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Alkamine Esters of Substituted *p*-Xenylglycolic Acids[1]

BY JOHN A. FAUST, R. F. FELDKAMP AND MAURICE L. MOORE

A series of alkamine esters of substituted *p*-xenylacetic acids has been prepared by Blicke and Grier[1a] and found to possess antispasmodic activity.[1a,2] Subsequent investigation of a series of alkamine esters of substituted α-thienylacetic acids[3] has shown that, in general, the spasmolytic activity of the esters of hydroxyacetic acids (glycolates) is much greater than that of the esters of acetic acids.[3,4] Since the observed activity of some of the esters of alkyl-*p*-xenylacetic acids is relatively high, in comparison with known antispasmodic agents, the present work was concerned with the synthesis of a series of related esters of substituted *p*-xenylglycolic acids for pharmacological investigation.

The necessary substituted *p*-xenylglycolic acids have been prepared previously by the reaction of the appropriate Grignard reagent on *p*-xenylglyoxylic acid.[1a] These acids were dissolved in isopropanol and heated with a molecular equivalent of the desired basic alkyl chloride for the preparation of the esters, according to the general method of Horenstein and Pählicke.[5] The hydrochloride salts of two of the esters could not be isolated in crystalline form. These were converted to methobromides and isolated as crystalline quaternary salts The properties of these compounds are summarized in Table I.

The β-diethylaminoethyl ester hydrochlorides of the propyl- and butyl-*p*-xenylglycolic acids were found to have nearly identical melting points and there was no depression in the melting point of a mixture of the two compounds. This was also true of the β-N-piperidinoethyl ester hydrochlorides of the same acids. In checking these results new acids were prepared and esterified with the appropriate basic alkyl chloride to yield new samples of the four esters. The properties of three of the new samples coincided with those of the first. However, the β-diethylaminoethyl ester hydrochloride of butyl-*p*-xenylglycolic acid had a much lower melting point than that of the initial material, although the analytical data on both were acceptable. The melting point of a mixture of the two was the same as that of the higher melting form and both yielded the same acid upon saponification.

TABLE I

ALKAMINE ESTERS OF SUBSTITUTED *p*-XENYLGLYCOLIC ACIDS

p-$C_6H_5C_6H_4CR'OHCOOR \cdot HCl$

No.	R	R'	Yield, %	M. p., °C.[e]	Formula	Analyses, %[a] Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Antispasmodic activity[b] average max. effective dilution on isolated rabbit jejunum: Acetylcholine	Barium chlorine
1	$-CH_2CH_2N(C_2H_5)_2$	CH_3	82	160–161	$C_{21}H_{28}O_3NCl$	3.71	3.78	9.39	9.66	1M[c]	200–500T[d]
2		C_2H_5	84	157–158	$C_{22}H_{30}O_3NCl$	3.57	3.68	9.05	9.33	100–200T	100–200T
3		C_3H_7	55	137–139	$C_{23}H_{32}O_3NCl$	3.45	3.37	8.73	8.81	100–200T	100–200T
4		C_4H_9 I	61	135–137	$C_{24}H_{34}O_3NCl$	3.34	3.28	8.44	8.63	100–200T	100–200T
		II	67	119–120			3.36		8.51	100–200T	100–200T
5	$-CH_2CH_2CH_2N(C_2H_5)_2$	CH_3	87[f]	115–117	$C_{22}H_{30}O_3NCl$	3.57	3.55	9.06	9.03	500T–1M	200T
6		C_2H_5	62	122–123	$C_{23}H_{32}O_3NCl$	3.45	3.38	8.74	8.74	200–500T	200–500T
7		C_3H_7[g]	31	126–128	$C_{25}H_{36}O_3NBr$	2.93	3.18	16.70	16.81	200–500T	200–500T
8		C_4H_9[g]	57	155–156	$C_{26}H_{38}O_3NBr$	2.84	3.00	16.23	16.39	500T–1M	200–500T
9	$-CH_2CH_2NC_5H_{10}$[h]	CH_3	92[f]	207–208	$C_{22}H_{28}O_3NCl$	3.59	3.79	9.09	9.46	500T–1M	200–500T
10		C_2H_5	70	146–147	$C_{23}H_{30}O_3NCl$	3.47	3.62	8.78	8.69	100–200T	100–200T
11		C_3H_7	64	183–184	$C_{24}H_{32}O_3NCl$	3.35	3.37	8.48	8.43	100–200T	100–200T
12		C_4H_9	73	181–182	$C_{25}H_{34}O_3NCl$	3.24	3.24	8.21	8.22	100–200T	100–200T

[a] We are indebted to Mary Jane Eastwood and Elizabeth B. Macks for the analytical data on these compounds. [b] The figures recorded represent preliminary results only but they are sufficiently accurate to permit a relative comparison of the compounds. [c] 1:1,000,000. [d] 1:200,000–500,000. [e] All the melting points reported are uncorrected. [f] Crude yields. [g] Methobromides. [h] NC_5H_{10} = Piperidino. Compound no. 6 was recrystallized from benzene, compound 9 from methanol, compounds 11 and 12 from isopropanol, compounds 1 and 5 from a mixture of methanol and isopropyl ether, and all others from a mixture of isopropanol and isopropyl ether.

We are indebted to Dr. A. M. Lands and Miss V. L. Nash, of the Pharmacological Research Laboratories, for a preliminary report on the antispasmodic activity of these compounds as included in Table I. In general, the spasmolytic activity is about the same as for the corresponding esters in the *p*-xenylacetic acid series. The esters of methyl-*p*-xenylglycolic acid are the most active in the series, with β-diethylaminoethyl methyl-*p*-xenylglycolate having an activity against acetylcholine on the isolated rabbit

(1) Prepared for the 1945 meeting-in-print of the Division of Medicinal Chemistry, A. C. S.

(1a) Blicke and Grier, THIS JOURNAL, **65**, 1725 (1943).

(2) Lewis, Lands and Geiter, *Federation Proc.*, **2**, 29, 86 (1943).

(3) Blicke and Tsao, THIS JOURNAL, **66**, 1645 (1944).

(4) Lands and Nash, *Proc. Soc. Exptl. Biol. Med.*, **57**, 55 (1944).

(5) Horenstein and Pählicke, *Ber.*, **71**, 1654 (1938).

jejunum in a dilution of 1:1,000,000. It was surprising to note that the esters of glycolic acids were of the same order of activity as the esters of the corresponding acetic acids.

Experimental

Basic Esters. (a) Hydrochlorides.—A homogeneous solution of equimolecular quantities of the glycolic acid and the basic alkyl chloride in an appropriate volume (50 ml. per 0.03 mole) of isopropanol was refluxed for fifteen hours. After filtration the solvent was removed by evaporation at room temperature with a current of air and the oily residue became crystalline, in most cases, after being repeatedly rubbed with fresh portions of anhydrous ether. The product was recrystallized from a suitable solvent as indicated in the table.

(b) Methobromides.—Hydrochlorides which persisted as oils were converted to methobromides according to the procedure of Blicke and Maxwell.[6] A cold aqueous solution of the hydrochloride was made alkaline with 10% aqueous sodium carbonate and the liberated basic ester extracted with ether. After washing with water, the extract was dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered off and the ether evaporated leaving an oil which was dissolved in ethanol. This solution, contained in a citrate bottle, was cooled in an ice–salt mixture and treated with four to six equivalents of methyl bromide. The bottle was stoppered and allowed to stand at room temperature for twenty-four hours after which the product was worked up in the manner described for the hydrochlorides.

(6) Blicke and Maxwell, THIS JOURNAL, **64**, 428 (1942).

Summary

Twelve alkamine esters of substituted *p*-xenylglycolic acids were prepared by the reaction of a molecular equivalent of the appropriate acid and basic alkyl chloride. The properties of these compounds are described. The anomalous data on certain of these derivatives are discussed.

All of the esters possess antispasmodic activity, although it was surprising to find that they were of the same order of activity as the esters of the corresponding acetic acids.

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[CONTRIBUTION FROM THE SCIENTIFIC LABORATORIES, FREDERICK STEARNS AND COMPANY DIVISION OF STERLING DRUG, INC.]

Alkamine Esters of Substituted 1-Naphthaleneglycolic Acids[1]

BY R. F. FELDKAMP AND MAURICE L. MOORE

In view of the observations noted in the preceding article of this series,[1a] it was of interest to synthesize a series of alkamine esters of substituted 1-naphthaleneglycolic acids for pharmacological investigation in comparison with the previously prepared esters of substituted 1-naphthaleneacetic acids,[2] several of which have been reported to possess relatively high antispasmodic activity.

The substituted 1-naphthaleneglycolic acids were prepared according to the method already described by the reaction of the appropriate Grignard reagent on 1-naphthaleneglyoxylic acid.[2] Whereas a large excess (50%) of Grignard reagent was previously employed in this synthesis it was found that a small excess (10%) gave a granular solid complex and yields of 78–88%. Two of these acids have not been reported and are noted in the Experimental Part. The desired esters were prepared by the method of Horenstein and

TABLE I

ALKAMINE ESTERS OF SUBSTITUTED 1-NAPHTHALENEGLYCOLIC ACIDS, 1-$C_{10}H_7CR'OHCOOR \cdot HCl$

No.	R	R′	Yield, %	M. p., °C.	Formula	Analyses, %[a] Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Antispasmodic activity[b] av. max. effective dilu. on isolated rabbit jejunum Acetylcholine	Barium chloride
1	$-CH_2CH_2N(C_2H_5)_2$	CH_3	87	139–141	$C_{19}H_{23}O_3NCl$	3.98	3.95	10.07	10.25	2M[c]	500T[d]
2	$-CH_2CH_2N(C_2H_5)_2$	C_2H_5	90	147–148	$C_{20}H_{25}O_3NCl$	3.83	3.84	9.69	9.82	500T–1M	200–500T
3	$-CH_2CH_2N(C_2H_5)_2$	C_3H_7	95	153–155	$C_{21}H_{27}O_3NCl$	3.69	3.83	9.33	9.55	500T–1M	250–500T
4	$-CH_2CH_2N(C_2H_5)_2$	C_4H_9	82	133–135	$C_{22}H_{29}O_3NCl$	3.56	3.58	9.00	9.35	500T–1M	250–500T
5	$-CH_2CH_2CH_2N(C_2H_5)_2$	CH_3	74	134–135	$C_{21}H_{30}O_3NBr$[e]	3.30	3.49	18.83	18.73	200–500T	100–200T
6	$-CH_2CH_2CH_2N(C_2H_5)_2$	C_2H_5	89	138–140	$C_{21}H_{28}O_3NCl$	3.69	3.78	9.33	9.33	250–500T	250–500T
7	$-CH_2CH_2CH_2N(C_2H_5)_2$	C_3H_7	83	153–154	$C_{22}H_{30}O_3NCl$	3.56	3.52	9.00	9.00	250–500T	100–200T
8	$-CH_2CH_2CH_2N(C_2H_5)_2$	C_4H_9	77	123–125	$C_{23}H_{32}O_3NCl$	3.43	3.46	8.69	8.58	100–200T	200T
9	$-CH_2CH_2CH_2N(C_2H_5)_2$	C_5H_{11}	93	163–165	$C_{24}H_{34}O_3NCl$	3.27	3.24	8.29	8.33	500T–1M	200–500T
10	$-CH_2CH_2NC_5H_{10}$[f]	CH_3	74	148–149	$C_{21}H_{28}O_3NBr$[e]	3.32	3.31	18.92	18.69	500T–1M	250–500T,
11	$-CH_2CH_2NC_5H_{10}$[f]	C_2H_5	50	164–166	$C_{22}H_{30}O_3NCl$	3.71	3.63	9.38	9.38	200–500T	100–200T,
12	$-CH_2CH_2NC_5H_{10}$[f]	C_3H_7	81	143–145	$C_{23}H_{32}O_3NCl$	3.57	3.77	9.05	8.85	100–200T,	100T
13	$-CH_2CH_2NC_5H_{10}$[f]	C_4H_9	89	128–130	$C_{24}H_{34}O_3NCl$	3.45	3.52	8.74	8.32	100–200T	100–200T,

[a] We are indebted to Mary Jane Eastwood and Elizabeth B. Macks for the analytical data on these compounds. [b] The figures recorded represent preliminary results only but they are sufficiently accurate to permit a relative comparison of the compounds. [c] 1:2,000,000. [d] 1:500,000. [e] Methobromides. [f] NC_5H_{10} = Piperidino. Compounds 1, 2, 3, 4, 5, 6, 10 and 11 were recrystallized from isopropanol and isopropyl ether, compounds 7, 8, 9 and 12 from isopropanol and ethyl ether, and compound 13 from isopropanol.

(1) Prepared for the 1945 meeting-in-print of the Division of Medicinal Chemistry, A. C. S.

(1a) See THIS JOURNAL, **67**, 1897 (1945).

(2) Blicke and Feldkamp, *ibid.*, **66**, 1087 (1944).