[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

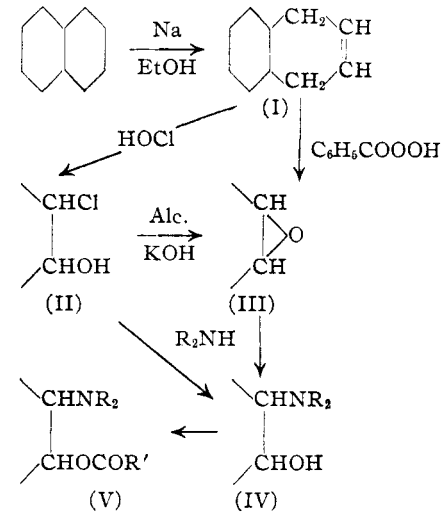
Local Anesthetics Derived from Tetrahydronaphthalene. I. Esters of 2-Dialkylamino-3-hydroxy-1,2,3,4-tetrahydronaphthalenes[1]

BY ELTON S. COOK[2] AND ARTHUR J. HILL

Most local anesthetics of the procaine type are amino ester derivatives of the benzene nucleus. Substitution of naphthalene for benzene is of interest because of the similarity between the two rings and because naphthalene is stated to be less toxic than benzene.[3] Hill and co-workers[4,5,6] have prepared a number of amino esters of naphthoic acids which possess local anesthetic activity, the best of these being 2-ethoxy-3-diethylaminopropyl naphthoate which is superior to cocaine for corneal anesthesia. Bjerregaard and Houstin[7] also have reported some simple naphthalene alkamine esters. Recently Blicke and Parke[8] have prepared active esters of aminonaphthoic acids.

At the time the present work was done, no previous publications had appeared on local anesthetics derived from partially reduced naphthalene.[9] Since completion of this work two series of reduced naphthalene esters have been reported, one derived from *ac*-tetrahydro-β-naphthylamine[10] and the other consisting of esters of 1 - hydroxy - 2 - (dialkylaminomethyl) - 1,2,3,4-tetrahydronaphthalenes.[11] Shriner[12] has also prepared some substituted tetrahydronaphthalenes with local anesthetic activity. Owing to their partially reduced nature the tetrahydronaphthalene compounds probably should be characterized by a lower toxicity[13] than those derived from unreduced naphthalene. Although the alicyclic β - dialkylaminotetrahydronaphthalenes possess a masked phenethylamine grouping, the compounds described in the present paper would not be expected to have pressor activity since tertiary phenethylamines appear to be uniformly depressor.[14]

The work on unreduced naphthalene derivatives had shown, (1) that β-substituted naphthalenes are more active and less toxic than α-naphthalenes and (2) that β,β-disubstituted naphthalenes where both substituents are in the same ring are superior to other disubstituted naphthalenes. Hence, in the present investigation, work was concentrated on alicylic β,β-disubstituted compounds. Entrance into the series was effected by the following reactions due, in part, to Bamberger and Lodter.[15]



The reduction of naphthalene was accomplished by an improvement of Bamberger and Lodter's method. The preparation of the chlorohydrin presented considerable difficulty. The methods mentioned below were tried; in none of them did cupric chloride[16] prove of value as a catalyst. The low yields are due, at least in part, to the formation of a multiplicity of by-products found in the oil which is produced in considerable quantity during the hypochlorous acid addition.

Methods for Preparation of 1,2,3,4-Tetrahydronaphthalene-2,3-chlorhydrin.—The use of

(1) From a dissertation presented in 1933 to the faculty of the Graduate School of Yale University by Elton S. Cook in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Institutum Divi Thomae, Cincinnati, Ohio.

(3) Francis and Fortescue-Brickdale, "The Chemical Basis of Pharmacology," London, 1908, p. 45.

(4) Robinson and Hill, Organic Chem. Symposium, Columbus, Ohio, Dec., 1927.

(5) Smith, Dissertation, Yale University, 1929.

(6) Fisk and Underhill, *J. Pharmacol.*, **49**, 329 (1933).

(7) Bjerregaard and Houstin, *Proc. Oklahoma Acad. Sci.*, **14**, 77 (1934).

(8) Blicke and Parke, THIS JOURNAL, **61**, 1200 (1939); *cf.* also Sergievskaya and Nesvad'ba, *J. Gen. Chem.* (U. S. S. R.), **8**, 924 (1938).

(9) The compounds to be described may, however, be compared with the *o*-diethylaminocyclohexyl *p*-aminobenzoates of Osterberg and Kendall, THIS JOURNAL, **43**, 1370 (1921), and of Heckel and Adams, *ibid.*, **49**, 1303 (1927).

(10) Coles and Lott, *ibid.*, **58**, 1989 (1936).

(11) Mannich, Borkowsky and Lin, *Arch. Pharm.*, **275**, 54 (1937).

(12) Shriner and Teeters, THIS JOURNAL, **60**, 936 (1938).

(13) *Cf.* Dyson, "The Chemistry of Chemotherapy," Ernest Benn, London, 1928, p. 21.

(14) Speer and Hill, *J. Org. Chem.*, **2**, 139 (1937).

(15) Bamberger and Lodter, *Ann.*, **288**, 74 (1895).

(16) Irvine and Haworth, U. S. Patent 1,496,675; Frahm, *Rec. trav. chim.*, **50**, 261 (1931).

various sources of hypochlorous acid resulted in these yields (based on pure dihydronaphthalene): bleaching powder and boric acid, 10%[15]; bleaching powder and acetic acid, 20%[17]; sodium hypochlorite and boric acid, 18%; sodium hypochlorite and acetic acid, 26.5%; sodium hypochlorite and chlorine gas, 10%[18]; chlorine gas and water, trace (mostly dichloride)[19,20]; $ClNHCONH_2$ and water, trace.[21]

The oxide could be prepared very readily by a modification of Bamberger and Lodter's technique. Contrary to the observation of these authors, we did not find that a large excess of potassium hydroxide over the theoretical was required. Owing, however, to the low yields of chlorohydrin, it is preferable to prepare the oxide directly from 1,4-dihydronaphthalene by the action of perbenzoic acid.

Experimental Part

1,4-Dihydronaphthalene (I).[22]—In a three-liter three-neck flask equipped with a powerful mercury-sealed stirrer, a dropping funnel, and a long condenser were placed 128 g. (1 mole) of naphthalene and 92 g. (4 moles) of sodium cut into small pieces. The mixture was heated in an oil-bath at 140–145° and, as the naphthalene and sodium melted, the mixture was stirred vigorously until a thorough emulsion of sodium and naphthalene was obtained. Continuing the stirring, the mixture was allowed to cool to a bath temperature of 60° when 300 cc. of dry benzene was run in. The bath was raised to 90–100° to effect moderate refluxing of the benzene and 1200 cc. of absolute alcohol was added at such a rate as to maintain well-controlled reflux. After about three-fourths of the alcohol was added, it was well to add more benzene to permit efficient stirring. After the alcohol was added, the mixture was allowed to cool. The precipitated sodium ethylate was decomposed by pouring the reaction products into a solution of 450 g. of concentrated hydrochloric acid in 3 liters of chopped ice. The upper benzene layer was removed and the aqueous layer was extracted with two 100-cc. portions of benzene. The combined benzene extracts were washed with saturated sodium bicarbonate solution and dried over sodium sulfate. The benzene was removed by fractionation through a column. The fraction boiling at 210–212° was saved as 1,4-dihydronaphthalene and the yield was 122 g. or 94% of the theoretical. This material contains an average of 66% of 1,4-dihydronaphthalene as determined by preparation of the mercuric acetate addition product.[23] The impurities are unreduced naphthalene and a trace of isomeric 1,2-dihydronaphthalene. Pure 1,4-dihydronaphthalene may be obtained by treating the crude reduction product with mercuric acetate according to the Sand and Genssler[23] technique. Pure 1,4-dihydronaphthalene distills at 96° at 18 mm. and melts at 25°. However, the crude reduction product was used satisfactorily in most of the following procedures.

1,2,3,4-Tetrahydronaphthalene-2,3-chlorohydrin (II).—Into an ice-cooled solution of 30 g. of sodium hydroxide in 906 cc. of water was passed 26.6 g. of chlorine. With mechanical stirring, 50 g. of crude dihydronaphthalene was added dropwise followed by 94 cc. of 25% acetic acid during twenty minutes. Stirring and cooling were continued for three and one-half to four hours. The chlorohydrin was filtered off, washed with dilute hydrochloric acid and with water, and crystallized from 95% alcohol; yield, 12 g. of white crystals melting at 117.5° (26.5% yield based on 66% dihydronaphthalene).

Anal. Calcd. for $C_{10}H_{11}OCl$: Cl, 19.43. Found: Cl, 19.19, 19.49.

2,3-Epoxy-1,2,3,4-tetrahydronaphthalene (III). Method I.—Ten grams of the chlorohydrin was dissolved in the minimum amount of absolute alcohol in a bath of cold water. Absolute alcoholic potassium hydroxide was added very slowly during stirring, each successive addition being made only when alkalinity had disappeared. When the solution remained alkaline for one hour, the reaction was considered complete. After filtering from the potassium chloride, the alcohol was removed *in vacuo* at room temperature. The oxide was crystallized from petroleum ether giving 6.8 g. (85%) of naphthalene-like plates melting at 43–43.5°.

Method II.[24]—To a solution of 42 g. (0.3 mole) of perbenzoic acid dissolved in 700 cc. of chloroform was added 37.7 g. (0.29 mole) of purified 1,4-dihydronaphthalene dissolved in 50 cc. of chloroform. The resulting solution was kept at 0° for three days. The benzoic acid was re-

TABLE I

2-DIALKYLAMINO-3-HYDROXY-1,2,3,4-TETRAHYDRONAPHTHALENES (IV)

R		Ethyl	Butyl	NR_2 = Piperidino
B. p.	°C.	138–145[a] 210–212	155–157	170–172[e]
	Mm.	3 46	3	3
Yield, %	Method I	84[b]	50[d]	80[f]
	Method II	85	..	85
Nitrogen anal., %	Calcd.	6.39	5.09	6.06
	Found	6.29	5.00	6.00
		6.31	4.95	5.97
Hydrochloride	M. p., °C.	168–170[c]	..	235–237[c]
	Chlorine anal., % Calcd.	13.84	..	13.27
	Found	13.9	..	13.26
		14.00	..	13.19

[a] Reported by Bamberger and Lodter[15] by Method I, b. p. 202° at 38 mm. [b] Twelve hours in a sealed tube at 100°. [c] From acetone. [d] Fifteen hours on the steam-bath. [e] Solid from petroleum ether, m. p. 51–52°. Bamberger and Lodter[15] give m. p. 46–48° and do not report b. p. or hydrochloride. [f] Five hours on the steam-bath.

(17) Chattaway, *J. Chem. Soc.*, **87**, 145 (1905).

(18) Shilov, *J. Chem. Ind., U. S. S. R.*, **5**, 1273 (1928).

(19) Gomberg, THIS JOURNAL, **41**, 1414 (1919).

(20) The use of bromine water (*cf.* Read and Williams, *J. Chem. Soc.*, **111**, 240 (1917)), likewise gave almost wholly the dibromide and only a trace of bromohydrin.

(21) Detoeuf, *Bull. soc. chim.*, **31**, 102, 162, 176 (1922).

(22) The method as given here is an improved version by Dr. J. F. Lontz, who found that the use of benzene as a diluent caused less isomerization to 1,2-dihydronaphthalene than did toluene which we used originally.

(23) Sand and Genssler, *Ber.*, **36**, 3705 (1903).

(24) For this procedure we are indebted to Dr. J. F. Lontz.

TABLE II

ESTERS OF 2-DIALKYLAMINO-3-HYDROXY-1,2,3,4-TETRAHYDRONAPHTHALENES (V)

Ester	M. p., °C.	Yield, %	Nitrogen analyses, % Calcd.	Found		Hydrochloride M. p., °C.	Analyses, % Calcd.	Found	
			A. Phenyl Urethans						
R = ethyl	Form I, 125–126[a]	85	8.28	8.28	8.31	179–180[c]	Cl 9.48	9.40	9.47
	Form II, 79–80[b]			8.20	8.30				
Butyl	110–111[a]	93	7.12	6.97	7.05	198–200[d]	Cl 8.25	8.08	8.15
NR_2 = piperidino	81–82[a]	100	8.00	7.96	7.86	204–206 dec.[e]	Cl 9.18	9.10	9.21
			B. Benzoates						
R = ethyl	Oil, not isolated					Non-cryst. hygroscopic yellow solid	N 3.89	3.50	3.52
Butyl						191–192[f]	N 3.37	3.30	3.20
NR_2 = piperidino	154–156[g]	50	4.18	4.01	4.10	245–246[h]	N 3.76	3.92	3.70
			C. *p*-Nitrobenzoates						
R = ethyl	110–111[i]	50	7.61	7.50	7.48				
Butyl	157–160[j]	50	6.60	6.49	6.45				
			D. *p*-Aminobenzoates						
R = ethyl	150–150.5[k]	90	8.28	8.25	8.21				
Butyl	192–195[l]	90	7.11	7.00	6.95				

[a] Needles from alcohol. [b] Rhomboidal plates. [c] From acetone and ether. [d] Forms gel from acetone and alcohol. [e] From 1:1 acetone–EtOH. [f] Prismatic needles from acetone–ether. [g] Needles from MeOH or acetone. [h] Needles from EtOH–acetone–ether. [i] Plates from alcohol–petroleum ether. [j] Plates from acetone. [k] Needles from EtOH. [l] Orange solid from EtOH.

moved by shaking with 125 cc. of ice-cold 10% sodium hydroxide solution and the excess alkali was then removed by shaking with two portions of ice-water. The chloroform solution was dried over sodium sulfate and the chloroform was removed through a fractionating column by heating on a water-bath. The oxide may be distilled at 97–99° at 17–18 mm., or the residue from the evaporation of chloroform may be taken up with boiling petroleum ether, from which the oxide crystallizes. The yield was 35 g., or 85% of the theoretical.

2 - Dialkylamino - 3 - hydroxy - 1,2,3,4 - tetrahydronaphthalenes (IV). Method I.—Two moles of the amine were heated with 1 mole of the chlorohydrin. The reaction products were extracted with dry ether, filtered from the amine hydrochloride, and, after drying and removal of the ether, distilled under diminished pressure.

Method II.—Equimolecular quantities of the amine and oxide were heated on the steam-bath for five hours and purified as in Method I. The hydrochlorides were prepared by passing dry hydrogen chloride gas into an absolute ether solution of the alkamine, avoiding an excess of hydrogen chloride. The compounds are given in Table I.

Esters (V).—The phenyl urethans, benzoates, and *p*-nitrobenzoates were prepared in the usual manner. The phenyl urethan of the diethylamino alcohol was isolated in two forms, a small amount of the lower melting form remaining in the mother liquor, the higher melting form predominating. The benzoates, with the exception of the piperidino, are oils which do not solidify readily and were converted directly into the hydrochlorides. The aminobenzoates were prepared by the catalytic reduction of the nitrobenzoates using 95% alcohol as the solvent. The compounds are shown in Table II.

Pharmacology of the Esters.—Several of the amino esters have been tested (as the hydrochlorides) for local anesthetic activity. The pharmacological data reported deal with the anesthesia of the rabbit cornea. These data are summarized in Table III.

TABLE III

LOCAL ANESTHETIC ACTIVITY OF 1,2,3,4-TETRAHYDRONAPHTHALENES. (RABBIT CORNEA)

Compd.[a]	Strength of soln., %	Duration of anesthesia, min.	Irritation
1	2	Inactive	Slight
2	2	120	Definite
2	0.2	30	None
2	.5	60	Definite
3	Not soluble 0.5%	No test	
4	1	20	Slight
Procaine	2	10	None
Cocaine	2	38	None

[a] 1, 2-Diethylamino-3-*p*-aminobenzoate; 2, 2-diethylamino-3-phenylurethan; 3, 2-dibutylamino-3-phenylurethan; 4, 2-piperidino-3-phenylurethan.

Compound 2 is the outstanding member of the series. It has a low toxicity (of the order of procaine) but is, unfortunately, rather irritating. The isomeric *p*-aminobenzoate (1) is inactive. This supports the suggestion[25] that the phenyl-

(25) Cook and Rider, THIS JOURNAL, **58**, 1079 (1936); Cook, *Studies Inst. Divi Thomae*, **2**, 63 (1938).

urethan group is more active than the *p*-aminobenzoate in causing anesthesia of mucous surfaces.

Summary

Improved procedures have been described for the preparation of 1,4-dihydronaphthalene and the corresponding chlorohydrin and oxide. Several amino alcohols have been synthesized from the two latter compounds and the benzoyl, *p*-nitrobenzoyl, *p*-aminobenzoyl, and phenylcarbamyl esters of these alkamines have been made. Several of these esters show local anesthetic activity and 2-diethylamino-1,2,3,4-tetrahydronaphthalene-3-phenylurethan is especially active.

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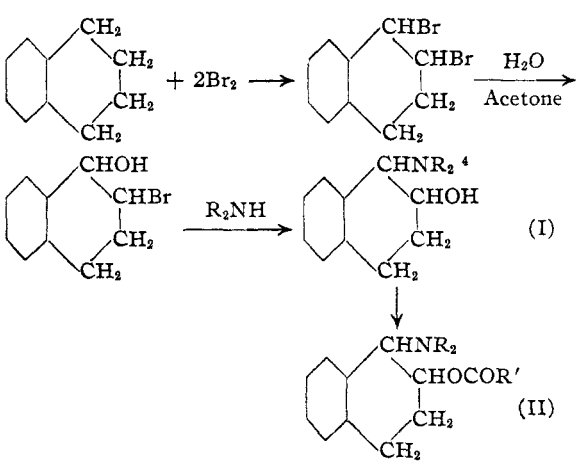
[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Local Anesthetics Derived from Tetrahydronaphthalene. II. Esters of 1-Dialkylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalenes

BY ELTON S. COOK[1] AND ARTHUR J. HILL

In a previous paper[2] the authors described certain esters of 2-dialkylamino-3-hydroxy-1,2,3,4-tetrahydronaphthalenes. The local anesthetic properties of these compounds aroused interest in the isomeric 1-dialkylamino-2-hydroxy compounds and the present paper offers preliminary work in this series.

The following reactions, due essentially to von Braun and co-workers,[3] were employed in the synthesis of the alkamine esters:



Preliminary pharmacological tests on the benzoates and phenyl urethans show them to possess pronounced local anesthetic activity.

(1) Present address: Institutum Divi Thomae, Cincinnati, Ohio.

(2) Cook and Hill, THIS JOURNAL, **62**, 1995 (1940).

(3) (a) Von Braun and Kirschbaum, *Ber.*, **54**, 597 (1921); (b) v. Braun, Braunsdorf and Kirschbaum, *ibid.*, **55**, 3648 (1922); (c) Straus and Lemmel, *ibid.*, **46**, 232 (1913); and (d) Straus and Rohrbacher, *ibid.*, **54**, 40 (1921), have entered the series by preparing the dibromide from 1,2-dihydronaphthalene.

(4) Von Braun and Weissbach, *ibid.*, **63**, 3052 (1930), have shown that the 1-amino-2-hydroxy compound is formed, probably through the intermediate oxide.

Experimental Part

1,2-Dibromo-1,2,3,4-tetrahydronaphthalene and **1-hydroxy-2-bromo-1,2,3,4-tetrahydronaphthalene** were prepared from commercial tetralin according to the directions of v. Braun and Kirschbaum.[3a]

1-Dialkylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalenes were prepared essentially according to Straus and Rohrbacher[3d] and our previous method.[2]

1-Diethylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalene was obtained in 90% yield; b. p. 181° at 18 mm. (Straus and Rohrbacher[3d] give 166–167° at 12–13 mm.). *Anal.* Calcd. for $C_{14}H_{21}ON$: N, 6.39. Found: N, 6.25, 6.24.

1-Di-*n*-butylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalene, b. p. 206–208° at 17 mm., was obtained in 65% yield. *Anal.* Calcd. for $C_{18}H_{29}ON$: N, 5.11. Found: N, 4.91, 4.96.

1-Piperidino-2-hydroxy-1,2,3,4-tetrahydronaphthalene was crystallized as needles from petroleum ether in a 90% yield; m. p. 74–75° (Straus and Rohrbacher[3d] give 73–74°). *Anal.* Calcd. for $C_{15}H_{21}ON$: N, 6.06. Found: N, 6.01, 5.98.

Benzoate Hydrochlorides.—The amino alcohol and two equivalents of benzoyl chloride were mixed, allowed to stand for forty-eight hours and heated on a steam-bath for three to five hours. The excess benzoyl chloride was removed with dry ether and the hydrochlorides were purified by adding dry ether to their solution in methyl alcohol or ethyl acetate.

1-Diethylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalene benzoate hydrochloride was obtained in 86% yield as prismatic needles from ethyl acetate; m. p. 192–193°. *Anal.* Calcd. for $C_{21}H_{26}O_2NCl$: N, 3.89; Cl, 9.87. Found: N, 3.85, 3.90; Cl, 9.79, 9.90.

1-Piperidino-2-hydroxy-1,2,3,4-tetrahydronaphthalene benzoate hydrochloride was obtained in 90% yield as needles from methanol; m. p. 208–209°. Straus and Rohrbacher[3d] report a m. p. of 176.5–177.5°. *Anal.* Calcd. for $C_{22}H_{26}O_2NCl$: N, 3.76; Cl, 9.55. Found: N, 3.75, 3.67; Cl, 9.50, 9.45.

1-Piperidino-2-hydroxy-1,2,3,4-tetrahydronaphthalene benzoate was prepared (because of the discrepancy between the melting points of the hydrochloride). It was