Summary

A series of compounds has been prepared by the addition of mercuric acetate and methyl alcohol to N-allyl amides. The high toxicity of these mercurials lessens their possible usefulness as diuretics.

MILWAUKEE 1, WISCONSIN RECEIVED JUNE 30, 1950

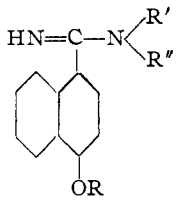
[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

N,N-Disubstituted Amidines. III. 4-Alkoxy-α-naphthamidines[1]

BY EMIL LORZ AND RICHARD BALTZLY

Physiological examination of the amidines previously reported from these laboratories[2] has shown that the type possesses considerable potency in topical anesthesia. This potency increases within certain limits with the size of the attached groups, N,N-di-*n*-butyl-α-naphthamidine being thrice as active as cocaine whereas the corresponding benzamidine is one-half as active. Alkoxyl substitution in the benzamidines increases potency and, except in the ortho-position, diminishes toxicity. It thus seemed probable that 4-alkoxy-α-naphthamidines, readily obtainable from the appropriate 4-alkoxy-α-naphthonitriles, would be powerful local anesthetics. In agreement with this hypothesis, N,N-di-*n*-butyl-4-methoxy-α-naphthamidine hydrochloride was found to have a potency about twenty-five times that of cocaine, as tested on the cornea of guinea pigs.

A considerable series of analogous and homologous amidines, representable by Formula A, was then prepared by the addition of the appropriate bromomagnesium dialkylamides to 4-alkoxy-α-naphthonitriles.



A

These compounds are listed in Table I, the numbering being consecutive with our earlier papers.[2] Only one 4-butoxyamidine, Compound LX (A, R = R′ = R″ = *n*-butyl) was prepared since this substance proved too irritant for testing. Except for LX and LIX (A, R = *n*-propyl; NR′R″ = 4-methylpiperazino) R was ethyl or methyl. In these main series the N,N-dialkyl amidines having N-alkyl groups of four to five carbon atoms consistently showed a high potency—more than twenty times that of cocaine. The diethyl- and diisopropylamidines (XXXVI and XXXVIII) were relatively impotent. The di-*n*-hexyl derivative (XLIV) produced a film on the eye and could not be assayed. Replacement of one N-alkyl group by benzyl or by an aryl group (Compounds XLV-XLIX, and LVI) had a rather erratic but not especially beneficial effect. Replacement of –NR′R″ by heterocyclic radicals gave compounds of lowered toxicity but of no great potency. Local anesthetic activity is indicated in Table I by +, ++ and +++. Compounds marked + are less than ten times as active as cocaine; those marked ++ are ten to twenty times as active and +++ indicates activity over twenty times that of cocaine.[3] The N,N-dialkylamidines were two to four times as toxic as cocaine. Substances marked T in Table I could not be tested because of local irritant action.

Electrometric titrations in 50% methanol[2b] were run on some representative compounds. The basicities (expressed as pK_a) were very close to those of benzamidines having similar substitutions although the N,N-dialkyl-α-naphthamidines appear slightly less basic than the corresponding benzamidines and the N-alkyl-N-aryl-α-naphthamidines slightly more basic. It is tempting to assign this latter phenomenon to steric inhibition of resonance (in the aniline moiety) but the deviations may not be significant. The dissociation constants are presented in Table II.

Experimental

The additions of bromomagnesium secondary amides to the appropriate nitriles were carried out by the methods described previously.[2] The yields and properties of the resultant amidines are shown in Table I, the methods of isolation (A, A′, B, etc.) referring to the procedures of our earlier papers.[2]

Nitriles.—Of the four nitriles employed, only 4-ethoxy-α-naphthonitrile has been reported previously.[4] All were prepared by a modification of the method of Newman[5] which consists of doubling the proportion of pyridine and halving the reflux time. Under these circumstances yields of 75–80% were obtained consistently whereas the original method gave very poor results—the yield of nitrile was poor and that of tars was large. The effect of the increased quantity of pyridine is to lower the reaction temperature. Examination of Newman's experimental details indicates that the exchange reaction with α-bromonaphthalene must require much less than 15 hours to reach completion (Newman records a 70% yield from α-chloronaphthalene after 6 hours) but α-naphthonitrile is not affected by the longer and more drastic treatment. Since there is no reason for suspecting exaltation of the activity of the bromine atom from the presence of a para alkoxyl group and since the nitrile func-

(1) The work here reported is part of a joint research carried out in collaboration with a pharmacological group in these laboratories.

(2) Lorz and Baltzly, THIS JOURNAL, (a) **70**, 1904 (1948); (b) **71**, 3992 (1949).

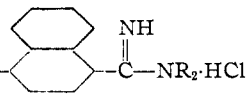
(3) Pharmacological results are to be published separately. Precise evaluation of activities, always difficult in animal experiments, is complicated in this series by the presence of very steep dose-response curves. Many of these amidines will produce anesthesia lasting several hours in 0.03% concentration (anesthesia from 1% cocaine is found to last 40–50 minutes in control experiments) but 0.02% solutions may produce no anesthesia at all. The general behavior of the amidines suggests that local anesthetic potency in this series is a function of partition coefficients and diffusion speeds in the penetration of the tissues rather than of the inherent properties of the compounds toward the nervous tissues. In agreement with this is the fact that as injection anesthetics the α-naphthamidines differ relatively little among themselves in potency and are not especially active.

(4) Karrer, Rebmann and Zeller, *Helv. Chim. Acta*, **3**, 261 (1920).

(5) Newman, THIS JOURNAL, **59**, 2472 (1937); *Org. Syntheses*, **21**, 89 (1941).

TABLE I

4-ALKOXY-α-NAPHTHAMIDINE HYDROCHLORIDES

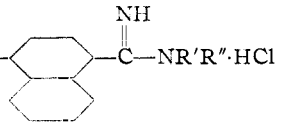


Compd. no.	X	NR₂	Meth. of isol.	Yield, %[a]	M. p., °C.[b]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Potency as local anes.
XXXVI	MeO	$-N(C_2H_5)_2$	A′	93	232	$C_{16}H_{21}ClN_2O$	65.63	65.40	7.23	7.32	+
XXXVII	MeO	$-N(C_3H_7)_2\ n$	A′	56	228	$C_{18}H_{25}ClN_2O$	67.39	67.55	7.80	7.42	++
XXXVIII	MeO	$-N(C_3H_7)_2\ i$	A′	50[c]	241	$C_{18}H_{25}ClN_2O$	67.39	67.63	7.80	7.66	+
XXXIX	MeO	$-N(C_4H_9)_2\ n$	C	83[c]	230	$C_{20}H_{29}ClN_2O$	68.87	69.18	8.32	8.38	+++
XL	MeO	$-N(C_4H_9)_2\ s$	A′	62	241	$C_{20}H_{29}ClN_2O$	68.87	69.20	8.32	8.22	+++
XLI	MeO	$-N(C_4H_9)_2\ i$	A′	89	238	$C_{20}H_{29}ClN_2O$	68.87	69.22	8.32	8.22	+++
XLII	MeO	$-N(C_5H_{11})_2\ n$	A′	53	206	$C_{22}H_{33}ClN_2O$	70.12	70.46	8.77	8.95	+++
XLIII	MeO	$-N(C_5H_{11})_2\ i$	A′	90	208	$C_{22}H_{33}ClN_2O$	70.12	70.38	8.77	8.54	+
XLIV	MeO	$-N(C_6H_{13})_2\ n$	B	60	183	$C_{24}H_{37}ClN_2O$	71.20	71.08	9.15	9.05	T
XLV	MeO	$-NEtC_6H_4CH_3\ o$	C	62	235	$C_{21}H_{23}ClN_2O$	71.09	70.99	6.49	6.40	+
XLVI	MeO	$-NEtC_6H_4CH_3\ m$	A′	5[d]	212	$C_{21}H_{23}ClN_2O$	71.09	71.19	6.49	6.26	++
XLVII	MeO	$-NEtC_6H_4CH_3\ p$	B′	50	226	$C_{21}H_{23}ClN_2O$	71.09	71.19	6.49	6.26	+++
XLVIII	MeO	$-NEtCH_2C_6H_5$	A′	60	232	$C_{21}H_{23}ClN_2O$	71.09	71.47	6.49	6.36	++
XLIX	MeO	$-N(n\text{-}C_4H_9)C_6H_4OCH_3\ p$	B′[e]	35	223	$C_{23}H_{27}ClN_2O_2$	69.26	68.96	6.87	6.60	++
L	EtO	$-N(C_3H_7)_2\ n$	C	85[c]	230	$C_{19}H_{27}ClN_2O$	68.16	68.37	8.07	7.94	++
LI	EtO	$-N(C_4H_9)_2\ n$	C	85	235	$C_{21}H_{31}ClN_2O$	69.52	69.37	8.55	8.62	+++
LII	EtO	$-N(C_4H_9)_2\ s$	A′[f]	68	245[g]	$C_{21}H_{31}ClN_2O$	69.52	69.70	8.55	8.27	+++
LIII	EtO	$-N(C_4H_9)_2\ i$	A′[f]	90	235[h]	$C_{21}H_{31}ClN_2O$	69.52	69.52	8.55	8.90	+++
LIV	EtO	$-N(C_5H_{11})_2\ n$	C[f]	60	234[i]	$C_{23}H_{35}ClN_2O$	70.68	70.50	8.96	8.96	++
LV	EtO	$-N(C_5H_{11})_2\ i$	A′	80	199	$C_{23}H_{35}ClN_2O$	70.68	70.65	8.96	8.53	+++
LVI	EtO	$-NEtCH_2C_6H_5$	C	56	228	$C_{22}H_{25}ClN_2O$	71.64	71.63	6.78	6.90	+++
LVII	EtO	$-N(CH_2CH_2)_2NCH_3$	[j]	41	246[k]	$C_{18}H_{25}Cl_2N_3O$	58.38	58.14	6.77	6.81	+
LVIII	EtO	$-N(CH_2CH_2)_2O$	[l]	50	222	$C_{17}H_{21}ClN_2O_2$	63.65	63.67	6.55	6.65	+
LIX	n-C_3H_7O	$-N(CH_2CH_2)_2NCH_3$	A′[f]	50	>250[k,m]	$C_{19}H_{27}Cl_2N_3O$	59.11	59.45	7.03	6.71	+++
LX	n-C_4H_9O	$-N(C_4H_9)_2\ n$	C	76	220	$C_{23}H_{35}ClN_2O$	70.68	70.51	8.96	8.66	T

[a] Yield calculated on amount of purified hydrochloride unless otherwise noted. [b] Melting points below 220° are corrected. [c] Yield of crude base. [d] 88% of the ethyl *m*-toluidine was recovered. [e] Purification was actually by a variation of the B′ procedure. The aqueous solution of the hydrochloride was successively neutralized with bicarbonate to *p*H 5, 6 and 8 and extracted with ether at each stage. The amidine base was removed by the extraction at *p*H 8. [f] These hydrochlorides could not be obtained analytically pure by the usual procedures. It was necessary to liberate the bases and distil them before pure hydrochlorides were secured. [g] The base distilled at 120° at 0.5 μ pressure. [h] The base distilled at 130° at 0.25 μ pressure. [i] The base distilled at 130–135° at 0.5 μ pressure. [j] The reaction mixture after hydrolysis with iced ammonium chloride solution was extracted with ether and the extract was washed repeatedly with water to remove methyl piperazine. The dihydrochloride was obtained by addition of ethanolic hydrogen chloride solution. [k] A dihydrochloride. [l] Isolation as in note *j*. Except that extraction was with benzene, the base being insoluble in ether. [m] The base distilled at 30–140° at 0.5 μ pressure.

TABLE II

ACID DISSOCIATION CONSTANTS OF α-NAPHTHAMIDINE HYDROCHLORIDES IN 50% METHANOL



X	R′	R″	pK_a	Compd. no.
H	n-C_4H_9	n-C_4H_9	10.96	IX
CH_3O	iso-C_3H_7	iso-C_3H_7	11.49	XXXVIII
CH_3O	n-C_4H_9	n-C_4H_9	11.33	XXXIX
CH_3O	C_2H_5	2-$CH_3C_6H_4$	10.80	XLV
CH_3O	C_2H_5	3-$CH_3C_6H_4$	10.64	XLVI
CH_3O	C_2H_5	4-$CH_3C_6H_4$	10.49	XVLII
CH_3O	n-C_4H_9	4-CH_3O-C_6H_4	10.54	XLIX
n-C_4H_9O	n-C_4H_9	n-C_4H_9	11.08	LX

tion ought itself to be less reactive through the presence of the para alkoxyl, it seems probable that the alkoxyl is labilized by the para-cyano group.

The necessary 4-alkoxy-1-bromonaphthalenes were prepared from the corresponding α-alkoxynaphthalenes by bromination in methanol solution; the yields were over 90%.

4-*n*-Propoxy-1-bromonaphthalene, b.p. 146–148° (1 mm.). *Anal.* Calcd. for $C_{13}H_{13}BrO$: C, 58.87; H, 4.91. Found: C, 59.40; H, 4.77.

4-*n*-Butoxy-1-bromonaphthalene, b.p. 185–186° (2 mm.).

4-Methoxy-α-naphthonitrile, needles from benzene; m.p. 104°. *Anal.* Calcd. for $C_{12}H_9NO$: C, 78.67; H, 4.95. Found: C, 78.96; H, 5.00.

This compound was also prepared by dehydration with acetic anhydride of the known 4-methoxy-α-naphthaldoxime.

4-*n*-Propoxy-α-naphthonitrile, colorless needles from ethyl acetate, m.p. 45°. *Anal.* Calcd. for $C_{14}H_{13}NO$: C, 79.62; H, 6.16. Found: C, 79.33; H, 5.97.

4-*n*-Butoxy-α-naphthonitrile is an oil, b.p., at 1.5 mm., 185–186°.

4-Methoxy-1-bromonaphthalene was chlorinated in carbon tetrachloride solution yielding **4-methoxy-3-chloro-1-bromonaphthalene**, m.p. 42°. *Anal.* Calcd. for $C_{10}H_{12}BrClO$: C, 50.44; H, 4.52. Found: C, 50.57; H, 4.58.

Attempts to convert this substance into 4-methoxy-3-chloro-α-naphthonitrile were unsuccessful. Attempts to brominate 4-methoxy-α-naphthamidines were also without useful result.

Secondary Amines.—Most of the secondary amines employed were redistilled from samples of commercial origin. All but one of the others are readily available by published procedures. The preparation of *n*-butyl-*p*-anisidine involved a new method that seems useful on a laboratory scale. The familiar Diepolder[6] reduction of nitrosamines by stannous chloride and hydrochloric acid, while eminently satisfactory in the preparation of most N-alkyl aniline derivatives gives poor results for secondary anisidines and phenetidines. The low yields (10–25%) are due to dealkylation during the reduction. In the present case the N-nitroso-N-*n*-butyl-*p*-anisidine, obtained by nitrosation of the bases from the reaction of *n*-butyl iodide with *p*-anisidine, was dissolved in methanol and hydrogenated with Raney nickel in a Burgess-Parr hydrogenator. The yield of

(6) Diepolder, *Ber.*, **32**, 3514 (1899).

N-*n*-butyl-*p*-anisidine was 56% based on the *p*-anisidine used. Adams platinum catalyst and palladized charcoal were inefficient for this reduction, both with and without added acetic acid.

Acknowledgment.—The authors wish to express their gratitude to Mr. Samuel Blackman for the micro-analyses here recorded.

Summary

1. A series of N,N-disubstituted 4-alkoxy-α-naphthamidines has been prepared.

2. Several of these amidines are local anesthetics of high potency.

TUCKAHOE 7, NEW YORK RECEIVED JUNE 16, 1950

[CONTRIBUTION FROM ABBOTT LABORATORIES]

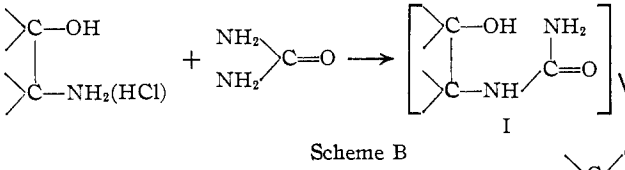
Anticonvulsant Drugs. IV. Some 2-Oxazolidones[1]

BY W. J. CLOSE

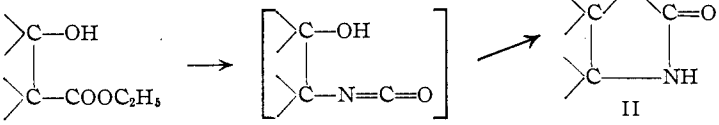
A few years ago it was discovered that certain 2,4-oxazolidinedione derivatives had anticonvulsant properties.[2] It seemed desirable, therefore, to undertake a study of the closely related 2-oxazolidones (II).

Several methods for the synthesis of 2-oxazolidones had been described prior to and during this investigation. The condensation of β-amino alcohols with ethyl carbonate in the presence of a basic catalyst[3] appeared to be the most generally useful procedure. It seemed likely, however, that the oxazolidones could be prepared more simply by heating β-amino alcohols or their hydrochlorides with urea (scheme A).[4] This method proved to be general and convenient, combining ease of manipulation with reasonable yields (generally 50–80%).

Scheme A



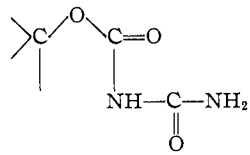
Scheme B



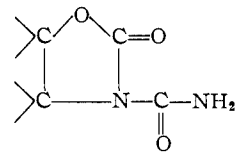
Although the mechanism of this conversion has not been definitely established, it is probable that the urea first breaks down to cyanic acid, which then attacks the basic group with the formation of the intermediate I. Finally, cyclization takes place with the elimination of ammonia. In one case selected for detailed study (5,5-dimethyl-2-oxazolidone) it was possible to isolate the intermediate I in good yield and to convert it to the oxazolidone by continued heating.

Where the requisite amino alcohols were not readily available, the oxazolidones were obtained directly from β-hydroxy esters by means of the Curtius reaction (scheme B), a synthetic method which has found occasional use by others.[5] Over-all yields from the ester were comparable to those obtained by the urea procedure.

During the course of the present work it was discovered that allophanic esters (III) exhibited anticonvulsant activity.[1] It was apparent that



III

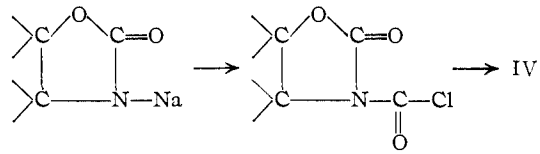


IV

similarly constituted molecules (IV) could be obtained by the introduction of a carbamyl group onto the nitrogen atom of the oxazolidones. A procedure was therefore developed whereby this type of compound could be obtained. The oxazolidone was converted to its sodio derivative, which was then treated with an excess of phosgene, followed by ammonia (scheme C). Over-all yields of 48–78% were obtained.

N-Alkyloxazolidones were obtained from the parent compounds by treatment of the sodio derivatives with alkyl halides or sulfates in an inert solvent. Alkylation could also be carried out in Cellosolve with the sodium alkoxide as a condensing agent. Alkylation in absolute alcohol with sodium ethoxide gave low yields.

Scheme C



Acetylation was accomplished by prolonged heating of the oxazolidones with acetic anhydride. Pyridine was used as a solvent and catalyst in acylation with higher acid radicals.

The oxazolidones were tested for anticonvulsant activity as described earlier[2] by Drs. R. K. Richards and G. M. Everett, to whom the author is indebted for the pharmacological data reported here

(1) Paper III in this series by Spielman, Barnes and Close, THIS JOURNAL, **72**, 2520 (1950). The present work was presented at the 117th Meeting of the A. C. S. at Philadelphia, April 11, 1950.

(2) Spielman and Everett, THIS JOURNAL, **70**, 1021 (1948); Everett and Richards, *J. Pharmacol.*, **81**, 402 (1944).

(3) Homeyer, U. S. Patents 2,399,188, 2,437,388, 2,437,389, 2,437,390.

(4) (a) Close, Tiffany and Spielman, THIS JOURNAL, **71**, 1265 (1949); (b) Stratton and Wilson, *J. Chem. Soc.*, 1133 (1932).

(5) Newman, THIS JOURNAL, **71**, 378 (1949); Ide and Baltzly, *ibid.*, **70**, 1084 (1948); Baltzly and Buck, *ibid.*, **62**, 164 (1940); Schroeter, German Patent 220,852.