TABLE I.

Dialkylaminoalkyl α-Alkyl-Cinnamate Hydrochloride.	Method.	M. P., ° C.	Solvent.	Formula.	Analyses, %. N. Calcd.	N. Found.	Cl. Calcd.	Cl. Found.
β-Diethylaminoethyl (α-methyl)	A	133–134.5	Acetone	$C_{16}H_{24}O_2NCl$	4.70	4.90	11.91	11.57
β-Diethylaminoethyl (α-ethyl)	A, B	145	Acetone-Abs. EtOH	$C_{17}H_{26}O_2NCl$	4.49	4.32	11.38	11.57
γ-Diethylaminopropyl (α-ethyl)	A	143.8–144.4	Benzene	$C_{18}H_{28}O_2NCl$	4.30	4.23	10.89	10.86
β-Diethylaminoethyl (α-n-propyl)	A	125–126	Acetone-Ether	$C_{18}H_{28}O_2NCl$	4.30	4.54	10.90	10.80
β-Diethylaminoethyl (α-isopropyl)	B	152–153	Benzene	$C_{18}H_{28}O_2NCl$	4.30	4.63	10.90	10.96
β-Diethylaminoethyl (α-n-butyl)	B	105.5–106.5	Acetone	$C_{19}H_{30}O_2NCl$	4.12	4.16	10.44	10.29
β-Diethylaminoethyl (α-n-amyl)	B	83–85	Acetone	$C_{20}H_{32}O_2NCl$	3.96	4.26	10.03	10.07
Ring Substituted Dialkylaminoalkyl α-Alkyl-Cinnamate Hydrochloride								
β-Diethylaminoethyl (α-ethyl)-o-chloro	A	127.5–128	Acetone	$C_{17}H_{25}O_2NCl_2$	4.04	4.32	10.25	9.72
β-Diethylaminoethyl (α-ethyl)-p-dimethylamino	B	170–171	Acetone-Abs. EtOH	$C_{19}H_{31}O_2N_2Cl$	7.87	7.95	9.97	9.35
γ-Diethylaminopropyl (α-ethyl)-p-amino	A	191–192	Abs. EtOH-Ether	$C_{18}H_{30}O_2N_2Cl_2$	7.42	7.54	18.80	18.80
γ-Diethylaminopropyl (α-ethyl)-o-amino	A	170–170.5	Abs. EtOH-Ether	$C_{18}H_{30}O_2N_2Cl_2$	7.42	..	18.80	18.80
Dialkylaminoalkyl (β-Alkyl)-Cinnamate Hydrochloride								
β-Diethylaminoethyl (β-methyl)	C	141–142	Abs. EtOH	$C_{16}H_{24}O_2NCl$	4.70	4.85	11.91	11.93
β-Diethylaminoethyl (β-propyl)	C		.....	$C_{18}H_{28}O_2NCl$	4.30	4.94	10.90	10.33
N-(Dialkylaminoalkyl) (α-Alkyl)-Cinnamamide Hydrochloride								
N-(β-Diethylaminoethyl)-(α-methyl)	D	111–112.5	Acetone-Benzene	$C_{16}H_{25}ON_2Cl$	9.44	9.62	11.95	11.84
N-(β-Diethylaminoethyl)-(α-n-propyl)	D	134.2–134.9	Methyl-Ethyl Ketone	$C_{18}H_{29}ON_2Cl$	8.62	8.71	10.92	10.89
N-(β-Diethylaminoethyl)-(α-ethyl)	D	163–164	Abs. EtOH	$C_{17}H_{27}ON_2Cl$	9.02	9.11	11.41	11.46
N-(β-Diethylaminoethyl)-(α-n-butyl)	D	124.5	Acetone	$C_{19}H_{31}ON_2Cl$	8.27	8.62	10.47	10.25
N-(β-Diethylaminoethyl)-(α-amyl)	D	92–95	.....	$C_{20}H_{33}ON_2Cl$	7.94	8.00	10.05	9.97

SUMMARY.

1. A series of compounds derived from α-alkyl- and β-alkyl-cinnamic acids designed to be local anesthetics were prepared. Included were:

β-diethylaminoethyl α-alkyl-cinnamate hydrochlorides.

β-diethylaminoethyl β-alkyl-cinnamate hydrochlorides.

N-(β-diethylaminoethyl)-α-alkyl-cinnamamide hydrochlorides.

2. These compounds have all proved to be potent local anesthetics in pharmacological tests and the details of these studies are to be presented shortly.

REFERENCES.

(1) Claisen, *Ber.*, 23, 978 (1890).

(2) Rupe, *Ann.*, 369, 322 (1909); cf. also Schroeter, *Ber.*, 41, 5 (1908).

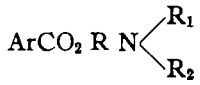
A SERIES OF CONTRIBUTIONS TO THE QUESTION OF THE RELATION BETWEEN CHEMICAL CONSTITUTION AND LOCAL ANESTHETIC ACTIVITY.

IV. LOCAL ANESTHETICS CONTAINING AN EPHEDRINE-LIKE NUCLEUS.

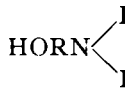
BY W. A. LOTT AND W. G. CHRISTIANSEN.

Researches described in Parts II and III of this series have dealt primarily with the acidic component of local anesthetics—the term acidic as used here refers

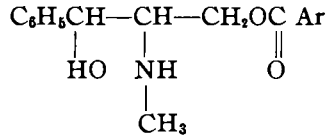
to the portion of the molecule designated as $ArCO_2$—in the following general formula:



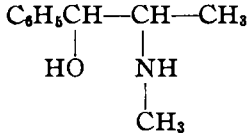
The research now being reported relates to the alcohol component, namely, the



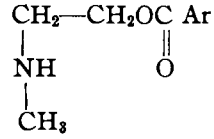
which is esterified with a suitable acid. It was thought that by so adjusting the configuration of the alcohol that it would bear some structural resemblance to ephedrine, it might be possible to obtain anesthetics possessing vasopressor activity as well. It was our initial aim to prepare an anesthetic ester corresponding to the following formula:



It will be noted from the following formula for ephedrine and an anesthetic ester that the above represents a combination of these two types of structures:

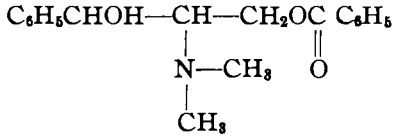


Ephedrine

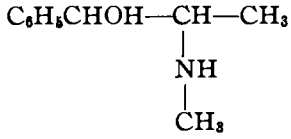


Anesthetic ester

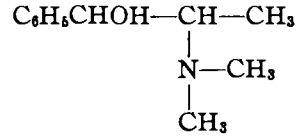
The attempts to produce this substance failed and for reasons of chemical feasibility it was decided to prepare the analogous dimethyl amino compound having the following formula:



This was done in full realization of the fact that the pressor activity of a tertiary amino body is expected to be less than that of a secondary amino body. Thus, *N* methylated ephedrine has less pressor activity than ephedrine,



Ephedrine



N-Me Ephedrine

and, similarly, the following tertiary amino alcohol would be expected to have less pressor activity than the corresponding secondary amino alcohol.

It was hoped, however, that the 1-phenyl-2-dimethylamino-1,3-propanediol 3-monobenzoate hydrochloride and analogous esters might still exhibit discernible pressor activity, or possibly some qualitatively different advantages, and a series of such esters was prepared.

The series successfully synthesized included:

1. 1-Phenyl-2-dimethylamino-1,3-propanediol 3-monobenzoate hydrochloride.
2. 1-Phenyl-2-diethylamino-1,3-propanediol 3-monobenzoate hydrochloride.
3. 1-Phenyl-2-diethylamino-1,3-propanediol 3-mono-α-ethyl-cinnamate hydrochloride.
4. 1-Phenyl-2-diethylamino-1,3-propanediol 3-monocarbanilate hydrochloride.
5. 1-Phenyl-2-diethylamino-1,3-propanediol 3-mono-*p*-ethoxy-benzoate hydrochloride.
6. 3-Phenyl-3-methoxy-2-diethylaminopropyl-monocarbanilate hydrochloride.

All of these compounds proved to be potent local anesthetics in preliminary pharmacological tests. Although in several instances blanched areas about the site of injection were observed, no vasopressor activity was observable in actual blood pressure measurements. The pharmacological results will be published separately in publications emanating from the Biological Laboratories of E. R. Squibb and Sons, and the Department of Pharmacology, University of Nebraska, Medical School.

EXPERIMENTAL.

Preparation of Dialkyl Amino Alkanols.—The substituted amino alkanols were made essentially according to the methods described by Cherbuliez (1) and Beaufour (2). Thus, 1-phenyl-2-diethylamino-1,3-propanediol was prepared by adding the elements of hypobromous acid to cinnamic alcohol to form the corresponding bromohydrin, and then treating with diethylamine to replace the bromine with a diethylamino group.

$$C_6H_5—CH=CH—CH_2OH + HOBr \longrightarrow C_6H_5—CHOH.CHBr.CH_2OH$$
$$C_6H_5—CHOH—CHBr.CH_2OH + (C_2H_5)_2NH \longrightarrow C_6H_5—CHOH.CHN(C_2H_5)_2.CH_2OH + HBr$$

DIALKYL AMINO ALKANOLS.

Substance.	B. P. ° C.	Mm.	Formula.	N Analyses, %. Calcd.	Found.
1-Phenyl-2-diethylamino-1,3-propanediol	149–150[a]	2	$C_{13}H_{21}O_2N$	6.27	5.96
3-Phenyl-3-methoxy-2-diethylamino-1-propanol	128–133	4	$C_{14}H_{23}O_2N$	5.90	
1-Phenyl-2-dimethylamino-1,3-propanediol	150–157	4	$C_{11}H_{17}O_2N$	7.17	7.18

[a] The B. P. recorded by Cherbuliez is 175–178° C. (14 mm.).

1-Phenyl-2-Diethylamino-1,3-Propanediol 3-Benzoate Hydrochloride.—To a chilled solution of 24.5 Gm. of 1-phenyl-2-diethylamino-1,3-propanediol dissolved in 50 cc. of anhydrous benzene was added 15.6 Gm. of benzoyl chloride dissolved in 50 cc. of anhydrous benzene. Twenty cubic

centimeters of dry ether was added to the reaction mixture which then upon standing tightly stoppered over night in the ice box deposited a crop of white crystals of the hydrochloride. The product was drained on a Buchner funnel and washed with cold solvent. Two crystallizations from alcohol and ether with one decolorizing treatment with charcoal resulted in 27.4 Gm. of product of constant melting point 181–181.5° C.

Anal. Calcd. for $C_{20}H_{26}O_3NCl$: N, 3.85; Cl, 9.75
Found: N, 3.61; Cl, 9.75

1-Phenyl-2-Diethylamino-1,3-Propanediol 3-α-Ethyl-Cinnamate Hydrochloride.—4.4 Gm. of α-ethyl-cinnamylchloride dissolved in 25 cc. of anhydrous ether was added to 4.6 Gm. of 1-phenyl-2-diethylamino-1,3-propanediol dissolved in 60 cc. of anhydrous ether. After refluxing 6 hours then chilling and diluting the reaction mixture with ether a crystalline product was obtained which upon crystallization from alcohol had a melting point of 149–150° C.

Anal. Calcd. for $C_{24}H_{32}O_3NCl$: Cl, 8.49; N, 3.35
Found: Cl, 8.83; N, 3.78

1-Phenyl-2-Diethylamino-1,3-Propanediol 3-Mono-Carbanilate Hydrochloride.—7.8 Gm. of phenylisocyanate dissolved in 40 cc. of dry benzene was added dropwise to 14.6 Gm. of 1-phenyl-2-diethylamino-1,3-propanediol dissolved in 40 cc. of dry benzene. The reaction mixture, tightly stoppered, was allowed to stand at room temperature several days then rendered just acid to Congo red paper with ethereal hydrogen chloride. The product which separated was crystallized from acetone. Seventeen grams were obtained with melting point 203–204° C.

Anal. Calcd. for $C_{20}H_{26}O_3N_2Cl$: N, 7.40; Cl, 9.36
Found: N, 7.34; Cl, 9.65

1-Phenyl-2-Diethylamino-1,3-Propanediol 3-Mono-p-Ethoxy-Benzoate Hydrochloride.—To 5.5 Gm. of 1-phenyl-2-diethylamino-1,3-propanediol, b. p. 175–190° C. (13 mm.), dissolved in 25 cc. of anhydrous benzene was added a solution of 4.2 Gm. of *p*-ethoxybenzoyl chloride in 25 cc. of anhydrous benzene and the reaction mixture refluxed for six hours. The benzene was then removed by distillation and the residue recrystallized from absolute alcohol. The product obtained amounted to 2.4 Gm., m. p. 177–178° C.

Anal. Calcd. for $C_{22}H_{30}O_4NCl$: N, 3.51; Cl, 8.90
Found: N, 3.64; Cl, 8.10

3-Phenyl-3-Methoxy-2-Diethylaminopropyl-Mono-Carbanilate Hydrochloride—5.2 Gm. of phenylisocyanate dissolved in 25 cc. of anhydrous ether was added to 9.3 Gm. of 2-diethylamino-3-phenyl-3-methoxy-1-propanol, b. p. 128–133° C. (4 mm.), dissolved in 20 cc. of anhydrous ether The reaction mixture was refluxed four hours under anhydrous conditions then treated until acid to Congo red paper with ethereal hydrogen chloride. The crystalline product obtained from one crystallization from absolute alcohol had a melting point of 198–199.5° C.

Anal. Calcd. for $C_{21}H_{29}O_3N_2Cl$: Cl, 9.03; N, 7.13
Found: Cl, 9.20; N, 7.09

1-Phenyl-2-Dimethylamino-1,3-Propanediol 3-Mono-Benzoate Hydrochloride.—3.8 Gm. of benzoyl chloride dissolved in 50 cc. of anhydrous benzene was added to 5.1 Gm. of 1-phenyl-2-dimethylamino-1,3-propanediol, b. p. 150–157° C. (4 mm.) dissolved in 50 cc. of anhydrous benzene. The reaction mixture was refluxed fifteen hours and the crystalline product obtained was recrystallized from absolute alcohol, m. p. 215–216° C.

Anal. Calcd. for $C_{18}H_{22}O_3NCl$: N, 4.17; Cl, 10.57
Found: N, 4.18; Cl, 10.63

SUMMARY.

1. A series of 6 new local anesthetics derived from an ephedrine-like amino alcohol were prepared.

2. All of these compounds were potent local anesthetics but showed no measurable vasopressor action.

REFERENCES.

(1) Cherbuliez, Neumeier and Lorenz, *Helv. Chim. Acta*, 14, 186 (1931).

(2) Beaufour, *Bull. soc. chim.* (4), 11, 648 (1912); cf. also *Bull. soc. chim.* (4), 13, 349 (1913); (4), 14, 354 (1913).

STUDIES IN THE EXTRACTION OF CINCHONA.*

BY ADLEY B. NICHOLS[1] AND C. B. SHAH.

The experiments which are recorded in this report were undertaken primarily for the purpose of obtaining specific facts relative to extraction in general and to the extraction of cinchona in particular, because it was known to offer numerous extraction difficulties and because, being an alkaloidal drug, it presented an opportunity for basing the study upon something more tangible and of more relative importance than so-called extractive matter, which might or might not be indicative of drug activity and extraction efficiency.

Reports of other workers and the results of this study indicate that each drug must be considered as a specific problem and that what proves of value in one instance may be utterly lacking in another. Studies of the literature and the results of this study on cinchona bear evidence of both of these conditions. Consequently the results as here reported may or may not be indicative of what might be found with other drugs under similar conditions.

A carefully selected whole red cinchona bark was used in this study. The bark was ground to meet the specifications of numbers 10, 20, 40, 60 and 100 powders, and assays upon these showed the presence of 7.524, 7.436, 7.600, 7.416 and 6.872 per cent of alkaloids of cinchona, respectively.

Due to the nature of the experiments, U. S. P. alcohol was selected as the menstruum throughout, since a multiple-phase menstruum would not have worked satisfactorily under certain conditions and comparative results could not have been obtained unless a uniform menstruum was used in all cases.

EXPERIMENTAL PROCEDURE.

I and II.—To study the effects of vacuum and agitation on extraction in relation to the degree of comminution of the drug, the following maceration experiments were conducted with powders Nos. 10, 20, 40, 60 and 100: (*a*) vacuum but no shaking; (*b*) vacuum with shaking; (*c*) no vacuum and no shaking (plain maceration); (*d*) no vacuum but with shaking (plain maceration with shaking). Each of the experiments was performed in duplicate, and flasks of similar shape and size were used.

The experiments with vacuum were carried out in 250-cc. conical suction flasks whereas those without vacuum were made in similar, plain, conical flasks. Twenty grams of accurately weighed powder were placed in each flask. The suction flasks were closed with stoppers, each carrying a separatory funnel, the side arm of the flask was connected with the vacuum line and 100 cc. of alcohol were placed in the separatory funnel. The dry powders in the flasks were first subjected to a vacuum of 27 inches and maintained under such conditions for ten minutes; then the vacuum connection was closed and sufficient of the alcohol from the funnel was allowed to

* From a graduate thesis presented by C. B. Shah to the Philadelphia College of Pharmacy and Science.

[1] Associate Professor of Operative Pharmacy, Philadelphia College of Pharmacy and Science.