[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WALLACE & TIERNAN, INC.]

Electronegative Substitutions in Local Anesthetics of the Benzoic Acid Ester Type

BY SCOTT J. CHILDRESS, MICHAEL G. CORDASCO, O. J. PLEKSS AND L. REINER

RECEIVED MARCH 2, 1954

A series of substituted benzoic acid esters of various alkanolamines has been prepared and tested pharmacologically.

Although halogenated and other electronegatively ring substituted benzoic acid and *p*-aminobenzoic acid esters of alcohols and alkanolamines have been known and studied extensively in the last three decades, none of them has been accepted for use as a local anesthetic until recently.[1] The changes in the criteria used by pharmacologists and anesthetists are probably responsible for the renewed interest in these compounds. It has been shown that halobenzoic acid esters of alkanolamines are less stable than the corresponding parent compounds and the rapid hydrolysis rate of these esters has been considered undesirable as it tends to shorten the duration of anesthesia. Recent studies of the enzymic hydrolysis rate of 2-chloroprocaine which was previously synthesized in our laboratory[2] showed that this compound was about four times[3] as rapidly hydrolyzed by an esterase of human plasma as the parent compound, procaine, yet the duration of anesthesia was at least as long and in concentrations below 1% considerably more prolonged than that of procaine. Furthermore, the chloro compound was much less toxic on subcutaneous administration than procaine. Consequently, it seemed that increased hydrolysis rate when combined with satisfactory depth and duration of anesthesia might be advantageous. This was borne out by the clinical experience with 2-chloroprocaine.[1]

It was to be expected that the enzymic hydrolysis rate as well as the local anesthetic action would be affected not only by the character and position of the electronegative substitution but also by the structure of the alkanolamine moiety of the molecule. It was therefore of interest to prepare a series of esters of 4-amino-2-chlorobenzoic acid and various alkanolamines and for comparison some corresponding esters of other chlorobenzoic acids and 4-amino-2-nitrobenzoic acid.

In this communication we shall describe the preparation and properties of the new local anesthetics synthesized for this study. Details of the pharmacologic studies will be published elsewhere. In an attempt to increase the effects produced by the 2-chloro substitution, an ester of 4-amino-2,6-dichlorobenzoic acid also was prepared.

Esters of the tertiary amino alcohols were prepared either by condensation of the corresponding dialkylaminoalkyl chloride with the sodium salt of the acid (procedure I)[4] or by condensation of the acid chloride with the amino alcohol in the presence of excess base (procedure II). Esters of secondary amines were prepared by refluxing the hydrochloride of the secondary aminoalcohol with the acid chloride (procedure III).[5] The nitro esters were reduced to the amino esters by treating the hydrochlorides with iron powder in water or aqueous alcohol, some of the salts being more soluble in the latter mixture (procedure IV). Attempts to isolate the 2,6-dichloro-4-nitrotoluene required for the preparation of 2,6-dichloroprocaine from the mixture prepared by chlorination of 4-nitrotoluene with two equivalents failed. The compound was prepared by nitrating the crude chlorinated 4-nitrotoluene and isolating by crystallization the 2,6-dichloro-3,4-dinitrotoluene. Treating the latter with alcoholic ammonia yielded 3-amino-2,6-dichloro-4-nitrotoluene. The amino group was removed through diazotization.[6] The acid was then obtained by oxidizing the 2,6-dichloro-4-nitrotoluene with potassium permanganate in pyridine. For hydrolysis rate studies, 4-amino-2,6-dichlorobenzoic acid also was required. This could be prepared without affecting the reactive halogens by the catalytic reduction method of Kuhn[7] using palladium–charcoal and hydrazine.

An attempt was made to prepare diethylaminoethyl 4-amino-2-nitrobenzoate by the reduction of the corresponding 2,4-dinitrobenzoate using the method of Parkes and Farthing.[8] However, the reduction did not proceed to completion and diethylaminoethyl 4-hydroxylamino-2-nitrobenzoate was obtained. The desired compound was prepared (procedure I) from 4-amino-2-nitrobenzoic acid and the appropriate aminoalkyl chloride.

Because of incomplete conversion of 1-cyclohexylamino-2-propanol into its hydrochloride during the application of procedure III, N-[2-(2-chloro-4-nitrobenzoxy)-1-propyl]-N-cyclohexyl-2-chloro-4-nitrobenzamide also was formed.

For the preparation of 2-chlorotetracaine by procedure I, 4-*n*-butylamino-2-chlorobenzoic acid was needed. This was prepared by alkylation with 1-bromobutane yielding also some 4-di-*n*-butylamino-2-chlorobenzoic acid.

In Table I are listed the substituted benzoic acid esters which were prepared. These compounds possess moderate anesthetic activities, are relatively non-toxic but rather irritating.

The nitro esters, which were intermediates in the preparation of the 2-substituted *p*-aminobenzoin acid esters, are given in Table II. These compounds were not studied pharmacologically.

Table III contains the information collected on the 2-substituted *p*-aminobenzoic acid esters. In this group are a number of potent local anesthetics, some with favorable activity–toxicity ratio. Espe-

(1) F. F. Foldes and P. G. McNall, *Anesthesiology*, **13**, 287 (1952).
(2) M. Rubin, H. C. Marks, A. Wishinsky and A. Lanzilotti, THIS JOURNAL, **68**, 623 (1946).
(3) M. H. Aven and F. F. Foldes, *Science*, **114**, 206 (1951).
(4) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).
(5) A. C. Cope and E. M. Hancock, THIS JOURNAL, **66**, 1448 (1944).
(6) W. Davies and G. W. Leeper, *J. Chem. Soc.*, **129**, 1413 (1926).
(7) L. P. Kuhn, THIS JOURNAL, **73**, 1510 (1951).
(8) G. D. Parkes and A. C. Farthing, *J. Chem. Soc.*, 1275 (1948).

TABLE I

HYDROCHLORIDES OF ESTERS OF CHLORINATED BENZOIC ACIDS: $XYC_6H_3COOR \cdot HCl$

R	X	Y	Prepn.	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chloride, % Calcd.	Chloride, % Found	Local anesthetic activity Topical × cocaine	Local anesthetic activity Intradermal × procaine	Toxicity LD$_{50}$(mg./kg.) Subcutaneous	Toxicity LD$_{50}$(mg./kg.) Intravenous
$-CH_2CH_2N(C_2H_5)_2$	2-Cl	H	I	127–128[a,f]	$C_{13}H_{18}O_2NCl \cdot HCl$	4.79	4.72	12.14	12.10	0	0.4	>1000	120
$-CH_2CH_2NHCH_2CH(CH_3)_2$	2-Cl	H	III	141–142[b]	$C_{13}H_{18}O_2NCl \cdot HCl$	4.79	4.82	12.14	12.22	0	1.5	>1000	75
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	2-Cl	H	III	181–183[a]	$C_{13}H_{18}O_2NCl \cdot HCl$	4.79	4.67	12.14	11.99	0	1.2	>1000	91
$-CH_2CH_2NHC_6H_{11}$(cyclo)	2-Cl	H	III	203–205[c]	$C_{15}H_{20}O_2NCl \cdot HCl$	4.40	4.31	11.14	11.34	0.3	1.2	>1000	98
$-CH(CH_3)CH_2NHC_6H_{11}$(cyclo)	2-Cl	H	III	174–175[d]	$C_{16}H_{22}O_2NCl \cdot HCl$	4.22	4.16	10.67	10.62	1.7	1.1	250	36
$-CH_2CH_2N(C_2H_5)_2$	3-Cl	4-Cl	II	178.5–180[e,g]	$C_{13}H_{17}O_2NCl_2 \cdot HCl$	4.28	4.24	10.85	11.04	0	0.6	840	84
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	3-Cl	4-Cl	III	180–182[a]	$C_{13}H_{17}O_2NCl_2 \cdot HCl$	4.28	4.28	10.85	10.97	0.3	0.8	510	120

[a] Recrystallized from 95% alcohol. [b] From alcohol–ether. [c] From 50% alcohol. [d] From water by adding HCl. [e] From ethyl acetate–alcohol. [f] E. R. Andrews, M. G. Van Campen and E. L. Schumann, THIS JOURNAL, **75**, 4003 (1953), report 126–127°. [g] Andrews, *et al.*, ref. *f*, report 172°.

TABLE II

HYDROCHLORIDES OF ESTERS OF SUBSTITUTED 4-NITROBENZOIC ACIDS: $2\text{-X-4-}NO_2C_6H_3COOR \cdot HCl$

R	X	Prepn.	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
$-CH_2CH(CH_3)N(C_2H_5)_2$	Cl	II	150.5–152.5[a]	$C_{14}H_{19}O_4N_2Cl \cdot HCl$	7.98	7.89
$-CH(CH_3)CH_2N(C_2H_5)_2$	Cl	II	145–148[b]	$C_{14}H_{19}O_4N_2Cl \cdot HCl$	7.98	7.78
$-CH_2CH_2CH_2N(C_2H_5)_2$	Cl	II	125–126[b]	$C_{14}H_{19}O_4N_2Cl \cdot HCl$	7.98	7.80
$-CH_2CH_2NHCH(CH_3)_2$	Cl	III	188–189[a]	$C_{12}H_{15}O_4N_2Cl \cdot HCl$	8.67	8.67
$-CH_2CH_2NHCH_2CH_2CH_2CH_3$	Cl	III	162–163.5[a]	$C_{13}H_{17}O_4N_2Cl \cdot HCl$	8.32	8.28
$-CH_2CH_2NHCH_2CH(CH_3)_2$	Cl	III	172–174[a]	$C_{13}H_{17}O_4N_2Cl \cdot HCl$	8.32	8.14
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	Cl	III	160–161[a]	$C_{13}H_{17}O_4N_2Cl \cdot HCl$	8.32	8.12
$-CH_2CH_2NHC(CH_3)_3$	Cl	III	190–192[a]	$C_{13}H_{17}O_4N_2Cl \cdot HCl$	8.32	8.19
$-CH_2CH_2NHCH(C_2H_5)_2$	Cl	III	162–164[a]	$C_{14}H_{19}O_4N_2Cl \cdot HCl$	7.98	7.98
$-CH_2CH_2CH_2NHCH_2CH_2CH_2CH_3$	Cl	III	140–141[a]	$C_{14}H_{19}O_4N_2Cl \cdot HCl$	7.98	7.92
$-CH_2CH_2CH_2NHCH(CH_3)CH_2CH_3$	Cl	III	160–163[a]	$C_{14}H_{19}O_4N_2Cl \cdot HCl$	7.98	7.78
$-CH_2CH_2NHC_6H_{11}$(cyclo)	Cl	III	177–178[a]	$C_{15}H_{19}O_4N_2Cl \cdot HCl$	7.72	7.43
$-CH_2CH(CH_3)NHC_6H_{11}$(cyclo)	Cl	III	179–180.5[a]	$C_{16}H_{21}O_4N_2Cl \cdot HCl$	7.43	7.24
$-CH(CH_3)CH_2NHC_6H_{11}$(cyclo)	Cl	III	171–172.5[a]	$C_{16}H_{21}O_4N_2Cl \cdot HCl$	7.43	7.38
$-CH_2CH_2CH_2NHC_6H_{11}$(cyclo)	Cl	III	182.5–184[a]	$C_{16}H_{21}O_4N_2Cl \cdot HCl$	7.43	7.28
$-CH(C_6H_5)CH_2NHC_6H_{11}$(cyclo)	Cl	III	196–198[a]	$C_{21}H_{23}O_4N_2Cl \cdot HCl$	6.38	6.21
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	Br	III	157–158[a]	$C_{13}H_{17}O_4N_2Br \cdot HCl$	7.34	7.26
$-CH_2CH_2N(C_2H_5)_2$	NO_2	II	137–139[b]	$C_{13}H_{17}O_6N_3 \cdot HCl$	12.10	12.20

[a] Recrystallized from alcohol. [b] From alcohol–ether.

cially outstanding was the *sec*-butylaminoethyl 4-amino-2-chlorobenzoate which is at least four times as active as procaine and not significantly more toxic when tested by subcutaneous administration in mice.

In Table IV are given the data on benzoic acid esters with halogen and amino substitutions in other than the 2- and 4-positions, respectively. Physical and analytical constants on the corresponding nitro compounds are also included. Although some of these compounds showed good local anesthetic activity, the pharmacological properties as a whole were not satisfactory.

Experimental

All melting points are corrected.

2-*t*-Butylaminoethanol.—A mixture of 37 g. of *t*-butylamine, 22 g. of ethylene oxide and 2 ml. of methanol was kept in the refrigerator for three days, then fractionated by distillation and the portion boiling at 176–177° (uncor.) taken (6.5 g.).

Anal. Calcd. for $C_6H_{15}ON$: N, 11.97. Found: N, 11.74.

TABLE III: SALTS OF ESTERS OF SUBSTITUTED BENZOIC ACIDS: 2-Y-4-R'NHC$_6$H$_3$COOR·HX

R	R'	Y	Prepn.	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Local anesthetic activity Topical × cocaine	Local anesthetic activity Intradermal × procaine	LD$_{50}$(mg./kg.) Subcutaneous	LD$_{50}$(mg./kg.) Intravenous
$-CH_2CH(CH_3)N(C_2H_5)_2$	H	Cl	IV	156.5–157.5[a]	$C_{14}H_{21}O_2N_2Cl\cdot HCl$	8.73	8.72	1.1	2.2	240	44
$-CH(CH_3)CH_2N(C_2H_5)_2$	H	Cl	IV	156–157[b]	$C_{14}H_{21}O_2N_2Cl\cdot HCl$	8.73	8.65	1.3	3.1	220	55
$-CH_2CH_2CH_2N(C_2H_5)_2$	H	Cl	IV	198.5–199.5[b,e]	$C_{14}H_{21}O_2N_2Cl\cdot HCl$			2.9	2.5	205	50
$-CH_2CH_2NHCH(CH_3)_2$	H	Cl	IV	163–165[b]	$C_{12}H_{17}O_2N_2Cl\cdot HCO_2H$	9.26	9.15	0.9	1.0	>900	84
$-CH_2CH_2NHCH_2CH_2CH_2CH_3$	H	Cl	IV	161–163[b]	$C_{13}H_{19}O_2N_2Cl\cdot HCl$	9.12	9.20	0.9	6.0	320	47
$-CH_2CH_2NHCH_2CH(CH_3)_2$	H	Cl	IV	215–217[b]	$C_{13}H_{19}O_2N_2Cl\cdot HCl$	9.12	9.10	1.3	4.4	260	50
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	H	Cl	IV	195.5–197[b]	$C_{13}H_{19}O_2N_2Cl\cdot HCl$	9.12	9.02	2.6	4.1	570	45
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	H	Cl	IV	152–152.5[b]	$C_{13}H_{19}O_2N_2Cl\cdot HCO_2H$	8.85	8.68	2.3	4.9	670	46
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	H	Cl	IV	192–194[b]	$C_{13}H_{19}O_2N_2Cl\cdot {}^1/_2C_2H_4(CO_2H)_2$	8.51	8.50	...	4.9	...	..
$-CH_2CH_2NHC(CH_3)_3$	H	Cl	IV	270 dec.[b]	$C_{13}H_{19}O_2N_2Cl\cdot HCl$	9.12	8.98	1.0	1.0	750	63
$-CH_2CH_2NHCH(C_2H_5)_2$	H	Cl	IV	145–146.5[b]	$C_{14}H_{21}O_2N_2Cl\cdot HCO_2H$	8.48	8.38	1.9	1.3	740	37
$-CH_2CH_2CH_2NHCH_2CH_2CH_2CH_3$	H	Cl	IV	168–170[b]	$C_{14}H_{21}O_2N_2Cl\cdot HCl$	8.73	8.68	1.8	3.1	140	23
$-CH_2CH_2CH_2NHCH(CH_3)CH_2CH_3$	H	Cl	IV	208–209.5[b]	$C_{14}H_{21}O_2N_2Cl\cdot HCl$	8.73	8.75	2.7	1.4	220	29
$-CH_2CH_2NHC_6H_{11}$(cyclo)	H	Cl	IV	224.5–226[b]	$C_{15}H_{21}O_2N_2Cl\cdot HCl$	8.41	8.31	2.4	3.1	280	29
$-CH_2CH(CH_3)NHC_6H_{11}$(cyclo)	H	Cl	IV	162.5–164[b]	$C_{16}H_{23}O_2N_2Cl\cdot HCO_2H$	7.85	7.68	3.0	2.1	330	24
$-CH(CH_3)CH_2NHC_6H_{11}$(cyclo)	H	Cl	IV	159–161[b]	$C_{16}H_{23}O_2N_2Cl\cdot HCl$	8.06	8.10	3.4	3.1	57	17
$-CH_2CH_2CH_2NHC_6H_{11}$(cyclo)	H	Cl	IV	188.5–189.5[e]	$C_{16}H_{23}O_2N_2Cl\cdot HCl$	8.06	8.02	2.2	3.4	120	17
$-CH(C_6H_5)CH_2NHC_6H_{11}$(cyclo)	H	Cl	IV	239–241 dec.[b]	$C_{21}H_{25}O_2N_2Cl\cdot HCl$	6.85	6.98	..	..	..	..
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	H	Br	IV	202–204[b]	$C_{13}H_{19}O_2N_2Br\cdot HCl$	7.97	8.03	2.5	2.7	450	43
$-CH_2CH_2N(C_2H_5)_2$	H	NO_2	I	177–179[b]	$C_{13}H_{19}O_4N_3\cdot HCl$	13.22	12.95	0.2	1.4	850	130
$-CH_2CH(CH_3)N(C_2H_5)_2$	H	NO_2	I	182–185[b]	$C_{14}H_{21}O_4N_3\cdot HCl$	12.69	12.48	0	1.5	800	71
$-CH_2CH_2CH_2N(C_2H_5)_2$	H	NO_2	I	221–223[b]	$C_{14}H_{21}O_4N_3\cdot HCl$	12.69	12.58	0.5	1.0	430	49
$-CH_2CH_2N(CH_3)_2$	n-C_4H_9	Cl	I	84–86[a]	$C_{15}H_{23}O_2N_2Cl\cdot HCl\cdot H_2O$[d]	7.94	7.99	0.1[g]	1.9	1000	72
$-CH_2CH_2N(CH_3)_2$	n-C_4H_9	Cl	I	167–170 dec.[b]	$C_{15}H_{23}O_2N_2Cl\cdot 2HCl$	7.54	7.54	..	..	...	..
$-CH_2CH_2N(C_2H_5)_2$	n-C_4H_9	Cl	I	151–154[b]	$C_{17}H_{27}O_2N_2Cl\cdot 2HCl$	7.01	6.94	..	..	...	..
$-CH_2CH_2N(C_2H_5)_2$	HO	NO_2	[f]	170–172[b]	$C_{13}H_{19}O_5N_3\cdot HCl$	12.60	12.65	0	0.5	790	55

[a] Recrystallized from alcohol–ethyl acetate. [b] From alcohol. [c] From alcohol–ether. [d] Calcd.: C, 51.05; H, 7.42; Cl, 20.10. Found: C, 51.03; H, 7.63; Cl, 20.25. A crystalline, dehydrated compound could not be obtained. [e] Ruben, *et al.*, reference 2, report 197–198°. [f] Experimental section. [g] × tetracaine.

TABLE IV: SALTS OF ALKANOLAMINE ESTERS OF SUBSTITUTED BENZOIC ACIDS

(Di)alkylaminoalkyl moiety	Ring substituents	Prepn.	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Local anesthetic activity Topical × cocaine	Local anesthetic activity Intradermal × procaine	Toxicity LD$_{50}$(mg./kg.) Subcutaneous	Toxicity LD$_{50}$(mg./kg.) Intravenous
$-CH_2CH_2N(C_2H_5)_2$	2-Cl-5-NO_2	II	197–198[a]	$C_{13}H_{17}O_4N_2Cl\cdot HCl$	8.32	8.19				
$-CH_2CH_2N(C_2H_5)_2$	2-Cl-5-NH_2	IV	152.5–154.5[b]	$C_{13}H_{19}O_2N_2Cl\cdot HCl$	9.12	9.21	0	0.6	>1200	110
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	2-Cl-5-NO_2	III	158.5–159.5[a]	$C_{13}H_{17}O_4N_2Cl\cdot HCl$	8.32	8.18				
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	2-Cl-5-NH_2	IV	121–123[b]	$C_{13}H_{19}O_2N_2Cl\cdot HCl$	9.12	9.13	0	2.0	>1200	75
$-CH_2CH_2N(C_2H_5)_2$	3-Cl-4-NH_2	I	148–150[d,e]	$C_{13}H_{19}O_2N_2Cl\cdot HCl$			1.2	0.7	>450	45
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	3-Cl-4-NO_2	III	174–175[a]	$C_{13}H_{17}O_4N_2Cl\cdot HCl$	8.32	8.24				
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	3-Cl-4-NH_2	IV	108–109[c]	$C_{13}H_{19}O_2N_2Cl\cdot HCO_2H$	8.85	8.74	0.8	1.5	490	45
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	4-Cl-3-NO_2	III	185–187[a]	$C_{13}H_{17}O_4N_2Cl\cdot HCl$	8.32	8.32				
$-CH_2CH_2NHCH(CH_3)CH_2CH_3$	4-Cl-3-NH_2	IV	179–180.5[a]	$C_{13}H_{19}O_2N_2Cl\cdot HCl$	9.12	9.04	0.3	2.0	570	68
$-CH_2CH_2N(C_2H_5)_2$	2,6-diCl-4-NO_2	I	170–171[a]	$C_{13}H_{16}O_4N_2Cl_2\cdot HCl$	7.54	7.48				
$-CH_2CH_2N(C_2H_5)_2$	2,6-diCl-4-NH_2	IV	154–155.5[d]	$C_{13}H_{18}O_2N_2Cl_2\cdot HCl$	8.20	8.13	2.8	3.5	130	31
$-CH_2CH_2N(C_2H_5)_2$	3,5-diCl-4-NH_2	I	237–238[a,f]	$C_{13}H_{18}O_2N_2Cl_2\cdot HCl$	8.20	8.15	0.7	2.0	290	44

[a] Recrystallized from alcohol. [b] From 2-propanol. [c] From alcohol–ether. [d] From alcohol–ethyl acetate. [e] Rubin, *et al.*, reference 2, report 149–150°. [f] No physical constants were given in the report by J. Frejka and J. Pirkl, *Czechoslov. farm.*, **1**, 309 (1952); *C. A.*, **46**, 11583 (1952).

The picrate from water melted at 159–160°; Holmen and Carroll[9] report 156–157°.

4-*n*-Butylamino-2-chlorobenzoic Acid.—A mixture of 34.3 g. of 4-amino-2-chlorobenzoic acid, 30 g. of 1-bromobutane and 13.2 g. of potassium hydroxide in 250 ml. of 75% alcohol was refluxed overnight. An additional portion of 13.2 g. of potassium hydroxide and 30 g. of 1-bromobutane was added and refluxing continued for eight hours. The solution was then concentrated *in vacuo*, poured into 200 ml. of water, made basic with potassium hydroxide and extracted with ether. Acidification of the aqueous portion gave 20 g. of solid which was extracted with 3 l. of boiling water and allowed to crystallize and the procedure repeated with the mother liquor. The crystals so obtained were recrystallized from 95% alcohol three times, leaving 7.5 g. of 4-*n*-butylamino-2-chlorobenzoic acid, white crystals, m.p. 112–114°.

Anal. Calcd. for $C_{11}H_{14}O_2NCl$: N, 6.16. Found: N, 6.04.

The residue from the water extraction solidified. It was recrystallized twice from absolute alcohol to give 4-di-*n*-butylamino-2-chlorobenzoic acid, white crystals, m.p. 127–129°.

Anal. Calcd. for $C_{15}H_{22}O_2NCl$: N, 4.94; Cl, 12.49. Found: N, 4.86; Cl, 12.58.

2,6-Dichloro-4-nitrobenzoic Acid.—Twelve grams of purified 2,6-dichloro-4-nitrotoluene was dissolved in 50 ml. of pyridine and 40 ml. of water. The mixture was brought to the boiling point and 4.3 g. of potassium permanganate was added. Five additional portions of 4.3 g. were used after the permanganate was consumed. Following the removal of the manganese dioxide, the filtrate was concentrated *in vacuo* to one-fourth its volume. Addition of concentrated HCl precipitated an oil which solidified. Treatment with aqueous sodium hydroxide served to separate 6 g. of unreacted material. After reacidification 2 g. of yellow crystals was obtained. Repeated recrystallization from water and drying gave crystals which sintered at 157°, then melted at 172–174°.

Anal. Calcd. for $C_7H_3O_4NCl_2$: N, 5.93. Found: N, 5.93.

In attempting to prepare 2-diethylaminoethyl 4-amino-2,6-dichlorobenzoate by procedure II, 7 g. of 2,6-dichloro-4-nitrobenzoic acid was refluxed for four hours with 25 g. of thionyl chloride. The esterification with the crude acid chloride proceeded in poor yield. However, a portion of 2,6-dichloro-4-nitrobenzoic anhydride could be recovered from the solution. The yellow needles, from alcohol, melted at 190–191.5°.

Anal. Calcd. for $C_{14}H_4O_7N_2Cl_4$: N, 6.17. Found: N, 6.26.

4-Amino-2,6-dichlorobenzoic Acid.—Following the procedure of Kuhn,[7] 1.9 g. of 2,6-dichloro-4-nitrobenzoic acid and 1.5 g. of 5% palladium-on-charcoal were added to 60 ml. of methanol. Then with stirring, 1 g. of hydrazine hydrate in 5 ml. of methanol was added during five minutes. After standing over the weekend, the solution was filtered and concentrated to 10 ml. This was poured into 25 ml. of water and acidified. The product was twice crystallized from water, yielding 0.4 g. of cream-colored crystals, m.p. 178–179° dec.

Anal. Calcd. for $C_7H_5O_2NCl_2$: N, 6.80. Found: N, 6.45.

N-[2-(2-Chloro-4-nitrobenzoxy)-1-propyl]-N-cyclohexyl-2-chloro-4-nitrobenzamide.—In the preparation of 1-cyclohexylamino-2-propyl 2-chloro-4-nitrobenzoate by procedure III, the aminoalcohol was incompletely neutralized and the ester-amide was obtained as a by-product. The cream-colored solid, from chloroform–ether, melted at 156.5–158°.

Anal. Calcd. for $C_{23}H_{23}O_7N_3Cl_2$: N, 8.02. Found: N, 7.88.

2-Diethylaminoethyl 4-Hydroxylamino-2-nitrobenzoate Hydrochloride.—Six-tenths of a gram of 2-diethylaminoethyl 2,4-dinitrobenzoate hydrochloride in 20 ml. of alcohol and 1 ml. of 3 *N* ammonia was treated at room temperature for 30 minutes with hydrogen sulfide, filtered and the solution concentrated. Yellow needles, 0.2 g., crystallized from alcohol, m.p. 170–172°. The compound gave the Tollens test for the hydroxylamino group.

Anal. Calcd. for $C_{13}H_{19}O_5N_3 \cdot HCl$: N, 12.60. Found: N, 12.65.

Pharmacological.—Intradermal and topical anesthetic activities were measured on guinea pig wheal and rabbit cornea, respectively. Comparisons were made with procaine or cocaine, to each of which the value of unity was assigned. The acute toxicities were determined in albino mice.

NEWARK, N. J.

(9) R. E. Holmen and D. D. Carroll, THIS JOURNAL, **73**, 1859 (1951).

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Derivatives of Benzo[f]quinoline

BY F. F. BLICKE AND J. E. GEARIEN[1,2]

RECEIVED DECEMBER 15, 1953

The preparation of 2-methylbenzo[f]quinoline and of the β-diethylaminoethyl ester and the 2-(1-hydroxy)-propylamide of 1-hydroxybenzo[f]quinoline-2-carboxylic acid has been described.

A quantity of benzo(f)quinoline-2-carboxylic acid was desired for the preparation of substituted amides which were to be tested for oxytocic activity. It was expected that 2-bromobenzo(f)quinoline could be converted into the corresponding cyano derivative and that the latter could then be hydrolyzed to the desired acid. However, we could not obtain the bromo compound by the method described in the literature.[3] It was then decided to synthesize the unknown 2-methylbenzo(f)quinoline in the hope that this substance could be oxidized to the 2-carboxylic acid. 2-Naphthylamine (I) was condensed with diethyl methylmalonate (II) to form 2-methylbenzo(f)quinoline-1,3-dione (III). When a portion of III was oxidized with sodium hypobromite,[4] 2-amino-1-naphthoic acid (IV) was produced. This experiment proved that a benzo(f)quinoline, not a benzo(g)quinoline had been obtained; the latter substance would have yielded 3-amino-2-naphthoic acid on oxidation.

Compound III reacted with phosphorus oxychloride to form 1,3-dichloro-2-methylbenzo(f)-quinoline (V). Hydrogenation, in the presence of palladium, removed the nuclear chlorine atoms and 2-methylbenzo(f)quinoline (VI) was obtained.

(1) This paper represents part of a dissertation submitted by J. E. Gearien in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1949.

(2) Parke, Davis and Company Fellow.

(3) A. Claus and H. Besseler, *J. prakt. Chem.*, **57**, 60 (1898).

(4) We used this process since W. R. Vaughan (THIS JOURNAL, **68**, 324 (1946)) had shown that 2,4-dihydroxy-3-acetyl-7-chloroquinoline is oxidized by sodium hypobromite to 4-chloroanthranilic acid.