)	Empirical formula	Calculated N (in %)
2 3 4 4 4 4 4 4	Nothing	$\begin{array}{c} CH_3 \\ C_2H_5 \\ CH_3 \\ n - C_3H_7 \\ iso-C_3H_7 \\ n - C_4H_9 \\ iso-C_4H_9 \\ C_2H_5 \\ C_2H_5 \end{array}$	86,2 92,8 94,7 96,7 71,8 83,7 97 69,8 66,7	88 88—9 141—3 111—2 120—1 112—3 115—6 57,5—58,5 110—1	5,74 4,93 5,84 5,06 5,17 5,12 4,96 5,19 4,85	C ₁₂ H ₁₃ NO ₅ C ₁₃ H ₁₅ NO ₅ C ₁₂ H ₁₃ NO ₅ C ₁₄ H ₁₇ NO ₅ C ₁₄ H ₁₇ NO ₅ C ₁₅ H ₁₉ NO ₅ C ₁₅ H ₁₉ NO ₅ C ₁₄ H ₁₇ NO ₅ C ₁₄ H ₁₇ NO ₆	5,58 5,20 5,58 5,02 5,02 4,78 4,78 5,02 4,75

TABLE 1. Carbalkoxy-oxanilic Acid Ethyl Esters (II)

^{*}The authors express their appreciation to Professor Yu. S. Grosman for carrying out the tests.

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TABLE 2. Basic Amides of Carbalkoxy-oxanilic Acids (III)

Position of

ı	1	(.qt
1 °)	Hydro- chloride	186 (decomp.) 183—4 195—6 223—4 1133—4 149 126—7 126—7 148—9 115 (decomp.)
Mp (in °)	Methio- dide	1835 1812 1856 2345 1401 1273 1378 1534
in %)	z	13,09 12,54 13,09 13,67 12,03 11,57 11,57 11,57 11,57
Calculated (in %)	н	7,17 7,46 7,17 6,85 7,74 7,79 7,79 7,79 7,79
Calcı	ပ	59,85 60,95 58,85 58,65 61,89 62,90 62,90 61,89 59,25
Empírical formula		CL6 H2.8 N 8.04 C1, H2.6 N 3.04 C1, H2.6 N 3.04 C1, H2.1 N 3.04
(9)	z	13,31 12,65 13,21 13,83 12,15 12,21 11,68 11,77 11,60
Found (in %)	Н	7,25 7,73 7,01 7,91 7,83 8,04 7,93 7,87
Four	ပ	59,73 60,85 59,71 58,51 61,67 61,73 62,73 62,78 61,74 59,07
Mp (in °), recry-	vent ethanol	102—3 101—2 131—2 143—4 104—5 109—10 118—9 117—8 93—3,5
Yield (in%)		63,8 77,6 71,6 92,5 66,6 83,5 89,5
	<u> </u>	C_2H_5 C_4H_5 C_2H_5
	¥	CH ₃ C ₂ H ₃ C ₂ H ₃ C ₂ H ₃ C ₂ H ₃ n - C ₃ H ₇ iso - C ₃ H ₇ iso - C ₄ H ₉ C ₂ H ₅ C ₂ H ₅
-	∢	Nothing " " " " " " " " " " " " " " " " " " "
3	VC001	20044444444

* Iodoethylate, m.p. 195-196°. †Benzenesulfomethylate.

EXPERIMENTAL

IR spectra were taken on an UR-10B spectrophotometer in $CHCl_3$; concn. = 0.0014-0.0016 M; length = 0.8762 cm.

4-(Ethoxy-oxalylamino)phenoxyacetic Acid Ethyl Ester (II, $R=C_2H_5$, $A=OCH_2$). To a solution of 11.9 g p-aminophenoxyacetic acid ethyl ester (I, $R=C_2H_5$, $A=OCH_2$) in 20 ml dry pyridine, 10.7 g monoethyl oxalyl chloride was added, the mixture kept 1 h at room temperature, then poured into 50 ml water and acidified with hydrochloric acid. The precipitate was filtered off and crystallized. Yield 13.55 g.

N,N-Diethylaminoethylamide of 4-Carbethoxymethoxyoxanilic Acid. The product (5.9 g) obtained in the previous experiment and 2.34 g N,N-diethylethylenediamine in 20 ml ethanol was heated for 30 min, the greater part of the alcohol was distilled off, and the precipitate which separated filtered off and crystallized. Yield 6.5 g.

On storing an acetone solution of the amide with methyl iodide for 12 h the methiodide was obtained. The hydrochloride was isolated by mixing an alcoholic solution of the substance with hydrogen chloride.

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