TABLE I

PROPERTIES OF *cis*-9,10-EPOXYOCTADECANE AND ITS INTERMEDIATES

Compound	B.P., °C./Mm.	M.P.,[a] °C.	F.P.,[a] °C.	Iodine Values Calcd.	Iodine Values Found	n_D^{25}	n_D^{35}
Oleyl alcohol[b]	184–187/4.5	—	—	94.8	93.5	1.4590	—
Oleyl tosylate	—	—	−30	60.2	59.7	1.4904	1.4866
cis-9,10-Octadecene	109/0.1	—	−35[c]	100.8	99.0	1.4448[c]	1.4410
cis-9,10-Epoxyoctadecane	—	22–23[d]	22	0.0	0.8[e]	1.4432	1.4395

[a] Uncorrected. [b] Contains 2% *trans* by infrared absorption[3] and 1–4% saturates (from iodine values). [c] Reported by Elsner and Paul[7] to be −30.5° and 1.4450, respectively. Reported by Boeseken and Belinfante[2] to be −15° and 1.4483 at 20°, respectively. [d] Reported by Boeseken and Belinfante[2] to be 0°. [e] Trace of *trans* olefin (determined by infrared analysis).

stream of nitrogen. The resulting tosylate (iodine value 54–57) was poured into three times its volume of diethyl ether and was refrigerated overnight. A white precipitate (m.p. 115–117°, 2.67% N, 7.01% S, water soluble), possibly the octadecenyl pyridinium complex of *p*-toluenesulfonic acid, was filtered out. (The presence of pyridine hinders the precipitation.) When the ether was removed, the yield of oleyl tosylate was 65%. Iodine value 59.7 (calcd. 60.2), n_D^{25} 1.4904.

Anal. Calcd. for $C_{25}H_{42}O_3S$: C, 71.04; H, 10.02; S, 7.59. Found: C, 68.21; H, 9.22; S, 7.15.

Cleavage of oleyl tosylate. A solution of 8.4 g. (0.02 mole) of oleyl tosylate dissolved in 60 ml. of distilled tetrahydrofuran (dried over sodium) was added in 1 hr. to a vigorously stirred, refluxing mixture of 1.2 g. of $LiAlH_4$ in 100 ml. of tetrahydrofuran. Agitation and refluxing were continued for a total of 10 hr. At the end of 5 and 7 hr., respectively, additional 0.3-g. portions of $LiAlH_4$ were added. This maneuver improved the yield of octadecene considerably. During the reflux period the refractive index of the oil (after the solvent from a 5 ml. sample had been evaporated) was observed to drop from 1.4904 to 1.4455 at 25°. Longer refluxing did not lower the refractive index.

Excess $LiAlH_4$ was decomposed in the usual manner with ethyl acetate, metallic complexes were decomposed with dilute HCl, and the organic layer was extracted with ether and separated. The ethereal layer was washed with cold water until acid free, dried over $CaSO_4$, and the solvents distilled off. The crude yield of *cis*-9,10-octadecene was 5.0 g. (100%).

Some purification was achieved by adsorption of the crude oil on a column of activated alumina and elution with diethyl ether. On removal of the ether from the eluate, 4.6 g. (92% recovery) of colorless oil was obtained which had an iodine value of 96.5 (calcd. 100.8), n_D^{25} 1.4452. A second alumina treatment raised the iodine value to 98.5 and lowered the refractive index to 1.4448 without loss in yield.

Anal. Calcd. for $C_{18}H_{36}$: C, 85.63; H, 14.37. Found: C, 85.81; H, 13.96.

On a larger scale, 168.8 g. (0.4 mole) of oleyl tosylate were reduced by the same method and purified by distillation to give an 85% yield of 98.6% pure *cis*-9,10-octadecene, n_D^{35} 1.4410, b.p. 109°/0.1 mm., iodine value 99.0.

Epoxidation to cis-9,10-epoxyoctadecane. The procedure of Findley, Swern, and Scanlan[8] for the epoxidation of unsaturated fatty materials with peracetic acid was employed. The yield of *cis*-9,10-epoxyoctadecane was 82%, m.p. (uncorr.) 22–23°, n_D^{25} 1.4395.

Anal. Calcd. for $C_{18}H_{36}O$: C, 80.52; H, 13.52; Oxirane O, 5.96. Found: C, 80.43; H, 13.22; Oxirane O,[9] 5.86.

(7) B. B. Elsner and P. F. M. Paul, *J. Chem. Soc.*, 3156 (1953).

(8) T. W Findley, D. Swern, and J. T. Scanlan, *J. Am. Chem. Soc.*, **67**, 412 (1945).

(9) A. J. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956).

Acknowledgment. We wish to thank C. R. Eddy and his staff at the Eastern Utilization Research and Development Division for the infrared analyses.

EASTERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION
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Synthesis of Possible Neuromuscular Blocking Agents Related to Succinylcholine[1]

KENNETH T. MECKLENBORG AND MILTON ORCHIN

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Succinylcholine iodide (Ia), a neuromuscular blocking agent, exhibits a depolarizing action at the myoneural junction, which cannot be antagonized by cholinesterase inhibitors. It has been reported[2]

$$[CH_2CO_2CH_2CH_2N^+(CH_3)_2RX^-]_2$$

Ia, R = CH_3, X^- = I^- Ib, R = *p*-nitrobenzyl, X^- = Br^- that the related compound, Ib, exhibits a nondepolarizing action similar to that of the naturally occurring (+)-tubocurarine, which can be antagonized by cholinesterase inhibitors. The reversal of physiological action observed with Ib was attributed to the added bulk placed at the nitrogen centers of Ib.

In the present investigation compounds related to succinylcholine iodide have been prepared. In one series, bulky groups were added at the nitrogen atom (Table I, Formula I). In a second series (Formula II), the quaternary nitrogen was incorporated in a ring system with two carbon atoms separating the nitrogen and oxygen atoms whereby the spacing between quaternary nitrogens, characteristic of many active neuromuscular agents, was preserved. In a third series (Formula III)

(1) Taken in part from the Ph.D. thesis of Kenneth T. Mecklenborg. Present address, Research Laboratories, Standard Oil of Indiana, Whiting, Ind.

(2) L. Randall, E. Giuliano, B. Kappell, and E. Allen, *J. Pharmacol. Exptl. Therap.*, **105**, 16 (1952).

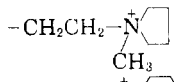
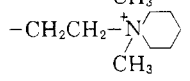
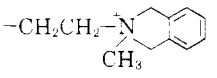
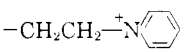
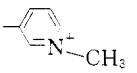
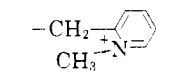
TABLE I

COMPOUNDS RELATED TO SUCCINYLCHOLINE

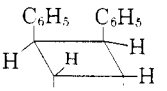
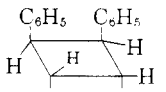
Derivatives of General Formula $[CH_2CO_2CH_2CH_2N^+(CH_3)_2RX^-]_2$, I

Compound No.	R	X^-	Procedure	M.P., °C	Calculated C, %	Calculated H, %	Found* C, %	Found* H, %
1	$C_6H_5CH_2$	I	A & B	206–209°	44.84	5.50	44.80	5.37
2[a]	p-$NO_2C_6H_4CH_2$	Br	A	221–222° (*d*)	45.10	5.24	44.91	5.41
3	p-$BrC_6H_4COCH_2$	Br	A	215–216° (*d*)	41.20	4.44	41.26	4.73
4	$C_6H_5CH_2CH_2$	Br	A	201–202°	53.34	6.72	53.24	6.80
5[b]	1-$C_{10}H_7CH_2$	I	A	197–198° (*d*)	51.28	5.32	51.05	5.72
6	C_6H_5	I	A	180–181°	43.13	5.13	43.59	4.89
7	H	I	—	154–155°	27.92	5.08	28.02	5.24
8[c]	H	Cl	—	201–203°				

Derivatives of General Formula, $[CH_2CO_2R]_2$, II

	R							
9		I	A	173–175°	36.25	5.75	36.32	5.76
10		I	A	183–185°	38.47	6.13	37.52	6.45
11		I	A	227–229° (*d*)	46.68	5.32	46.56	5.42
12		I	B	189–191°	37.01	3.79	37.13	3.87
13		I	B	226–228° (*d*)	34.55	3.26	34.55	3.10
14		I	B	191–192° (*d*)	37.01	3.79	37.16	3.79

Derivatives of General Formula, -Y-$[CO_2CH_2CH_2N^+(CH_3)_3X^-]_2$, III

	-Y-							
15		I	A	193–195°	46.55	5.58	46.88	5.60
16		ClO_4	A	166–168°	50.38	6.04	50.57	6.13
17[d]	$-CH_2CH(CH_3)-$	I	A	187–189°	32.27	5.78	32.48	5.80
18[e]	$-CH(C_6H_5)CH_2$ $CH_2CH(C_6H_5)-$	ClO_4	A	161–163°	50.15	6.29	50.23	6.32
19[e]	$-CH(C_2H_5)CH_2$ $CH_2CH(C_2H_5)-$	I	A	171–172°[g,h]	38.24	6.74	38.36	6.87
20[f]	$-CH(C_2H_5)CH_2$ $CH_2CH(C_2H_5)-$	I	A	173–175°[g,i]	38.24	6.74	38.25	6.61

* All analyses by Geller Laboratories, P. O. Box 158, West Englewood, N. J.

[a] Reported by Randall *et al.*, ref. 2, but no details given. [b] 1-(Iodomethyl)naphthalene. [c] Reported by D. Bovet, F. Bovet-Nitti, V. Longo, S. Guarine, and R. Fusco, *Arch. intern. pharmacodynamie*, **88**, 1 (1951), but no details given. % Cl. Calcd., 21.29. [d] Starting acid was DL mixture. [e] Starting acid was *racemic* modification. [f] Starting acid was *meso* modification. [g] Mixed melting gave no depression. The stereochemistry of the isolated acid was not determined. Compounds 19 and 20 are probably identical. [h] % N: Calcd., 4.46. Found, 4.38. [i] % N: Calcd., 4.46. Found, 4.43.

bulky groups were added in the acid moiety because such compounds have not been studied systematically but also because of the known retarding effect on hydrolysis of esters containing alpha (especially ethyl) substituents.[3]

Most of the preparations were carried out according to the three step procedure[4] of condensing the dibasic acid chlorides with two moles of the amino alcohol and converting the basic esters to their bis-quaternary salts. The preparation of the

(3) M. S. Newman, "Steric Effects in Organic Chemistry," Chap. 4, John Wiley & Sons, New York, 1956.

(4) R. Fusco, G. Palazzo, S. Chiavarelli, and D. Bovet, *Gass. Chim. Ital.*, **79**, 129 (1949).

final quaternary through this series of reactions is hereafter denoted as Procedure A.

With easily hydrolyzable esters contact with alkali was avoided and the amino alcohols were esterified in the form of their quaternized salts (Procedure B, compounds 13 and 14).

EXPERIMENTAL

Acids. β-Truxinic acid was prepared according to Bernstein and Quimby[5,6] in a 14% yield, m.p. 206–209°. DL-α-Methylsuccinic acid, m.p. 111°, *racemic*-2,5-diethyladipic acid, m.p. 68–69°, *meso*-2,5-diethyladipic acid, m.p. 136–137°, and *racemic*-2,5-diphenyladipic acid, m.p. 207–208° were a gift of the U.S.I. division of National Distillers and Chemicals Co.

Acid chlorides. Succinyl chloride was Eastman Kodak 2281. The adipyl chlorides were prepared from the corresponding acid and thionyl chloride. The remaining acid chlorides were prepared from the acid and phosphorous pentachloride. No attempt was made to isolate and purify the acid chloride.

Amino alcohols. 2-Dimethylaminoethanol was a redistilled Dow sample, $b_{750\ mm}$ 134–135°. 2-*N*-Methylanilinoethanol was Eastman Kodak 3709. 3-Hydroxypyridine and 2-pyridinemethanol were obtained from Sapon Laboratories. Other amino alcohols were prepared by known procedures from the commercially available amine and ethylene chlorohydrin.

Procedure A. Two moles of the amino alcohol were added dropwise with agitation to a chilled ether solution of one mole of acid chloride. The precipitate was dissolved in water, the aqueous solution was saturated with sodium chloride and made strongly alkaline, and the alkaline solution was then extracted with ether. The ether extracts were dried over Drierite and were treated with excess organic halide. The product was usually crystallized from methanol ether or methanol ethyl acetate to yield a sample suitable for pharmacological assay. Over-all yields amounted to 5–10%. No attempt was made to optimize the yields.

Procedure B. The amino alcohol was allowed to react with excess organic halide, in ether or acetone. The product was isolated and purified. Two moles of the quaternary salt were combined with one mole of succinyl chloride in toluene and refluxed until the evolution of hydrogen chloride had almost ceased. Although the system was heterogeneous, the reaction proceeded at a reasonable rate at the reflux temperature of toluene. The product was crystallized from methanol ether or methanol ethyl acetate to yield an analytical sample. In the case of compounds 13 and 14, purification was hampered by apparent decomposition in air or light. Over-all yields were about the same as secured by Procedure A.

Iodides. In those cases where a chloride was used for quaternization (compounds 1, 5, and 12), the product was converted to the iodide by treatment with an acetone solution of sodium iodide.

Perchlorates. The crude iodide was dissolved in a minimal amount of water and treated with 70% perchloric acid dropwise until precipitation was complete. The product was crystallized from methanol ether.

The pharmacology of all these compounds is being examined by the Wm. S. Merrell Co.

(5) H. I. Bernstein and W. C. Quimby, *J. Am. Chem. Soc.*, **65**, 1845 (1943).

(6) E. H. White and H. C. Dunathan, *J. Am. Chem. Soc.*, **78**, 6055 (1956).

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Studies on Sterically Hindered Phenols II.[1] Overcrowded Phenols Obtained by Condensation of Aldehydes with Alkyl Hydroxynaphthyl Ketones

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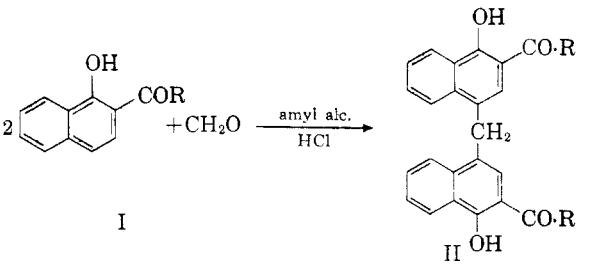
In general, phenols react readily with formaldehyde in the presence of both alkaline and acidic catalysts, producing a variety of substances ranging from simple methylene derivatives to complex resins. Very little seems to be known about the action of formaldehyde on alkyl hydroxynaphthyl ketones in an acidic medium.

We have investigated the condensation of paraformaldehyde with 2-acetyl-1-naphthol (Ia),[2] 2-propionyl-1-naphthol (1b)[3] and 2-butyryl-1-naphthol (1c)[4] and found that almost quantitatively the 3,3′-diacyl-4,4′-dihydroxydinaphthylmethanes IIa-IIc were formed.



(I) and (II):
(a) R = CH_3
(b) R = $CH_2 \cdot CH_3$
(c) R = $CH_2 \cdot CH_2 \cdot CH_3$

IIa gave diacetyl and dibenzoyl derivatives and a color reaction with ferric chloride.[5] The dioxime of IIb was prepared. The fact that 2-acetyl-4-bromo-1-naphthol[6] (III) does not condense with

(1) Part I: A. Schönberg, A. Mustafa, and A. Shalaby, *J. Am. Chem. Soc.*, **77**, 5756 (1955).

(2) E. J. Chu, Z. Shen, T. Chien, and T. S. Tuan, *J. Am. Chem. Soc.*, **66**, 653 (1944).

(3) C. M. Brewster and G. G. Watters, *J. Am. Chem. Soc.*, **64**, 2578 (1942).

(4) Yuoh Fong Chi, *J. Am. Chem. Soc.*, **61**, 2487 (1939).

(5) The tests with ferric chloride mentioned in this paper were carried out by adding a few drops of an aqueous ferric chloride solution to the alcoholic solution of the substance to be investigated.

(6) M. Akram, R. D. Desai, and Ahmad Kamal, *Proc. Indian Acad. Sci.*, **11A**, 139 (1940).