[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SAINT LOUIS UNIVERSITY AND DEPARTMENT OF PATHOLOGY, MARQUETTE UNIVERSITY SCHOOL OF MEDICINE]

Synthesis of Potential Rickettsiostatic Agents.[1a] I. 4,4′-Dicarboxy-α,ω-diphenoxyalkanes[1b]

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A series of 4,4′-dicarboxy-α,ω-diphenoxyalkanes have been prepared as potential rickettsiostatic agents. The acids were prepared by alkylation of either *p*-hydroxybenzaldehyde or ethyl *p*-hydroxybenzoate followed by oxidation or saponification. All compounds tested were less active than the reference *p*-aminobenzoic acid.

During the past few years a structure-activity relationship study has been conducted for which a number of compounds structurally related to *p*-aminobenzoic acid have been prepared for testing as rickettsiostatic agents.[3] Among the compounds studied were simple *p*-alkoxybenzoic acids, some of which exhibited an activity which approached that of *p*-aminobenzoic acid.

As a continuation of that study, a series of bis-alkoxybenzoic acids (Table I) have been prepared and tested for rickettsiostatic activity.

TABLE I

4,4′-DICARBOXY-α,ω-DIPHENOXY ALKANES

$HO_2C—C_6H_4—O—(CH_2)_n—O—C_6H_4—CO_2H$

		Yield, %			Carbon, %		Hydrogen, %	
n	M.P.	Method A	Method B	Formula	Calcd.	Found	Calcd.	Found
1	287–288	90	91	$C_{15}H_{12}O_6$	62.50	62.38	4.20	3.92
2	352–355[a]	92	88	$C_{16}H_{14}O_6$	63.56	63.01	4.67	4.46
3	332–334[b]	90	92	$C_{17}H_{16}O_6$	64.55	64.03	5.10	5.15
4	338–341[c]	90	87	$C_{18}H_{18}O_6$	65.35	65.30	5.48	5.57
5	285–288	90	92	$C_{19}H_{20}O_6$	66.26	65.79	5.85	5.69
6	290–292	90	90	$C_{20}H_{22}O_6$	67.03	66.89	6.19	6.14
7	245–248	90	88	$C_{21}H_{24}O_6$	67.73	67.45	6.49	6.51
8	284–287	95	90	$C_{22}H_{26}O_6$	68.38	67.94	6.78	6.83
9	255–258	91	94	$C_{23}H_{28}O_6$	69.00	68.73	7.04	7.25
10	273–274	87	90	$C_{24}H_{30}O_6$	69.55	69.22	7.30	7.02

[a] Neish (ref. 4) reported 339–340°. [b] Neish (ref. 4) reported 310–312°. [c] Neish (ref. 4)reported 324°.

A synthesis of the 4,4′-dicarboxy-α,ω-diphenoxyalkanes was reported by Neish[4] in which the polymethylene chain was 2, 3, and 4 carbons in length. These acids were prepared by condensing the sodium salt of *p*-hydroxybenzaldehyde with the appropriate dihalide and oxidation of the diformyl derivative (Table II) with alkaline permanganate to the acid. It was determined by experiment that this oxidation gave a product which was difficult to purify. The oxidation procedure was changed to the method of Burtner and Cusic[5] which used moist silver oxide. The products obtained by this method (Method A) were easily separated in high purity and good yield.

A second method (Method B) consisted of the reaction of the sodium salt of ethyl *p*-hydroxybenzoate with an alkyl dihalide followed by saponification of the resulting ester (Table III). Method B was preferred for the preparation of the octane and decane derivatives because their sodium salts were practically insoluble in dilute sodium hydroxide. As a result, when method A was used it was difficult to separate the insoluble sodium salt of the acids from the precipitated silver.

Considerable difficulty was encountered in the purification and identification of the diformyl derivatives. Neish[4] had noted that when heated slowly these derivatives would not give sharp and reproducible melting points. As such behavior could be a result of oxidation, it was found

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(3) D. Greiff, H. B. Donahoe, M. Chiga, and H. Pinkerton, *J. Immun.*, 74, 32 (1955).

(4) W. J. P. Neish, *Rec. Trav. Chem.*, 66, 433 (1947).

(5) R. R. Burtner and J. W. Cusic, *J. Am. Chem. Soc.*, 65, 262 (1943).

TABLE II

4,4′-DIFORMYL-α,ω-DIPHENOXY ALKANES

OHC—C_6H_4—O—$(CH_2)_n$—O—C_6H_4—CHO

n	M.P.[a]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	83–84	50	$C_{15}H_{12}O_4$	70.30	69.84	4.72	4.49
2	122–123[b]	55	$C_{16}H_{14}O_4$	71.10	71.09	5.22	5.29
3	130[c]	44	$C_{17}H_{16}O_4$	71.81	71.61	5.67	5.67
4	103–104[d]	60	$C_{18}H_{18}O_4$	72.43	72.03	6.08	5.83
5	80–81	67	$C_{19}H_{20}O_4$	73.06	72.80	6.45	6.10
6	106–107	66	$C_{20}H_{22}O_4$	73.60	73.43	6.80	6.72
7	62–64	56	$C_{21}H_{24}O_4$	74.10	73.91	7.10	7.02
8	82–83	73	$C_{22}H_{26}O_4$	74.55	74.59	7.39	7.26
9	81–83	66	$C_{23}H_{28}O_4$	74.96	74.84	7.66	7.28
10	78–80	46	$C_{24}H_{30}O_4$	75.37	75.14	7.90	7.82

[a] All melting points taken in evacuated capillaries. [b] Neish (ref. 4) reported 120–121°. [c] Neish (ref. 4) reported 134–135° [d] Neish (ref. 4) reported 110° (turbidly), clears 130–140°.

TABLE III

4,4′-DICARBETHOXY-α,ω-DIPHENOXY ALKANES

$C_2H_5O_2C$—C_6H_4—O—$(CH_2)_n$—O—C_6H_4—$CO_2C_2H_5$

n	M.P.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	97.5–98.5	58	$C_{19}H_{20}O_6$	66.26	66.46	5.85	5.49
2	106–107	26	$C_{20}H_{22}O_6$	67.03	67.68	6.19	6.01
3	108–109.5	15	$C_{21}H_{24}O_6$	67.73	67.44	6.49	6.29
4	98–100	30	$C_{22}H_{26}O_6$	68.38	68.88	6.78	7.38
5	93–94	50	$C_{23}H_{28}O_6$	69.00	68.74	7.04	6.64
6	132–133.5[a]	59	$C_{24}H_{30}O_6$	69.55	69.25	7.30	7.53
7	94.5–95.5	43	$C_{25}H_{32}O_6$	70.07	70.43	7.53	7.25
8	101–103	37	$C_{26}H_{34}O_6$	70.56	70.11	7.74	8.08
9	79–82	37	$C_{27}H_{36}O_6$	71.02	70.79	7.95	8.07
10	108.5–110	51	$C_{28}H_{38}O_6$	71.46	71.17	8.14	8.03

[a] Recrystallized from ethylene glycol monomethyl ether.

that if the compounds were sealed in melting point tubes under reduced pressure sharp melting points were obtained which could be duplicated.

Rickettsiostatic testing. All acids were tested for rickettsiostatic activity against *Rickettsia mooseri*, the etiologic agent of typhus fever, in the yolk sacs of embryonate eggs. Rickettsiae were injected on the fifth day of incubation and the compounds (as sodium salts) were injected on the seventh day. When experiments were terminated, smears from the yolk sac membranes were stained and the degree of infection determined by estimating the numbers of rickettsiae per oil immersion field. All compounds were compared on a molar basis to a standard rickettsiostatic dose of *p*-aminobenzoic acid.

All compounds in this series were less active than *p*-aminobenzoic acid. A marked difference was observed in compounds having an odd or even number of methylene groups. The acids with odd numbers of methylene groups were more active at all dosage levels than those with even numbers of methylene groups. A more complete report on the rickettsiostatic activity of compounds described in this paper is presented elsewhere.[6]

(6) D. Greiff, H. B. Donahoe, and B. Hoerl, *Arch. int. Pharmacodyn.*, **127**, 413 (1960).

EXPERIMENTAL[7]

4,4′-Diformyl-α,ω-diphenoxyalkanes. To 300 ml. of absolute ethanol in a 500 ml. round bottom flask were added 3.45 g. (0.15 g.-atom) of sodium metal followed by 18.3 g. (0.15 mole) of recrystallized *p*-hydroxybenzaldehyde and 0.075 mole of an α,ω-dibromoalkane. The mixture was refluxed on a steam bath for 6 hr. and then poured into 500 ml. of cold water and cooled until crystallization was complete. The waxy solid was filtered, washed with water, and dried *in vacuo* over sulfuric acid. An analytically pure compound was obtained after one to three recrystallizations from absolute ethanol.

In the preparation of the monomethylene derivative 30 g. (0.5 mole) of methylene chloride and 15 g. (0.1 mole) of sodium iodide replaced the α,ω-dibromoalkane and a reflux time of 68 hr. was used.

4,4′-Dicarbethoxy-α,ω-diphenoxyalkanes. After treating 2.3 g. (0.1 g.-atom) of sodium metal with 100 ml. of absolute ethanol in a 250-ml. round bottom flask, 16.6 g. (0.1 mole) of ethyl *p*-hydroxybenzoate and 0.05 mole of an α,ω-dibromoalkane were added to the solution and the mixture was refluxed on a steam bath for 3 to 4 hr. The solution was then poured into 400 ml. of warm water which contained 2 g. of sodium hydroxide. Crystallization occurred when the mixture was placed in an ice bath. The white waxy precipitate was collected and dried *in vacuo* over sulfuric acid. Except where indicated in Table II, three recrystallizations from 95% ethanol gave a pure product.

(7) Analyses are by Weiler & Strauss, Oxford, England. All melting points are corrected.

In the preparation of the monomethylene derivative 30 g. (0.5 mole) of methylene chloride and 15 g. (0.1 mole) of sodium iodide replaced the α,ω-dibromoalkane and a reflux time of 68 hr. was used.

4,4'-Dicarboxy-α,ω-diphenoxy alkanes. Method A. In a 500 ml. three neck flask, fitted with a condenser and mechanical stirrer, were placed 0.02 mole of a pure 4,4'-diformyl-α,ω-diphenoxyalkane and 100 ml. of absolute ethanol. The mixture was heated until all solid had dissolved and 13.6 g. (0.08 mole) of silver nitrate in 28 ml. of water and 4.8 g. (0.12 mole) of sodium hydroxide in 10 ml. of water were added. At the end of a 30-min. heating period the mixture was placed into 500 ml. of hot water and filtered while hot. When necessary the extraction was repeated using another 500 ml. of hot water. The filtrate was acidified to congo red with 6*N* hydrochloric acid. When the white precipitate was filtered, washed thoroughly with water, and dried at 110°, a product of high purity was obtained. One recrystallization from ethylene glycol monomethyl ether gave an analytically pure product.

Method B. After dissolving 0.02 mole of a 4,4'-dicarbethoxy-α,ω-diphenoxyalkane in hot absolute ethanol or its recrystallization solvent, the solution was cooled to 60° and 500 ml. of a saturated solution of potassium hydroxide in absolute methanol were added. The mixture was refluxed for 30 min. If no precipitation occurred within the first 10 min. of refluxing, solid potassium hydroxide was added until precipitation began. At the end of the reflux period the mixture was cooled in an ice bath for 15 min. and the precipitate was collected. The precipitate was dissolved in 500 to 1000 ml. of hot water and acidified to congo red with 6*N* hydrochloric acid. When the white solid was filtered, washed thoroughly with water, and dried at 110° an acid of high purity was obtained. Recrystallization from ethylene glycol monomethyl ether gave analytically pure crystals.

Preparation of sodium salts of 4,4'-dicarboxy-α,ω-diphenoxyalkanes. A 4,4'-dicarboxy-α,ω-diphenoxyalkane (5 g.) was placed in a 500 ml. flask and 25–50 ml. of hot water containing a very slight excess of the equivalent amount of sodium hydroxide were added. The mixture was boiled until solution was complete, more water being added when necessary After filtering, the solution was placed in an ice bath for 20 min. At the end of the cooling period, 250 ml. of absolute ethanol was added to the cold solution to initiate or complete precipitation of the sodium salt. The solution was kept in an ice bath for 1 hr. before filtering. The excess of sodium hydroxide was removed by washing the salt with 25 ml. portions of absolute ethanol until the washings were neutral to litmus. The salt was dried at 110°. The yield was nearly quantitative.

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Synthetic Analgesics. II. Basic Anilides and Carbanilates[1]

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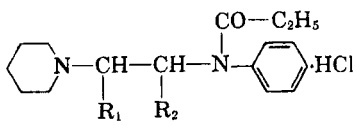
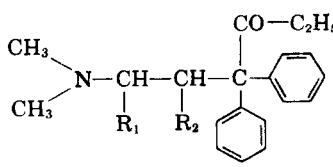
N-(*tert*-Aminoalkyl)anilides and *N*-(*tert*-aminoalkyl)carbanilates were synthesized for analgesic testing. *N*-(1-Methyl-2-piperidinoethyl)propionanilide hydrochloride, phenampromid, was chosen as an analgesic worthy of clinical investigation in man. This compound was resolved, and analgesic activity was shown to reside largely in the *l*-enantiomorph.

In the previous paper of this series[2] a new potent analgesic, *N*-(1-methyl-2-piperidinoethyl)propionanilide hydrochloride, phenampromid[3] (Ia), was described. This compound may be considered an analog of isomethadone (IIa), in which the dimethylamino moiety has been replaced by the piperidino group and the quaternary carbon atom and one of its attached phenyl groups has been replaced by nitrogen.



Ia. $R_1 = H$, $R_2 = CH_3$
b. $R_1 = CH_3$, $R_2 = H$



IIa. $R_1 = H$, $R_2 = CH_3$
b. $R_1 = CH_3$, $R_2 = H$

Such a compound retains the steric requirements of a potent analgesic as set forth by Beckett and Casy and others,[4] and would be expected to fit the same receptor surface as active analgesics such as meperidine, methadone, and morphine.

The basic anilides studied in this program were prepared by acylation of the appropriate ethylenediamines and propanediamines with an acid halide or anhydride. The straight chain ethylenediamine (Table III) and 1,3-propanediamine (Table VII) intermediates were obtained by the well known procedure[5] of reacting a *tert*-aminoalkyl chloride with an aniline derivative (Method A). This reaction was not useful for the preparation of branched

(1) Presented in part at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959.

(2) Preliminary communication, W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959).

(3) The generic name "phenampromid" has been proposed for this compound.

(4) (a) A. H. Beckett and A. F. Casy, *J. Pharm. and Pharmacol.*, **6**, 986 (1954); (b) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).