Scientific Edition

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

A. G. DuMez, Editor, Baltimore, Maryland

Volume XXIX *JUNE, 1940* Number 6 Consecutive No. 11

Local Anesthetic Action of Some Aminonaphthoic Acid Esters

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For a number of years pharmacological work has been in progress in our laboratory on a series of esters of aminonaphthoic acids. These compounds have been prepared and the chemical data reported by Blicke and Parke (1). Very little can be found in the literature about the action of derivatives of naphthoic acid. Fisk and Underhill (2) have reported on the anesthetic action of esters of α- and β-naphthoic acid and also certain alkoxynaphthoic acids prepared by Hill and co-workers. In addition, when work in this laboratory already had been in progress for some time, two Russian chemists (3) described four esters of 4-amino-1-naphthoic acid and reported them to have marked local anesthetic action.

The naphthyl analog of procaine, namely, the diethylaminoethyl ester of 4-amino-1-naphthoic acid, as the hydrochloride ($C_{17}H_{22}O_2N_2.HCl$) was the first to be investigated in this laboratory and proved to have several desirable properties. It will be designated hereafter as Naphthocaine 4*A*.

EXPERIMENTAL

The two methods used chiefly for determining local anesthetic efficiency were the rabbit cornea and the frog sensory nerve as proposed by Sollmann (4) but the human wheal method was used in a few instances (5). Toxicity was determined by intraperitoneal injection into white mice and usually only three animals were used for the critical dose since great accuracy involving the use of large groups was not essential. Many other comparative effects with cocaine and procaine were determined on various animals and by a large number of methods.

In Table I are given the chemical names and formulas of the series of compounds investigated in comparison with cocaine and procaine. These are called naphthocaines and the symbol is given by which they are designated throughout this article.

The monohydrochlorides of these esters were all soluble in distilled water to at least 0.5% but it was found that the sulfamate ($NH_2.SO_3H$) salts were more soluble, so a few compounds were prepared and tested in that form also.

In Table II is given the comparative toxicity of these compounds when injected into white mice intrapertioneally as well as miscellaneous effects such as local irritant action, blood pressure action, etc. Large groups of mice were not used at the critical dose but the M. L. D. killed 3 out of 5 or at least 2 out of 3.

DISCUSSION

About half of these compounds show no appreciable local irritant action in concen-

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Table I.—Names and Symbols of Naphthocaines

Chemical Name	Formula as HCl	Symbol
Esters of 3-amino-1-naphthoic acid		
1. Beta-diethylaminoethyl	$C_{17}H_{22}O_2N_2.HCl$	3*A*
2. Beta di-*n*-butylaminoethyl	$C_{21}H_{30}O_2N_2.HCl$	3*B*
3. Beta diethylaminopropyl	$C_{18}H_{24}O_2N_2.HCl$	3*C*
4. Beta di-*n*-butylaminopropyl	$C_{22}H_{32}O_2N_2.HCl$	3*D*
5. Gamma diethylaminopropyl	$C_{18}H_{24}O_2N_2.HCl$	3*E*
6. Gamma di-*n*-butylaminopropyl	$C_{22}H_{32}O_2N_2.HCl$	3*F*
7. Beta, beta dimethyl γ-dimethylaminopropyl	$C_{18}H_{24}O_2N_2.HCl$	3*I*
Esters of 4-amino-1-naphthoic acid		
1. Beta diethylaminoethyl	$C_{17}H_{22}O_2N_2.HCl$	4*A*
2. Beta di-*n*-butylaminoethyl	$C_{21}H_{30}O_2N_2.HCl$	4*B*
3. Beta diethylaminopropyl	$C_{18}H_{24}O_2N_2.HCl$	4*C*
4. Beta di-*n*-butylaminopropyl	$C_{22}H_{32}O_2N_2.HCl$	4*D*
5. Gamma diethylaminopropyl	$C_{18}H_{24}O_2N_2.HCl$	4*E*
6. Gamma di-*n*-butylaminopropyl	$C_{22}H_{32}O_2N_2.HCl$	4*F*
7. Beta, beta dimethyl γ-dimethylaminopropyl	$C_{18}H_{24}O_2N_2.HCl$	4*I*
8. Beta, beta dimethyl γ-diethylaminopropyl	$C_{20}H_{28}O_2N_2.HCl$	4*J*
Esters of 5-amino-1-naphthoic acid		
1. Beta-diethylaminoethyl	$C_{17}H_{22}O_2N_2.HCl$	5*A*
2. Beta di-*n*-butylaminoethyl	$C_{21}H_{30}O_2N_2.HCl$	5*B*
3. Beta diethylaminopropyl	$C_{18}H_{24}O_2N_2.HCl$	5*C*
4. Beta di-*n*-butylaminopropyl	$C_{22}H_{32}O_2N_2.HCl$	5*D*
5. Gamma diethylaminopropyl	$C_{18}H_{24}O_2N_2.HCl$	5*E*
6. Gamma di-*n*-butylaminopropyl	$C_{22}H_{32}O_2N_2.HCl$	5*F*
Ester of 6-amino-1-naphthoic acid		
1. Beta diethylaminoethyl	$C_{17}H_{22}O_2N_2.HCl$	6*A*
Control Compounds		
1. Diethylaminoethyl-*p*-aminobenzoate	$C_{13}H_{20}O_2N_2.HCl$	Procaine
2. Methylbenzoylecgonine	$C_{17}H_{21}O_4N.HCl$	Cocaine
3. 4-Nitro naphthocaine HCl	$C_{17}H_{20}O_4N_2.HCl$	4-Nitro

Table II.—Comparative Toxicity and Other Effects of Compounds Tested

	Product	M. L. D., mg. per Gm.	Irritation	Blood Pressure Action	
1.	3*A*	0.30	Some in 0.5% Sol.	Transient depressor	1% 3 cc.
2.	3*B*	0.15	None in 0.2% Sol.	Very slight depressor	1% 2 cc.
3.	3*C*	0.22	Some in 0.1% Sol.	Slight depressor	1% 2 cc.
4.	3*D*	0.35	Serious in 0.05% Sol.	Slight pressor	1% 2 cc.
5.	3*E*	0.18	None in 0.3% Sol.	No effect	1% 3 cc.
6.	3*F*	0.18	None in 0.1% Sol.	Transient depressor	1% 3 cc.
7.	3*I*	0.25	Some in 0.25% Sol.	Slight depressor	1% 3 cc.
8.	4*A*	0.15	None in 0.5% Sol.	Transient depressor	1% 2 cc.
9.	4*B*	0.18	Serious in 0.5% Sol.	Very slight depressor	1% 3 cc.
10.	4*C*	0.09	Some in 0.5% Sol.	Some depressor	1% 2 cc.
11.	4*D*	0.18	Serious in 0.5% Sol.	Slight depressor	0.5% 6 cc.
12.	4*E*	0.10	Slight in 0.5% Sol.	Slight depressor	1% 2 cc.
13.	4*F*	0.11	None in 0.1% Sol.	Transient depressor	1% 3 cc.
14.	4*I*	0.18	None in 0.25% Sol.	Slight depressor	1% 2 cc.
15.	4*J*	0.15	None in 0.25% Sol.	Some depressor	1% 3 cc.
16.	5*A*	0.35	Some in 0.25% Sol.	Some depressor	1% 3 cc.
17.	5*B*	0.35	Some in 0.20% Sol.	Slight depressor	1% 3 cc.
18.	5*C*	0.18	None in 0.5% Sol.	Some pressor	1% 3 cc.
19.	5*D*	0.80	None in 0.5% Sol.	Very slight depressor	1% 1 cc.
20.	5*E*	0.18	None in 0.25% Sol.	Very slight depressor	1% 1 cc.
21.	5*F*	0.20	Some in 0.5% Sol.	More lasting depressor	1% 2 cc.
22.	6*A*	0.40	None in 0.25% Sol.	Slight depressor	1% 3 cc.
23.	4*A* as sulfamate	0.15	None in 0.5% Sol.	Transient depressor	1% 3 cc.
24.	Procaine	0.45	None in 0.5% Sol.	Transient depressor	2%
25.	Cocaine	0.10	None in 0.5% Sol.	Transient pressor	1%
26.	4-Nitro	0.30	Some in 0.1% Sol.	Slight depressor	1%

trations up to 0.5% which makes them compare favorably in this respect with both cocaine and procaine. Nearly all of the series produce a moderate and transient depressor effect upon the blood pressure of a chloretonized dog with doses of 1 to 3 cc. of a 1% solution. This is similar to the effect of procaine but cocaine causes a transient pressor action.

From the toxicity standpoint three compounds 4*C*, 4*E* and 4*F* are as toxic as cocaine; 16 compounds, namely 3*A*, 3*B*, 3*C*,

3*E*, 3*F*, 3*I*, 4*A*, 4*B*, 4*D*, 4*I*, 4*J*, 5*C*, 5*E*, 5*F*, 4*A* sulfamate and 4-nitro have M. L. D.'s from 0.15 mg. to 0.30 mg. per Gm. and are consequently less toxic than cocaine but more toxic than procaine; 5 compounds, namely, 3*D*, 5*A*, 5*B*, 5*D* and 6*A* have M. L. D.'s from 0.35 mg. to 0.80 mg. per Gm. and are therefore comparable to procaine in toxicity.

As for local anesthetic efficiency (from data in Table III) nearly all of the compounds are quite effective by the rabbit cornea method (mucous membrane penetration) although 5*D* was a notable exception (no effect with a 1% solution) and 3*A*, 3*I*, 5*A*, 5*C* are relatively weak. 4-Nitro is similar to cocaine by this method but is much too irritating. All the others proved stronger than cocaine by this method and cocaine is noted for its rapid and powerful local anesthetic action on mucous membranes.

By the frog sensory nerve method (to show local anesthesia by injection) 5*D* is again ineffective in 1% solution while 3*B*, 3*C*, 3*D*, 3*E*, 3*I*, 4*B*, 5*B*, 5*E*, 5*F* and 4-nitro are less effective than procaine or cocaine and 3*A*, 3*F*, 4*A*, 4*C*, 4*D*, 4*E*, 4*F*, 4*I*, 4*J*, 5*A*, 5*C*, 6*A* are fully as effective as cocaine by this method.

Only a few of the most promising compounds were tested by the human wheal or intradermal method. 3*A* was found to be less active than procaine by this method while 4*A* as the monohydrochloride and as the sulfamate was found to be fully as active as procaine.

Of all the compounds examined 4*A* was definitely the most promising when judged by its comparative local anesthetic action; its freedom from local irritant action and the fact that it is only two-thirds as toxic as cocaine. It is also effective when given intraspinally as shown by a few tests upon rabbits and dogs. In producing anesthesia by injection it appeared to be fully as active as cocaine by the accepted methods and for mucous membranes it seemed to be definitely more powerful than cocaine, the pharmacological data obtained indicating that it is three times as active as this valuable local anesthetic.

The nitro compound from which this powerful ester is obtained chemically was found to be definitely less active—not over one-fifth as active by the frog sensory nerve method and not over one-third by the rabbit cornea method.

The stability of the 4*A* ester in solution is quite good since a 0.1% solution without any preservative showed no appreciable loss in activity after two months at room temperature in a clear glass container.

Table III.—Local Anesthetic Efficiency of Compounds Tested

	Product	Frog Sensory Nerve	Rabbit Cornea	Human Intradermal
1.	3*A*	1.0% = 2 minutes	1.0% = 20 minutes	0.4% = 20 minutes
		0.6% = 3 minutes	0.75% = 12 minutes	0.2% = 10 minutes
		0.4% = 5 minutes	0.5% = 6 minutes	
2.	3*B*	2.0% = 4 minutes	0.2% = 60 minutes	.....
		1.5% = 5 minutes	0.1% = 25 minutes	
		1.0% = 9 minutes	0.05% = No effect	
3.	3*C*	1.0% = 4 minutes	0.5% = 20 minutes	.....
		0.5% = 7 minutes	0.25% = 12 minutse	
			0.10% = 5 minutes	
4.	3*D*	0.8% = 10 minutes	0.05% = 5–10 min.	.....
5.	3*E*	4.0% = 5 minutes	0.3% = 25 minutes	.....
		3.0% = 6 minutes	0.2% = 20 minutes	
		2.0% = 7 minutes	0.1% = 15 minutes	
6.	3*F*	1.0% = 3 minutes	0.05% = 50 minutes	.....
		0.5% = 5 minutes	0.04% = 30 minutes	
		0.25% = 9 minutes	0.03% = 10 minutes	
7.	3*I*	0.8% = 6 minutes	0.5% = 15 minutes	.....
		0.5% = 8 minutes	0.25% = 5 minutes	
		0.4% = 10 minutes		
8.	4*A*	0.5% = 1.8 minutes	0.5% = 45 minutes	0.20% = 20 minutes
		0.25% = 4 minutes	0.15% = 30 minutes	0.10% = 15 minutes
		0.10% = 7 minutes	0.10% = 12 minutes	
			0.05% = 6 minutes	
9.	4*B*	0.5% = 10–12 min.	0.10% = 60 minutes	.....
		0.4% = Over 15 min.	0.05% = 20 minutse	
10.	4*C*	1.0% = 4 minutes	0.10% = 35 minutes	.....
		0.5% = 6 minutes	0.05% = 20 minutes	
		0.25% = 8 minutes	0.025% = 5 minutes	

Table III (*Continued*)

	Product	Frog Sensory Nerve	Rabbit Cornea	Human Intraderma
11.	4*D*	1.0% = 3 minutes	0.10% = 60 minutes	.....
		0.5% = 5 minutes	0.05% = 30 minutes	
		0.25% = 8 minutes	0.02% = 10 minutes	
12.	4*E*	1.0% = 2 minutes	0.2% = 50 minutes	.....
		0.5% = 4 minutes	0.1% = 25 minutes	
		0.25% = 6 minutes	0.05% = No effect	
13.	4*F*	0.5% = 4 minutes	0.05% = 45 minutes	.....
		0.25% = 6 minutes	0.04% = 25 minutes	
		0.15% = 12 minutes		
14.	4*I*	1.0% = 3 minutes	0.10% = 30 minutes	.....
		0.5% = 6 minutes	0.05% = 15 minutes	
		0.25% × 9 minutes	0.025% = 5 minutes	
15.	4*J*	1.0% = 4 minutes	0.10% = 45 minutes	.....
		0.5% = 6 minutes	0.05% = 25 minutes	
		0.25% = 8 minutes	0.025% = Slight	
16.	5*A*	0.5% = 3 minutes	0.5% = 10 minutes	.....
		0.2% = 6 minutes	0.25% = 4 minutes	
		0.1% = 11 minutes		.....
17.	5*B*	2.0% = 5 minutes	0.5% = 30 minutes	
		1.0% = 15 minutes	0.25% = 20 minutes	
			0.10% = 5 minutes	
18.	5*C*	0.5% = 2 minutes	0.5% = 12 minutes	.....
		0.2% = 7 minutes	0.25% = 4 minutes	
		0.1% = 9 minutes		
19.	5*D*	1.0% = No effect	1.0% = No effect	.....
20.	5*E*	0.8% = 4 minutes	0.5% = 40 minutes	.....
		0.5% = 5 minutes	0.25% = 10 minutes	
		0.25% = 8 minutes	0.10% = 5 minutes	
21.	5*F*	2.0% = 4 minutes	0.25% = 25 minutes	.....
		1.0% = 7 minutes	0.15% = 15 minutes	
		0.5% = 10 minutes	0.10% = 9 minutes	
22.	6*A*	0.5% = 3 minutes	0.5% = 30 minutes	.....
		0.25% = 6 minutes	0.25% = 8 minutes	
		0.15% = 8 minutes		
23.	4*A*	1.0% = 2 minutes	0.5% = 45 minutes	0.10% = 15 minutes
	Sulfamate	0.5% = 4 minutes	0.2% = 30 minutes	0.05% = 8 to 10 min-
		0.25% = 6 minutes	0.1% = 20 minutes	utes
			0.05% = 10 minutes	
24.	Procaine	1.0% = 3 minutes	2.0% = 20 minutes	0.10% = 15 minutes
		0.5% = 5.5 minutes	1.0% = 15 minutes	
		0.5% = 11 minutes	0.5% = About 3 min.	
25.	Cocaine	0.5% = 2.5 minutes	0.5% = 16 minutes	0.05% = 15 minutes
		0.25% = 9 minutes	0.25% = 10 minutes	
		0.10% = 14 minutes	0.10% = Negative	
26.	4-Nitro	2.0% = 5.5 minutes	0.5% = Too irritating	.....
		1.0% = 8 minutes	0.25% = 10 minutes	
		0.5% = 11 minutes	0.10% = Negative	
27.	4*A* 0.1% Sol. 2 months old	0.1% = 10 minutes	0.10% = 11 minutes	.....

SUMMARY

1. Twenty-two esters of amino-naphthoic acid have been examined for local anesthetic action, relative toxicity and irritant action in comparison with cocaine and procaine.

2. Nearly all of these esters compare favorably with cocaine in local anesthetic action both by injection and by topical application to mucous membranes but the 4*A* ester was the outstanding member of the series. It was found to be fully as active as cocaine by injection and about three times as powerful in anesthetizing mucous membranes as well as somewhat less toxic to white mice than cocaine and non-irritating in its effective dilutions.

3. The 4*A* ester is effective intraspinally in rabbits and dogs and is reasonably stable to room temperature in dilute (0.1%) solution.

4. The nitro compound from which the 4*A* ester is derived is definitely less effective than the ester itself and produces local irritation while the 4*A* ester does not.

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