hydrochloric acid and ether and the base obtained by alkalizing the aqueous solution with ammonia and extracting with chloroform. The redistilled base was dissolved in methanol, the solution neutralized to congo red with methanolic hydrogen chloride, concentrated to a small volume and diluted dropwise with acetone, just short of incipient turbidity. On standing, the solution deposited the base hydrochloride which after several recrystallizations from methanol–acetone consisted of rosettes of small, colorless needles, m. p. 322–323°. The hydrochloride which is soluble in chloroform can be sublimed unchanged and a small quantity was isolated from the original distillate.

Anal. Calcd. for $C_{15}H_{20}O_2N_2 \cdot HCl$: C, 60.67; H, 7.12; N, 9.44. Found: C, 60.68, 60.86; H, 6.98, 7.02; N, 8.83.

The pure base was liberated from the perchlorate; it crystallized from acetone–ligroin in parallelogram-shaped plates, m.p. 210°, $[\alpha]^{18}D$ −147.7° (*c*, 0.325 in absolute ethanol).

Anal. Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.18; H, 7.74; N, 10.76. Found: C, 68.83, 68.63; H, 7.44, 7.60; N, 10.74. Total weight of baptifoline 380 mg. (yield, 0.018%). Owing to the difficulties of isolation, the yield given is probably low.

This base and its salts, in admixture with baptifoline isolated from *B. perfoliata*[6] and its corresponding salts, showed no depression in melting points.

Isolation of Alkaloid P4.—Refractionation of the base recovered from the baptifoline perchlorate mother liquors yielded an oil, b.p. 175–200° (0.05 mm.), from which a perchlorate was obtained as sheaves of colorless needles, m.p. 286°. This melting point was depressed by admixture with the perchlorates of anagyrine, cytisine or baptifoline. Insufficient material was obtained, however, for further investigation.

The mother liquors from the purification of the various fractions were systematically worked up and refractionated, but no bases other than those already described could be isolated. In all cases, the yields given are the final figures after complete examination of the residues.

Summary

1. *Baptisia minor*, Lehm., has been found to contain six alkaloids, three only of which are present in *B. australis*, *i.e.*, *d*-sparteine, cytisine and N-methylcytisine.

2. The remaining three bases are anagyrine, baptifoline and alkaloid P4. Baptifoline, first found in *B. perfoliata*, has been better characterized.

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[CONTRIBUTION FROM THE SOUTHERN RESEARCH INSTITUTE AND BRISTOL LABORATORIES]

Local Anesthetics: N-Dialkylaminoalkylimides of Naphthalic and Diphenylmaleic Acids

BY ALBERT M. MATTOCKS[1a] AND OLIVIA S. HUTCHISON[1b]

It has been reported by Moore and Rapala[1] that N-dialkylaminoalkylphthalimides are effective local anesthetics. In view of this and the fact that compounds containing larger aromatic nuclei frequently possess greater activity than their benzene analogs, it was believed important that N-dialkylaminoalkylimides of aromatic acids with large nuclei be investigated.

N-Dialkylaminoalkylimides of naphthalic and diphenylmaleic acids were synthesized by treating the corresponding dialkylaminoalkyl chlorides with sodium or potassium salts of the imides, or by the reaction of the dialkylaminoalkylamines with anhydrides.[1]

Pharmacological screening for local anesthetic activity was carried out in rabbits by the corneal and intradermal wheal tests. Subcutaneous toxicity ranges were determined on mice.

Experimental

Syntheses

N-Diethylaminoethylnaphthalimide.—A solution of 9.94 g. (0.152 mole) potassium hydroxide (85%) in 200 cc. alcohol was added to a hot alcoholic solution of 30 g. (0.152 mole) of naphthalimide,[2] and the mixture was stirred with gentle heating until quantitative precipitation had occurred, also about 37 g. (0.26 mole) diethylaminoethyl chloride was added and the mixture refluxed for thirty minutes. The grayish salt gradually reacted, going into solution with the appearance of an orange color. After it had cooled to room temperature, the solution was filtered to remove potassium chloride and the alcohol evaporated at reduced pressure. The residue was then subjected to a pressure of 1 mm. and a temperature of 100° to remove excess diethylaminoethyl chloride. The residual solid was redissolved in alcohol and treated with excess alcoholic hydrogen chloride; on cooling, yellow crystals of N-diethylaminoethylnaphthalimide hydrochloride precipitated. The product was recrystallized from isopropanol.

N-Dimethylaminoethylnaphthalimide and N-morpholinoethylnaphthalimide were prepared by the above procedure.

N-Diethylaminopropylnaphthalimide.—A mixture of 30 g. (0.152 mole) of naphthalic anhydride[3] and 19.7 g. (0.152 mole) of diethylaminopropylamine was heated at 165° for one hour. This mixture was then transferred to a beaker and dissolved in a mixture of equal parts isopropanol and benzene. The solution was washed with water and dried over sodium sulfate, the solvents and unreacted amine were removed by vacuum distillation, and the residue was redissolved in hot alcoholic hydrogen chloride. On cooling, yellow crystals of N-diethylaminopropylnaphthalimide hydrochloride precipitated. The product was recrystallized from isopropanol.

N-Diethylaminoethyldiphenylmaleimide.—Twenty grams (0.092 mole) of diphenylmaleimide[4] was added to a solution of sodium methoxide (prepared by dissolving 2.13 g. (0.092 mole) of sodium in 100 cc. of absolute methanol), the mixture was stirred at room temperature for one hour, and 25 g. (0.185 mole) of diethylaminoethyl

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(2) G. F. Jaubert, *Ber.*, **28**, 360 (1895).

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(4) P. M. Bartholdy, *ibid.*, **40**, 4400 (1907).

TABLE I

Compound	M. p., °C.	Yield, %	Empirical formula	Micro-Kjeldahl Nitrogen, % Calcd.	Found
N-(2-Diethylaminoethyl) naphthalimide-HCl	155–156 dec.	90	$C_{18}H_{31}O_2N_2Cl$	8.42	8.46 8.46
N-(3-Diethylaminopropyl) naphthalimide-HCl	226–227	65	$C_{19}H_{33}O_2N_2Cl$	8.02	8.22 8.26
N-(2-Dimethylaminoethyl) naphthalimide-HCl	261 dec.	28	$C_{16}H_{27}O_2N_2Cl$	9.19	9.25 9.23
N-(2-Morpholinoethyl) naphthalimide-HCl	244 dec.	64	$C_{18}H_{21}O_3N_2Cl$	8.08	7.87 7.85
N-(2-Diethylaminoethyl) diphenylmaleimide-HCl	182–183	54	$C_{22}H_{25}O_2N_2Cl$	7.28	7.26 7.33
N-(2-Dimethylaminoethyl) diphenylmaleimide-HCl	237	25	$C_{20}H_{21}O_2N_2Cl$	7.85	7.91 7.89

TABLE II

Compounds	LD50 mg./kg.	Relative toxicity	Corneal index	Corneal therapeutic ratio	Intradermal index	Intradermal therapeutic ratio
N-(2-Diethylaminoethyl) naphthalimide-HCl	56–125	0.8–1.79	2.54	1.4–3.2	1.11	0.7–1.4
N-(3-Diethylaminopropyl) naphthalimide-HCl	25–75	1.34–4.0	1.15	0.29–0.86	1.24	0.31–0.93
N-(2-Dimethylaminoethyl) naphthalimide-HCl	.....	.....	None	.....	None	.....
N-(2-Morpholinoethyl) naphthalimide-HCl	250–375	0.27–0.4	None	.....	0.60	1.5–2.2
N-(2-Diethylaminoethyl) diphenylmaleimide-HCl	625	0.16	3.13	19.6	0.28	1.8
N-(2-Dimethylaminoethyl) diphenylmaleimide-HCl	417–625	0.16–0.24	0.77	3.2–4.8	0.61	2.5–3.8
Cocaine-HCl	100	1.0	1.0	1.0	1.0	1.0

chloride was added. The temperature of the reaction was raised to 65° for three hours, and methanol was then removed from the mixture by distillation. The residue in the flask was cooled, acidified with dilute hydrochloric acid and washed with ether. The acid solution was neutralized with alkali and the crude product extracted with ether. Excess alcoholic hydrogen chloride was added to the ether extract, the solvents removed on a steam-bath, and the dark residue dried overnight *in vacuo*. The product was recrystallized as yellow needles from methyl isobutyl ketone.

N-Dimethylaminoethyldiphenylmaleimide was also prepared by this procedure.

Pharmacological Tests.—One per cent. solutions of the hydrochlorides of the compounds were used in all tests. Local anesthetic activity was determined by the well-known corneal and intradermal tests on rabbits. Toxicity was determined by subcutaneous injection into mice. The ratio obtained by dividing the duration in minutes of anesthesia produced by the test compound by that produced by cocaine was considered to be the significant result, this type of data being relatively unaffected by individual variation. Compounds exerting anesthesia that lasted less than five minutes were considered to be ineffective.

In most instances ranges are given for pharmacological values because a toxicity range, rather than an absolute LD50, was obtained. Anesthetic indices were obtained by dividing the duration of anesthesia in minutes resulting from injection of the compound by that produced by cocaine. Therapeutic ratios were obtained by dividing anesthetic indices by relative toxicity values. Relative toxicities were obtained by dividing the toxicity of cocaine (100 mg./kg., determined in this Laboratory on CFW strain white mice) by the toxicity ranges of the test compounds.

Discussion and Conclusions

Only one of the imides synthesized failed to show any local anesthetic activity in 1% aqueous solution. In the naphthalimide series, the diethylaminoethyl derivative possessed the maximum activity, though its toxicity was high. The morpholinoethyl derivative was much less toxic and at the same time less active, but the decreased intradermal activity was more than offset by lowered toxicity.

Of the diphenylmaleimides, the diethylaminoethyl derivative showed outstanding anesthetic activity on the cornea, while both it and the dimethylaminoethyl compound had low toxicities.

Summary

1. Four N-alkylaminoalkylimides of naphthalic acid and two of diphenylmaleic acid were synthesized for test as local anesthetics.

2. Five of the six imides described had local anesthetic activity, and all but one were considerably less toxic to mice than cocaine. The N-(2-diethylaminoethyl) derivatives of naphthalimide and diphenylmaleimide were outstanding in corneal anesthetic activity.

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