1928

Physiological action and chemical constitution: new local anesthetics

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PHYSIOLOGICAL ACTION AND CHEMICAL CONSTITUTION: NEW LOCAL ANESTHETICS

BY

Clarence C. Vernon

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

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ACKNOWLEDGMENT

The writer finds it a pleasure to acknowledge his indebtedness, and express his gratitude to Dr. Henry Gilman, who not only suggested this research, but furnished inspiration and guidance throughout its course.

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INTRODUCTION

The use of local anesthetics in surgery has shown a remarkable growth since the introduction of cocaine some forty years ago. Formerly only minor operations were attempted under local anesthesia, but now major operations on the abdominal cavity are often performed, using only local anesthetics. This practice has been made possible partly by improved technique, but mainly by the great variety of synthetic local anesthetics available. These synthetic local anesthetics may or may not fulfil the requirements specified by Gilman[1] for ideal substitutes for cocaine, but they do possess properties which render them acceptable to the surgeon for the operation at hand. Many seemingly peculiar substances have been used as local anesthetics. Allen[2] mentions water, phenol, alcohol, chloroform, and water solutions of magnesium salts. To this list Braun[3] adds cold, and for tonsilectomy a mixture of urea and quinine.

When the structure of cocaine was definitely established by the synthesis of this body from tropinone, by Willstätter, the field of research on local anesthetics was thrown open to

[1]Gilman, J. Ind. Eng. Chem., 14, 812-814 (1922). See also Braun, "Local Anesthetics", (Lea and Febinger, 1914) 128.
[2]Allen, "Local Anesthetics", (Saunders and Company, 1914) 71-72.
[3]Braun, "Local Anesthetics", (Lea and Febinger, 1914) 20.

organic chemists. Hundreds of compounds are now tested annually for local anesthetic action, and those most nearly fulfilling the requirements mentioned[1] find their way into the hands of the clinical anesthetist. A few of those most commonly used, and considered the best are procaine, butyn, holocaine, the borocaines, and isocaine. These have all been found either more efficient than cocaine, or less toxic. Some are adapted to one sort of operation, some to another, but they all have the desirable property of being non-habit forming.

Despite the large amount of work done on local anesthetics, and the advance in knowledge made, it is as yet possible to speak only in very general terms, concerning the effect of the various groups. Even then, there are unexplained contradictions to almost every statement. It is very evident that a complete correlation between chemical constitution and physiological action has not yet been reached.

In the field of local anesthetics a large part of the trouble is due to the lack of a satisfactory method for evaluating the effect of the compounds tested. The order of effectiveness varies according to the method of testing, for any one compound[4]. There are now in use some half dozen more or

[4]Gilman and Pickens, J. Am. Chem. Soc., 47, 245 (1925). Adams, Rideal, Burnett, Jenkins and Dreger, J. Am. Chem. Soc., 48, 1758-1770 (1926).

less approved methods[4] [5], the most widely used one being application of the compound tested to the cornea of a dog or rabbit. Even when the same method is used, different methods of evaluating the results are in vogue, so that the investigator encounters difficulty in finding data comparable to his own.

This state of affairs should not exist. A standardization of methods could be worked out as was done in the case of disinfectants[6], and the results evaluated in some such manner as has already been suggested by Gilman and Pickens[4], and by Copeland and Notton[7]. A method which seems to combine the best features of most of the others mentioned, is the one used by Adams and his coworkers[8] in which goldfish are used as test subjects. This method could be standardized, used in connection with some other when necessary, and the results expressed in comparison with cocaine or procaine. If such a thing be possible, and be universally adopted, the criticisms enunciated by Lynn and Lofgren[9] would no longer be so pertinent as they are at present.

[5]Heinekamp, J. Lab. Clin. Med., 11, 289-292 (1925); Meeker, ibid., 468-474 (1925); McGuigan and Brough, ibid., 479-482 (1925); Cohen, ibid., 174-176 (1925); Schulz, ibid., 176-182 (1925); McGuigan, J. Am. Pharm. Assoc., 13, 316-17 (1924).
[6]Anderson and McClintic, U. S. Pub. Health Service Hy. Lab. Bull. No. 82.
[7]Copeland and Notton, Brit. Med. J., 1925, I, 547.
[8]Adams, Rideal, Burnett, Jenkins and Dreger, J. Am. Chem. Soc., 48, 1758-1770 (1926).
[9]Lynn and Lofgren, J. Am. Pharm. Assoc., 14, 970 (1925), C. A., 20, 2727 (1926).

In a research of this type, the choice of a pharmacaphore[10-4] is attended by many difficulties. The β-diethylaminoethyl group ($(C_2H_5)_2NC_2H_4$-) was finally chosen as a satisfactory, representative pharmacaphore, since a large amount of data are available when it is used. True, this group is not found in many good local anesthetics such as butyn, holocaine, tutocaine, and others. It is not found in the esters of *p*-aminobenzoic acid, which Adams[8] and others[11 12] found to have local anesthetic action. There is no amino group whatever in benzyl alcohol, or the esters of it studied by Macht[13], yet these have local anesthetic action. On the other hand, β-diethylaminoethanol[14] itself has a marked local anesthetic action. It was felt that the objections mentioned were not sufficient to overbalance the advantages secured by using the β-diethylaminoethyl group as a pharmacaphore.

Since Lynn and Lofgren[9] have shown that β-diethylaminoethyl benzoate ($C_6H_5COOC_2H_4N(C_2H_5)_2$) has local anesthetic action slightly less powerful than procaine, it was concluded that the *p*-amino group found in procaine was not a part of

[10] A pharmacaphore may be defined as that group of atoms to which the physiological action may be attributed.
[11] Gilliard, Monnet and Cartier, Ger., 393783, Mch. 13 (1924).
[12] Brill, J. Am. Chem. Soc., 43, 1320 (1921).
Thoms and Ritsert, Ber. deut. pharm. Ges., 31, 65 (1921), C.A., 15, 2851 (1921).
Altwegg and Landrivon, U.S., 1334641, Mar. 23 (1920), C.A., 14, 1595 (1920).
[13] Macht, J. Pharmacol., 12, 263 (1918). C.A., 13, 41 (1919).
[14] See Table I, p. 42.

the principal pharmacaphore. The evidence previously mentioned seemed to indicate it was a secondary independent pharmacaphore, or an anchoring group, and that its influence was best included with the action of neighboring groups.

Hydrochloride salts of the anesthetic bases prepared in this research were submitted for tests. Again the choice was made on the basis of comparative data available, convenience, and stability.

EXPERIMENTAL PART

Diethyl β-Diethylaminoethyl-Malonate

$(C_2H_5)_2NC_2H_4CH(COOC_2H_5)_2$

Brockmühl and Schwarz[15] have prepared the β-diethylaminoethyl derivative of acetoacetic ester ($CH_3COCH.(C_2H_4N(C_2H_5)_2).COOC_2H_5$) by adding powdered potassium hydroxide to a mixture of the ester and the hydrobromide salt of β-diethylaminoethyl bromide[16]($(C_2H_5)_2NC_2H_4Br.HBr$). A solution, composed of 50 cc. benzene and 32 gm. (0.2 mole) diethyl malonate was mixed with 50 gm. β-diethylaminoethylbromide hydrobromide. To this mixture was added 22.4 gm. (0.4 mole) powdered potassium hydroxide, introduced one gram at a time. After five hours standing, the benzene solution was decanted, dried, and distilled. The fraction boiling at 145°/12mm. comprised the major portion of the distillate.

The purified oil, dissolved in dry ether and treated with hydrogen chloride, yielded a yellow oil, insoluble in ether, which required three months standing in an electric refrigerator before crystallizing. The crystals so formed were very hygroscopic, and melted at 65-68°. A solid chloroplatinate, or chloraurate derivative of the purified oil could not be prepared. Analysis was made by suspending a sample in water and titrating with standard hydrochloric acid,

[15]Brockmühl and Schwarz, U.S. 1429922, Sept. 26 (1922), C.A., 16, 4015 (1922).
[16]Meyer and Hopff, Ber., 54B., 2274-2282 (1921), C.A., 16, 1220 (1922).

using methyl orange as an indicator. As a check, a carbon and hydrogen analysis was made.

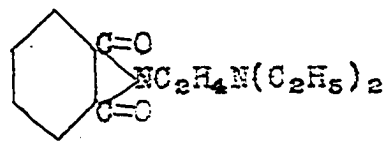
Analysis: Acid titration of free base. Carbon and hydrogen determination.

Calcd. amount hydrochloric acid to neutralize 0.5484 gm. $(C_2H_5)_2NC_2H_4CH(COOC_2H_5)_2$; 0.07731 gm. Found: 0.07723gm.

Calcd. for $(C_2H_5)_2NC_2H_4CH(COOC_2H_5)_2$: C, 60.27; H, 9.64.

Found: C, 60.41;:H, 9.31.

β-Diethylaminoethyl-Phthalimide



β-Chloroethyl-phthalimide[17] was prepared by heating potassium phthalimide with an excess of ethylene chloride in a sealed tube. The yield was 37 per cent.

7 gm. (0.03 mole) of this β-chloroethyl-phthalimide were placed in a pressure bottle with 7.3 gm. (0.1 mole) diethylamine. The flask was heated at 100° for 14 hours, then opened, and the excess diethylamine allowed to escape. The diethylamine hydrochloride was filtered out and the residual oil distilled, boiling at 203-4°/14 mm. When dissolved in dry ether and treated with hydrogen chloride, a white solid precipitated. This solid melted at 230° after recrystallization from acetone. When mixed with diethylamine hydro-

[17] Seitz, Ber., 24, 2624-2631 (1891).

chloride, the melting point was 175-186°.

Analysis:

Calcd. for $C_6H_4(CO)_2NC_2H_4N(C_2H_5)_2.HCl$; Cl, 12.54. Found 12.55 (by Volhard). 12.70 (by Carius).

β-Diethylaminoethyl β-Ethylacrylate

$C_2H_5CH=CHCOOC_2H_4N(C_2H_5)_2$.

The acid chloride of β-ethylacrylic acid ($C_2H_5CH=CHCOOH$) was prepared by treating 5 gm. (0.05 mole) of this acid in cold benzene solution with 8 gm. (0.075 mole) of thionyl chloride. After 2 hours stirring in the cold, 3.5 gm. (59 per cent) of a material boiling at 96-98°/7 mm. was secured on distillation of the reaction mixture.

This material was dissolved in dry ether and treated with a slight excess sodium β-diethylaminoethylate[18]. A white solid appeared immediately and the mixture was allowed to stand overnight. The solid was then dissolved in water, the water solution neutralized with sodium hydroxide, and the oil so formed dissolved in ether, and separated. This oil boiled at 55°/3 mm. and contained nitrogen, carbon, no chlorine or sulfur. It quickly decolorized bromine water and

[18] This material was prepared by treating an ether solution of β-diethylaminoethanol with the calculated amount of metallic sodium. It was soluble in ether to the extent of 0.1 mole in 100 cc. Frequent shaking facilitates the reaction which is quite slow toward the end.

potassium permanganate solution. When dissolved in ether, and treated with hydrogen chloride, a white solid formed, melting at 117-120°. The solid was surprisingly volatile, and could not be kept or weighed as such. The reason for this high volatility is not known.

The original benzene solution contained nothing but small amounts of β-diethylaminoethanol. The water layer after washing with ether, when acidified and evaporated gave no identifiable organic compound.

In a second run, using 0.1 molar quantities, the yield of supposed acid chloride was 6.5 gm. (55 per cent). Its boiling point was 129-130°/735 mm., however. Ether was used instead of benzene and the mixture was distilled after 2 hours standing at room temperature.

No yield of β-diethylaminoethyl β-ethylacrylate was secured in this second run. Instead, 3 gm. (25.6 per cent) β-diethylaminoethanol, and 3.5 gm. (35 per cent) β-ethylacrylic acid were recovered. No other products could be found, so it was believed that no acid chloride had really been formed by the treatment of the acid with thionyl chloride.

A third run was made, in which the yield of acid chloride was increased to a quantitative one by using more concentrated solutions. Only 50 cc. of ether were used altogether and the solution was allowed to stand 48 hours after mixing, at room temperature.

As before, this acid chloride was mixed with sodium β-diethylaminoethylate in cooled ether solution, and allowed to stand 4 days. The white solid was removed and the ether solution distilled. 3 gm. of a very pure product was finally secured representing 15.0 per cent yield. This material boiled at 145°/35 mm. and at 105-107°/7-8 mm. It contained carbon and nitrogen but no sulfur or chlorine. In dry ether solution, when treated with hydrogen chloride, it gave a white precipitate, which could not be analyzed because of its extreme volatility.

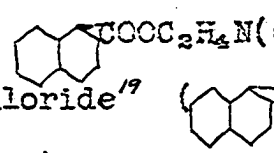
The free base was analyzed for carbon and hydrogen, the variation of the usual method, necessary for combustion of compounds containing nitrogen, being used.

Analysis: Carbon and hydrogen.

Calcd. for $C_2H_5CH=CHCOOC_2H_4N(C_2H_5)_2$; C, 66.27; H, 10.62.

Found, C, 66.11; H, 10.80.

β-Diethylaminoethyl α-Naphthoate



α-Naphthoyl chloride[19] () was prepared by treating 10 gm. (0.58 mole) α-naphthoic acid in ether solution, with 17 gm. (1.72 mole) of thionyl chloride. The yield was 90.5 per cent.

An ether solution of α-naphthoyl chloride was then treated with a slight excess of sodium β-diethylaminoethylate. A white solid formed immediately. This was filtered out, dis-

[19] Hoffman, Ber., 1, 38-43 (1868).

solved in water, neutralized with sodium hydroxide, and the yellow oil so formed, dissolved in ether. After drying over sodium sulfate, this ether solution was treated with dry hydrogen chloride. A yellow oil came down which solidified after standing. When recrystallized from acetone, this solid melted at 163°.

Analysis: Volhard for Cl.

Calcd. for α-$C_{10}H_7COOC_2H_4N(C_2H_5)_2.HCl$: Cl, 11.53. Found, 11.51.

The free base had a boiling point of 200-220°/10 mm. For this reason it was converted into the hydrochloride salt and purified by recrystallization from acetone.

β-Diethylaminoethyl β-Naphthoate

β-Naphthoyl chloride () was prepared from 9 gm. (0.52 mole) of -naphthoic acid and 17 gm. (1.72 mole) of thionyl chloride, in ether solution. The yield was 90 per cent.

An ether solution of the β-naphthoyl chloride so prepared was then treated with a slight excess of sodium β-diethylaminoethylate. A white solid precipitated, which was filtered out, dissolved in water, and neutralized with sodium hydroxide. The resulting insoluble oil was extracted with ether, the ether solution dried over sodium sulfate,

and the ether distilled off. The residual oil boiled at 183-185°/3-4 mm.

This oil was then treated with hydrogen chloride, in an ether solution. A white solid formed which melted at 165° after recrystallization from acetone. Equal portions of this material and the β-diethylaminoethyl α-naphthoate, when mixed, melted at 140°.

Analysis:

Calcd. for β-$C_{10}H_7COOC_2H_4N(C_2H_5)_2.HCl$: Cl, 11.53. Found: 11.50 (by Volhard), 11.39 (by Carius).

β-Diethylaminoethyl-Methylaniline

$C_6H_5N.CH_3.C_2H_4N(C_2H_5)_2$

A mixture of 10.7 gm. (0.1 mole) of methyl aniline ($C_6H_5NH.CH_3$) and 26 gm. (0.1 mole) of β-diethylaminoethylbromide hydrobromide was treated with 11.2 gm. (0.2 mole) of powdered potassium hydroxide, the latter being added in small amounts and the whole thoroughly mixed before further addition. It was necessary to cool the flask in water occasionally.

After standing one hour, the semisolid mass was shaken with benzene several times and the solution so secured, distilled. A fraction boiling at 155°/14 mm. was secured. It weighed 11 gm., and represented a 53.5 per cent yield. This yellow oil, dissolved in dry ether and treated with hydrogen chloride yielded a yellowish solid. This solid, recrystallized from a chloroform ether solution melted at 187°.

Analysis: Volhard for Cl.

Calcd. for $C_6H_5N.CH_3.C_2H_4N(C_2H_5)_2.2HCl$:[20] Cl, 25.43. Found 25.42.

β-Diethylaminoethyl Phenyl Ether

$C_6H_5OC_2H_4N(C_2H_5)_2$

An ether solution containing 15.7 gm. (0.1 mole) of β-chloroethyl phenyl ether[21] ($C_6H_5OCH_2CH_2Cl$) and 14.6 gm. (0.2 mole) of diethylamine was sealed in a flask and heated over a water bath for 8 hours. The diethylamine hydrochloride formed was filtered out, the ether evaporated, and the residual oil distilled. This yellow oil boiled at 98-100°/7 mm. A yield of 44 per cent was secured. An ether solution of this oil, when treated with hydrogen chloride yielded a white solid, melting at 135.5° after recrystallization from ethyl acetate.

Analysis: Volhard for Cl.

Calcd. for $C_6H_5OC_2H_4N(C_2H_5)_2.HCl$: Cl, 15.46. Found: 15.48.

β-Diethylaminoethyl p-Tolyl Sulfide

$p\text{-}CH_3C_6H_4SC_2H_4N(C_2H_5)_2$

An anhydrous ether-toluene solution containing 26.4 gm.

[20] Apparently, the formation of di-hydrochlorides by di-amines, while uncommon, is not unknown. See the following:
Trapesonzjanz, Ber., 25, 3280 (1892).
Colson, Bull. soc. chim., 48, 800.
Harries, Ann., 417, 107-191 (1918). See p. 134.

[21] Perkin, Bentley and Haworth, J. Chem. Soc., 69, 165 (1896).

(0.15 mole) of β-chloroethyl p-tolyl sulfide (p-$CH_3.C_6H_4S$ CH_2CH_2Cl) and 22 gm. (0.3 mole) of diethylamine was refluxed 4 hours at 60° without evidence of reaction. Then 0.15 mole of diethylaminomagnesiumbromide was prepared from phenylmagnesiumbromide and diethylamine. When this was added, a violent reaction took place. After 9 hours refluxing at 55°, the well-cooled mixture was hydrolyzed with dilute hydrochloric acid, the resulting two layers separated, and the toluene-ether layer discarded. The water layer was then treated with sodium hydroxide, and the yellow oil resulting separated, by extracting with ether.

Considerable difficulty was experienced in purifying this oil. A fraction was finally secured which boiled at 132-134°/3 mm. A qualitative analysis showed nitrogen, sulfur and carbon present, and the oil in dry ether when treated with hydrogen chloride formed a white solid. This solid also proved difficult to purify, but repeated recrystallizations from acetone gave a product melting at 124°, a melting point which could not be raised by further recrystallization.

Analysis: Volhard for Cl.

Calcd. for p-$CH_3.C_6H_4SC_2H_4N(C_2H_5)_2.HCl$: Cl, 13.66. Found: 13.21.

β-Diethylaminoethyl p-Tolyl-Sulfone

$p\text{-}CH_3.C_6H_4.SO_2.C_2H_4N(C_2H_5)_2$

A toluene solution containing 22.0 gm. (0.1 mole) of β-chloroethyl p-tolyl sulfone[22] ($p\text{-}CH_3.C_6H_4.SO_2.CH_2CH_2Cl$) was treated with 12.5 gm. (0.17 mole) of diethyl amine. A white solid was gradually deposited, which proved to be diethylamine hydrochloride. This solid was filtered out, and the ether solution shaken with dilute hydrochloric acid. The acid solution was then neutralized with sodium hydroxide, and the resulting oil dissolved in ether and thus separated from the water layer. Distillation yielded a fraction weighing 9.0 gm. (51 per cent yield) boiling at 205°/10 mm. This oil in dry ether, yielded a white solid when treated with hydrogen chloride. After recrystallization from ethyl acetate, this solid melted at 121°.

Analysis: Volhard for Cl.

Calcd. for $p\text{-}CH_3.C_6H_4.SO_2=C_2H_4N(C_2H_5)_2.HCl$: Cl, 12.15.

Found: 12.16.

An attempt to prepare β-diethylaminoethyl p-tolyl-sulfone by oxidation of the corresponding sulfide in acetic acid solution, with 40 per cent hydrogen peroxide[22], failed. A heavy oil which refused to crystallize resulted. It could

[22] The β-chloroethyl-p-tolyl-sulfone was prepared by oxidation of the corresponding sulfide with 40 per cent hydrogen peroxide. An almost quantitative yield of quite pure product was secured. See Fromm and Kohn, Ber., 54, 320-326 (1921).

not be identified.

β-Diethylaminoethyl-Phenyl-Thionurethane

$C_6H_5NH.C(=S)O-C_3H_4N(C_2H_5)_2$

Phenyl thioncarbamyl chloride ($C_6H_5NH.C(=S)Cl$) is apparently unknown, although phenyl carbamyl chloride is known[23]. It was believed possible to prepare phenyl-thioncarbamyl chloride by the means used to prepare the phenyl carbamyl chloride.

Accordingly, 13.5 gm. (0.1 mole) of phenyl isothiocyanate (C_6H_5NCS) were dissolved in 5 cc. ether and treated with dry hydrogen chloride. The product so formed was not isolated, but was treated with a slight excess of sodium β-diethylaminoethylate in ether solution, the flask being cooled meantime. A vigorous reaction took place, and a white hygroscopic solid formed. This solid was filtered out, dissolved in water, and the water solution neutralized with sodium hydroxide. The insoluble oil so formed was dissolved in ether, the layers separated, and the ether solution dried and treated with hydrogen chloride. A white solid was formed, which melted at 124° when once recrystallized from dry ether. This was the only hydrochloride salt of any of the bases prepared which was soluble in dry ether, from which it crystallized in long needles.

[23]Hentschel, Ber., 18, 1178 (1885).

Analysis: Volhard for Cl.

Calcd. for $C_6H_5NH.C(=S)OC_2H_4N(C_2H_5)_2.HCl$: Cl, 13.02. Found: 13.03.

The preceding experiment seems to prove the existence of phenyl thioncarbamyl chloride. Since the derivative prepared was previously unknown, the ethyl ester of phenyl thioncarbamic acid was made by the same method. The product was purified by recrystallization from petroleum ether, had a melting point of 68°, and other physical and chemical characteristics in agreement with those given by Bamesberger[24].

β-Diethylaminoethyl-Bromide Hydrobromide

$(C_2H_5)_2NC_2H_4Br.HBr$

β-Diethylaminoethyl bromide hydrobromide was prepared by Meyer and Hopff[16] by treating β-diethylaminoethanol with 66 per cent hydrobromic acid. They found it necessary to heat the reaction mixture in sealed tubes at a temperature of 130°. The product was crystallized from absolute alcohol. β-Diethylaminoethyl bromide was prepared by shaking the corresponding hydrobromide with strong sodium hydroxide and distilling the heavy oil resulting. The β-diethylaminoethyl bromide so prepared polymerized very quickly, becoming entirely solid within 30 minutes.

[24]Bamesberger, Ber., 15, 2164 (1882).
Lieberman, Ann., 207, 145 (1881).

β-Diethylaminoethyl bromide hydrobromide was prepared in this laboratory by heating β-diethylaminoethanol with 40 per cent hydrobromic acid in common pressure bottles. These bottles were immersed in an oil bath held at 130°, for 6 hours. The yields ranged from 30 to 55 per cent of the theoretical, the average being 50 per cent. The constants agreed with those given by Meyer and Hopff[16].

β-Diethylaminoethyl Chloride Hydrochloride

$(C_2H_5)_2NC_2H_4Cl.HCl$

β-Diethylaminoethyl chloride has been mentioned[15 25] but no directions for its preparation were available, so far as could be found. Since the corresponding bromide polymerizes so readily[16], it was desired to prepare the chloride.

Some β-diethylaminoethyl chloride hydrochloride had been made in an attempt to prepare the β-diethylaminoethyl esters of sulfurous and phosphorous acids. Accordingly, a dry ether solution containing 36 gm. (0.31 mole) sodium β-diethylaminoethylate was treated with 55 gm. (0.4 mole) phosphorous trichloride, since this had given the largest yield previously. The mixture stood undisturbed for one week, and was then shaken with water. The water layer was then drawn off and neutralized with sodium hydroxide. The neutral solution was extracted with ether, but nothing could be isolated from this

[25] Gilliard, Monnet and Cartier, Brit., 155748, May 27 (1920).

ether layer. 50 per cent of the diethylaminoethylate was recovered as β-diethylaminoethanol, from the original ether solution.

In a second run, with like quantities, sodium acetate was used as a base instead of sodium hydroxide, but no diethylaminoethyl chloride could be isolated.

A variation of the method used by Norris and Taylor[26] was next tried. A mixture of 11.5 gm. (0.1 mole) of diethylaminoethanol, 28 gm. (0.2 mole) of zinc chloride and 25 cc. concentrated hydrochloric acid was refluxed for 12 hours. Excess sodium hydroxide was added and the alkaline solution extracted with ether. The ether solution yielded 8 gm. (66 per cent) unchanged β-diethylaminoethanol, but no β-diethylaminoethyl chloride. A check run gave similar results.

The method used by Meyer and Hopff[16] for preparing β-diethylaminoethyl bromide was finally adopted. A convenient quantity of crystalline β-diethylaminoethanol hydrochloride was sealed in a thick walled glass tube, with an excess of very concentrated hydrochloric acid, and heated from 7 to 14 hours. The hydrochloric acid used was made by saturating very cold concentrated hydrochloric acid with hydrogen chloride. The product was placed in the cooled glass tube immediately, and the latter sealed while the closed end was still in the

[26]Norris and Taylor, J. Am. Chem. Soc., 46, 753 (1924). C. A., 18, 1977 (1924).

ice bath.

The β-diethylaminoethyl chloride hydrochloride secured by this method melts at 207° after recrystallization from alcohol. It was identified by a mixed melting point with the previously secured and analyzed β-diethylaminoethyl chloride[27].

The yields secured ranged from 50 to 95 per cent.

The β-diethylaminoethyl chloride prepared as above, polymerized and turned completely solid within one hour after being freed from the salt by treatment with sodium hydroxide. That prepared from phosphorus trichloride did not. Accordingly, two very pure samples of the β-diethylaminoethyl chloride, made with hydrochloric acid were prepared, to one of which was added two drops of phosphorus trichloride before distillation. Both were sealed in small glass tubes and allowed to stand. The sample without phosphorus trichloride showed some solid after 30 minutes, and was completely solid after 4 hours. The sample containing phosphorus trichloride was very faintly cloudy after 4 hours, 50 per cent solid after 18 hours, and completely solid only after 36 hours had elapsed. A later sample, treated in the same way with phosphorus trichloride was kept in the ice chest 12 months, and showed only 10-15 per cent solid at the end of that time.

The polymerization product was a greasy mass of flat

[27] See experiments on β-diethylaminoethyl phosphite, this paper, p. 33.

platelets, melting above 220°. It was insoluble in ether, ethyl acetate, and acetone, and soluble in alcohol and chloroform. It dissolved in water with a basic reaction, and was quite soluble in hydrochloric acid. When vacuum distilled, it yielded some diethylaminoethanol.

Diethylaminoethyl chloride is a clear, colorless liquid boiling at 147-148°/731 mm.

β-Diethylaminoethyl Chloride with Magnesium

A carefully purified sample of β-diethylaminoethyl chloride, containing traces of phosphorus trichloride, was sealed in a small tube with ether and the very reactive copper magnesium alloy, developed by Gilman, Peterson and Schulze[28]. It was then placed in the ice chest for 18 hours. A similar tube containing the same reagents was allowed to stand 12 hours at room temperature. A third tube, like the others except that it contained a trace of mercuric bromide as well, was shaken vigorously for 12 hours. When opened none of these solutions gave positive reactions for organomagnesium halides, when tested with the reagents developed by Gilman and Schulze[29] for this purpose.

[28] Gilman and Harris, J. Am. Chem. Soc., 49, 1827 (1927). Hurd and Webb, ibid., 49, 546 (1927).
[29] Gilman and Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

β-Diethylaminoethyl-Phenyl-Acetylene

$C_6H_5C{\equiv}CC_2H_4N(C_2H_5)_2$

A dry ether solution containing 10.2 gm. (0.1 mole) of phenyl acetylene ($C_6H_5C{\equiv}CH$) was treated with metallic sodium to prepare sodium phenyl acetylide. To this 10 gm. (0.05 mole) of β-diethylaminoethyl bromide hydrobromide was added. A white solid was precipitated immediately. After 72 hours standing, the white solid was filtered out, dissolved in hydrochloric acid, the solution neutralized with sodium hydroxide and washed with ether. When distilled, the ether washings yielded a small amount of material boiling at 190°/25 mm. This material, dissolved in dry ether and treated with hydrogen chloride, yielded a white solid melting at 142° when recrystallized from acetone.

Analysis: Volhard for Cl.

Calcd. for $C_6H_5C{\equiv}CC_2H_4N(C_2H_5)_2.HCl$: Cl, 14.93. Found: 14.45.

The ether solution and washings yielded about 50 per cent unchanged phenyl acetylene.

The above experiment was repeated several times, but in no other case was any of the product described, found. Why this was so could not be determined.

In another attempt, 15 gm. (0.15- mole) of phenyl acetylene and 40 gm. of β-diethylaminoethyl bromide hydrobromide were mixed and 18 gm. (0.3 mole) of powdered potassium hydroxide added, one gram at a time, with shaking and cooling when

necessary. After standing the mushy solid formed was washed with dry benzene, and the solution so secured, distilled. The main fraction, boiling at 98-115°/7 mm. when dissolved in dry ether and treated with hydrogen chloride, yielded a white solid melting at 210° when recrystallized from acetone. This material could not be identified.

Analysis: Volhard for Cl.

Calcd. for $C_6H_5C{\equiv}CC_2H_4N(C_2H_5)_2.HCl$: Cl, 14.93. Found: 17.37.

An attempt was made to prepare β-diethylaminoethyl-phenyl-acetylene by treating β-chloroethyl-phenyl-acetylene[30] ($C_6H_5C{\equiv}CCH_2CH_2Cl$) with diethylamine. Approximately one equivalent of diethylamine hydrochloride was formed, but none of the other products could be identified.

No physiological tests were made on the compound first described, because of the very small amount left after the analysis was completed. No more of this material could be made.

β-(β-Diethylaminoethyl) Styrene

$C_6H_5CH{=}CHC_2H_4N(C_2H_5)_2$

Styrylmagnesiumbromide was prepared in approximately 50 per cent yield, by using the specially activated magnesium developed by Gilman, Peterson and Schulze[28], with β-bromostyrene ($C_6H_5CH{=}CHBr$). To this material was added an equivalent

[30]Gilman and Beaber, J. Am. Chem. Soc., 45, 839-842 (1922).

amount of β-diethylaminoethyl bromide, freshly prepared. After stirring for 1 hour the reaction mixture was hydrolyzed in the cold, with dilute hydrochloric acid. The ether solution yielded some styrene and β-bromostyrene, but nothing else. The water solution, when neutralized with sodium hydroxide and washed with ether yielded no identifiable products. The water solution when acidified with hydrochloric acid, evaporated to dryness and extracted with various solvents, also yielded nothing identifiable.

Two attempts to prepare β-chloroethyl styrene from styrylmagnesiumbromide and β-chloroethyl p-toluenesulfonate[30] ($p\text{-}CH_3.C_6H_4.SO_3.CH_2CH_2Cl$) failed, giving only 30 to 40 per cent yields of symmetrical diphenylbutadiene ($C_6H_5CH{=}CH.CH{=}CHC_6H_5$).

β-Diethylaminoethyl Phenyl-Mercapto-Formate

$$C_6H_5\cdot S\cdot COOC_2H_4N(C_2H_5)_2$$

Sodium thiophenate was prepared by allowing metallic sodium to react with 10 gm. (0.91 mole) thiophenol in ether solution. Absolute alcohol was added until solution was complete, and then 14 gm. (0.1- mole) of β-chloroethyl chloroformate[31] ($ClCOOC_2H_4Cl$) was added. The whole was stirred 2 hours and allowed to stand overnight. 3 gm. of sodium chloride was filtered out and the solution remaining distilled, yielding 9.5 gm. (41 per cent) of an oil boiling at 180-183°

[30]Gilman and Beaber, J. Am. Chem. Soc., 45, 839-842 (1922).
[31]Nemirowsky, J. prakt. Chem., (2) 31, 174.

/25 mm. This product (representing 0.044 mole $C_6H_5 \cdot S \cdot COOC_2H_4Cl$) was dissolved in dry ether and treated with 4.5 gm. (0.06 mole) of diethylamine. After 12 hours standing, a white solid was filtered out, and separated into two parts by crystallization from ethyl acetate. One part was composed of 0.4 gm. diethylamine hydrochloride and the other of 1.6 gm. diphenyldisulfide. The solution remaining yielded 4.0 gm. of a material boiling at 90-100°/5 mm. This material contained carbon, nitrogen and sulfur, but was insoluble in hydrochloric acid, and gave no precipitate when an ether solution of it was treated with hydrogen chloride. It could not be identified. Since the simple esters of mercaptoformic acids are difficult to prepare, and relatively unstable[32], it was believed that if any β-diethylaminoethyl phenyl-mercapto-formate was formed, it had decomposed to form diphenyl disulfide and the unidentified liquid described.

<u>β-Diethylaminoethyl Sulfinylurethane</u>

$C_6H_5NH \cdot SO \cdot OC_2H_4N(C_2H_5)_2$

A dry petroleum ether solution of 13.9 gm. (0.1 mole) of thionyl aniline ($C_6H_5N:S:O$) was cooled and treated with hydrogen chloride[33]. The solution so prepared was treated with sodium β-diethylaminoethylate, the whole being well cooled and

[32]Hepworth and Clapham, J. Chem. Soc., 119, 1188 (1921).
[33]Michaeles, Ann., 274, 200-266 (1893). See p. 201.

stirred. A white precipitate immediately formed but the mixture was allowed to stand 72 hours, after which it was treated in the cold with enough dilute hydrochloric acid to neutralize it and dissolve the solid.

The ether layer was found to contain no appreciable amount of material, so the acid solution was neutralized with sodium hydroxide, an intensely red oil resulting. This oil, dissolved in ether and separated from the water layer, was dried over calcium chloride, and treated with hydrogen chloride. A greasy white solid appeared, which melted at 195° after recrystallization from acetone.

Analysis: Volhard for Cl.

Calcd. for $C_6H_5NH\cdot S(=O)\cdot OC_3H_4N(C_2H_5)_2\cdot 2HCl$: Cl, 21.54. Calcd. for $C_6H_5NH\cdot SOOC_2H_4N(C_2H_5)_2\cdot HCl$: Cl, 12.16. Found: 15.84.

In another run, 7.0 gm. (0.5 mole) thionyl aniline and 6 gm. (0.5 mole) diethylaminoethanol were placed in a glass tube, the tube sealed and allowed to stand 5 months. At the end of that time a small amount of white solid had formed. This solid melted with decomposition at 227°, was insoluble in ether, toluene, alcohol, acetone, ethyl acetate, and chloroform, very slightly soluble in water or hydrochloric acid.

The mother liquors yielded an oil boiling at 110-130°/25 mm. This oil, in dry ether solution, when treated with hydrogen chloride yielded a white solid, melting at 192° after

recrystallization from acetone. Mixed melting point determinations with the solid from the first run proved the two solids identical.

Evidently the desired ester cannot be prepared by the two methods tried.

β-Diethylaminoethyl-Dibenzoylmethane

$(C_2H_5)_2NC_2H_4 \cdot CH:(COC_6H_5)_2$

A mixture composed of 22.4 gm. (0.1 mole) of dibenzoylmethane ($C_6H_5CO \cdot CH_2COC_6H_5$), and 25 gm. (0.1 mole) of β-diethylaminoethyl bromide hydrobromide was treated with 11.2 gm. (0.2 mole) of powdered potassium hydroxide. A vigorous reaction resulted, so the flask was cooled and shaken during the slow addition of the potassium hydroxide. After 2 hours standing, the liquid was decanted and distilled, the main fraction coming over at 230-250°/15 mm. It was found to be unchanged dibenzoylmethane, and represented a 50 per cent recovery.

The solid residue was then dissolved in hydrochloric acid, the solution neutralized and extracted with ether. The dried ether extract yielded a very small amount of white solid, when treated with hydrogen chloride. This solid was insoluble in acetone, but melted sharply at 180° without recrystallization. It could not be identified.

In a second run, 11.2 gm. (0.05 mole) of dibenzoylmethane were treated with sodium, in absolute alcohol. An equivalent

quantity of β-diethylaminoethyl bromide hydrobromide was then added, and the whole allowed to stand one week. Since only a small amount of white solid had precipitated, 0.05 mole of sodium ethylate was added, and the mixture allowed to stand another week, being occasionally shaken. The white solid was then filtered out and found to be sodium chloride, weight 4.5 gm. The alcohol solution was then distilled, and the major fraction collected at 230°/30 mm. It was found to be unchanged dibenzoylmethane, weight 4.5 gm., representing 82 per cent recovery.

A third run, using the procedure just described gave similar results. Evidently the compound desired cannot be prepared by these methods.

β -Diethylaminoethyl Chlorocarbonate

$ClCOOC_2H_4N(C_2H_5)_2$

A variation of the method used by Hamilton and Johnson[34] for the preparation of ethyl chlorocarbonate ($ClCOOC_2H_5$) was used. 50 cc. of a 20 per cent toluene solution of carbonyl chloride (approximately 0.1 mole) were allowed to react with 11.7 gm. (0.1 mole) of β-diethylaminoethanol, being well stirred and cooled in the meantime. Dilute hydrochloric acid was then added and the toluene layer discarded. The acid solution was washed with ether, and then neutralized with sodi-

[34]Hamilton and Johnson, J. Am. Chem. Soc., 48, 1405 (1926).

um hydroxide, but no identifiable products were secured.

A duplicate run under carefully regulated anhydrous conditions resulted in a like result.

In a third run, β-diethylaminoethanol hydrochloride was used instead of β-diethylaminoethanol. The mixture was heated to 60° for 12 hours, and then allowed to stand 5 days. Approximately 75 per cent of the diethylaminoethanol hydrochloride was recovered, but nothing else could be identified.

In a fourth run 0.2 mole of β-diethylaminoethanol hydrochloride was sealed in a large bottle with approximately 0.2 mole carbonyl chloride in toluene. After 2 months standing in the shade, examination showed two layers, the lower one containing crystals melting at 211° after recrystallization from acetone.

Analysis: Volhard for Cl.

Calcd. for $ClCOOC_2H_4N(C_2H_5)_2$: Cl, 16.42.

Calcd. for $ClCOOC_2H_4N(C_2H_5)_2 \cdot HCl$: Cl, 32.84.

Calcd. for $C{=}O(OC_2H_4N(C_2H_5)_2)_2 2HCl$: Cl, 21.32. Found: 24.04.

An attempt to prepare from this product, the β-naphthol derivative mentioned by Einhorn and Rothlauf[35] was unsuccessful. Evidently then, β-diethylaminoethyl chlorcarbonate could not be prepared by the methods used.

In order to check the purity of the carbonyl chloride solu-

[35]Einhorn and Rothlauf, Ann., 382, 257 (1911).

tion benzyl chlorcarbonate[36] was prepared. The yield indicated the carbonyl chloride solution to be between 15 and 20 per cent strength, and to be reactive.

β-Diethylaminoethyl-Diphenyl-Arsene

$(C_6H_5)_2AsC_2H_4N(C_2H_5)_2$

A mixture composed of 19.5 gm. (0.1 mole) of diphenyl arsene ($(C_6H_5)_2AsH$) and a slight excess of β-diethylaminoethyl bromide hydrobromide was placed in a closed flask. To this mixture was added 12 gm. (0.2 mole) of powdered potassium hydroxide, a small amount at a time. The flask was well shaken after each addition, and when all the potassium hydroxide had been added, was allowed to stand 20 hours. The oily mass was twice washed with ether, the solid discarded and the ether washings shaken with dilute hydrochloric acid. The acid solution was then separated and neutralized with sodium hydroxide, the resulting oil being dissolved in ether and the two layers thus separated. From this ether solution 7 gm. of an oil boiling at 210-220°/15-20 mm. were secured. This oil contained carbon, nitrogen, and arsenic, and when treated with hydrogen chloride formed an ether insoluble solid. It was found impossible to purify this solid so that it had a sharp melting point, or a constant one, even, so quantitative anal-

[36]Thiele and Dent, Ann., 302, 257 (1898).

ysis was not made. Attempts to purify the free base also failed. No physiological tests were made.

Di-(β-Diethylaminoethyl) Sulfite

$((C_2H_5)_2NC_2H_4)_2SO_3$

Hixon and Allison[37] have found that many sodium alcoholates reacted with thionyl chloride to give esters of sulfurous acid.

Accordingly 11.7 gm. (0.1 mole) of β-diethylaminoethanol was converted into the sodium derivative and treated with 23.0 gm. (0.2 mole) of thionyl chloride, cooling being necessary to control the vigorous reaction. The white solid formed during the course of the reaction turned brown on warming to room temperature. A sample of it turned to a water soluble, black, tarry mass in 4 days. The solid was dissolved in water, washed with ether, and an excess of sodium hydroxide solution added. A very small amount of an oil boiling at 70°/10 mm. was secured, which in ether solution, with hydrogen chloride formed a solid, melting at 207° after recrystallization from acetone.

Analysis: Volhard for Cl.

Calcd. for $(C_2H_5)_2NC_2H_4Cl\cdot HCl$: Cl, 20.64. Found: 20.54.

None of the ether solutions contained any appreciable amounts of material.

[37] Hixon and Allison, J. Am. Chem. Soc., 48, 406-410 (1926).

A second run, using 0.15 mole of sodium β-diethylaminoethylate and 0.1 mole of thionyl chloride, yielded 1.0 gm. β-diethylaminoethyl chloride hydrochloride but no di(β-diethylaminoethyl) sulfite, or any other identifiable product.

Two check runs were made using sodium γ-diethylaminopropylate ($(C_2H_5)_2NCH_2CH_2CH_2ONa$) instead of sodium diethylaminoethylate. About 50 per cent of the alcohol was recovered unchanged, but nothing else could be identified.

Di-(β-Diethylaminoethyl) Sulfate

$((C_2H_5)_2NC_2H_4)SO_4$

Sodium β-diethylaminoethylate was prepared by treating 23.4 (0.2 mole) of β-diethylaminoethanol with sodium, in dry ether. While this solution was being stirred and cooled, 13.5 gm. (0.1 mole) of sulfuryl chloride in dry ether was slowly added. A white solid formed, which gradually turned a dark brown. After 3 hours water was added until all the solid was dissolved.

The ether layer yielded 5 gm. (21 per cent) of β-diethylaminoethanol. The water layer which was alkaline in reaction was treated with excess sodium hydroxide, but yielded no identifiable product. The water solution was then neutralized with hydrochloric acid, evaporated to dryness and extracted with chloroform, yielding 7 gm. of β-diethylaminoethanol hydrochloride. The total amount of recovered β-diethylaminoethanol was 40 per cent. No other identifiable products were found.

A second run, using 1 equivalent of sulfuryl chloride in excess gave no identifiable products and no recovered β-diethylaminoethanol.

A check run using 1 equivalent of sodium γ-diethylaminopropylate and 1 equivalent sulfuryl chloride resulted in 38 per cent of the alcohol used being recovered.

Using another method, 15 gm. (0.05 mole) of silver sulfate were stirred violently with an equivalent amount of freshly prepared β-diethylaminoethyl bromide. Apparently no reaction took place, and 50 per cent of the silver sulfate was recovered unchanged. A small amount of unidentified solid, melting at 121°, and containing nitrogen but no sulfur, crystallized from the ether solution. Complete evaporation of the ether gave an intractable tarry mass, some of which was char, and the rest tar.

Evidently di-(β-diethylaminoethyl) sulfate cannot be prepared by the two methods tried.

Tri-(β-Diethylaminoethyl) Phosphite

$((C_2H_5)_2NC_2H_4)_3PO_3$

Sodium β-diethylaminoethylate was prepared by treating 34 gm. (0.3 mole) of β-diethylaminoethanol in dry ether solution with the equivalent quantity of metallic sodium. To this solution, while being cooled and stirred, was added an ether solution containing 55 gm. (0.36 mole) of phosphorus trichloride. A white precipitate which quickly turned yellow, was

formed. After 3 days standing, enough water was added to dissolve the solid, and the two layers so formed, separated.

Sodium acetate was added to the water solution until an alkaline reaction was secured, and the oil formed dissolved in ether. This oil proved to be β-diethylaminoethyl chloride, boiling at 148°/739 mm. The amount secured represented a yield of 29 per cent.

No identifiable products could be secured from any of the other portions of the reaction mixture.

This experiment was repeated several times, as described under the preparation of β-diethylaminoethyl chloride. No tri-(β-diethylaminoethyl) phosphite was secured in any case. Evidently the β-diethylaminoethyl esters of sulfurous, sulfuric, and phosphorous acids cannot be prepared by Hixon and Allison's method[87].

Analytical Methods

Unless otherwise specified, the Volhard method for quantitative determination of ionizable chlorine was used. Except for one or two analyses on compounds containing sulfur, the end point was sharp and distinct.

To check its accuracy under the conditions to be used, analyses on known pure compounds were made.

Analysis: Volhard for Cl.

Calcd. for $(C_2H_5)_2NH \cdot HCl$: Cl, 32.38. Found: 32.32.

Calcd. for $(C_2H_5)_2NC_2H_4OH \cdot HCl$: Cl, 23.12. Found: 23.20.

No difficulty was experienced in checking duplicate analyses, or aliquots where aliquots were used, usually within 0.1 of one per cent.

As a further check on the validity of the method used, the following halogen determinations by the Carius method were made.

Analysis: Carius for Cl.

Calcd. for $\beta\text{-}C_{10}H_7COOC_2H_4N(C_2H_5)_2 \cdot HCl$: Cl, 11.53. Found: 11.39.

Calcd. for $C_6H_4(CO)_2NC_2H_4N(C_2H_5)_2 \cdot HCl$: Cl, 12.54. Found: 12.70.

PHYSIOLOGICAL TESTS

By Dr. L. W. Rowe of Parke, Davis and Company,
Detroit, Michigan.

Rabbit Cornea Method for Testing Local Anesthetic Action

I. $(C_2H_5)_2NC_2H_4 \cdot CH \cdot (COOC_2H_5)_2$:

6-22-27: 0.2 cc. of a 5 per cent solution instilled into right eye of gray rabbit at 2:59 p.m. At 3:00 there was complete anesthesia. Tests were made at 3:05, 3:12, 3:17 3:22, 3:26, 3:31, 3:35, 3:40, 3:45, 4:00, 4:20, and 4:30 p.m. Anesthesia was still complete at 4:30. The solution was irritant.

6-24-27: 0.2 cc. of a 2 per cent solution instilled into right eye of brown rabbit at 2:51 p.m. At 2:53, since no anesthesia was apparent, 0.2 cc. of the same solution was added. Anesthesia resulted at 2:54. Tests were made at 2:59, 3:07, 3:12, 3:17, 3:22, 3:27, and 3:33 p.m. Sensation had returned at 3:37 p.m.

6-25-27: 0.2 cc. of a 1 per cent solution instilled into right eye of gray rabbit at 2:27. There was no anesthesia at 2:27, 2:28, 2:30, p.m. There was anesthesia when tested at 2:38, 2:49 and 3:00. Sensation had returned at 3:01 p.m.

6-27-27: 0.2 cc. of an old 1 per cent solution instilled in left eye of brown rabbit, at 11:22 a.m. There was no

effect at 11:23. Another 0.2 cc. was added at 11:24. No effect was noticeable at 11:25 a.m.

6-28-27: 0.2 cc. of a 1 per cent solution instilled into eye of brown rabbit at 9:36 a.m. There was no effect at 9:37, so an additional 0.2 cc. was instilled. No effect had resulted at 9:38.

1-16-28: A 4 per cent solution of hydrochloride salt instilled in rabbit's eye with no effect. Frog sensory nerve method showed no effect. The solution was less than 10 per cent as active as cocaine.

II. $C_6H_4(CO)_2NC_2H_4N(C_2H_5)_2 \cdot HCl$:

6-22-27: 0.2 cc. of a 2 per cent solution instilled into left eye of red rabbit at 1:30 p.m. There was no effect at 1:31, 1:32, or 1:33 p.m. The solution was inactive .

III. $C_2H_5CH=CHCOOC_2H_4N(C_2H_5)_2$:

6-22-27: 0.2 cc. of a 5 per cent solution instilled into left eye of gray rabbit at 3:02 p.m. At 3:03 anesthesia was complete. Still anesthetized when tested at 3:10, 3:15, 3:20, 3:25, 3:30, 3:35, 3:40, 3:45, 4:00, 4:20 and 4:30 p.m. The solution was irritating.

6-24-27: 0.2 cc. of a 2 per cent solution instilled into left eye of brown rabbit at 3:01. Anesthetized at 3:02, 3:06, 3:11, and 3:16 p.m. Sensation had returned at 3:21.

6-25-27: 0.2 cc. of a 2 per cent solution instilled into left eye of gray rabbit at 2:35 p.m. There was no effect

at 2:36. Anesthetized at 2:37, 2:40 and 2:49 p.m. Sensation had returned at 2:55 p.m.

6-27-27: 0.2 cc. of a 1 per cent solution instilled into left eye of brown rabbit at 9:40 a.m. Slight anesthesia at at 9:41, and complete anesthesia at 9:46, 9:56 a.m.

6-27-27: 0.2 cc. of a 1 per cent solution instilled into right eye of brown rabbit at 11:15 a.m. There was no effect at 11:16 and 11:18. 0.2 cc. more instilled at 11:18. There was no effect at 11:19. An old solution used in this test and found very irritant.

1-16-27: 4 per cent solution of the hydrochloride salt instilled in eye of rabbit. A slight anesthesia was produced. With the frog sensory nerve method, there was no effect in 4 per cent solution. This local anesthetic was slightly more than 10 per cent as effective as cocaine.

IV. α-$C_{10}H_7COOC_2H_4N(C_2H_5)_2 \cdot HCl$:

6-21-27: 0.2 cc. of a 2 per cent solution instilled at 3:17 p.m. There was complete anesthesia at 3:18 and 3:23 p.m. Sensation returned at 3:31 p.m. Duration - 10 minutes.

6-20-27: 0.2 cc. of a 2 per cent solution instilled at 1:22 p.m. There was complete anesthesia at 1:23 and 1:28. Sensation returned at 1:34 p.m. Duration - 10 minutes.

V. β-$C_{10}H_7COOC_2H_4N(C_2H_5)_2 : HCl$:

6-20-27: 0.2 cc. of a 2 per cent solution instilled at 3:21 p.m. Anesthesia was complete at 3:22, 3:27. Sensation

began to return at 3:32 and had entirely returned at 3:37 p.m. Duration - 10 to 15 minutes.

6-20-27: 0.2 cc. of a 2 per cent solution instilled at 1:19 p.m. There was complete anesthesia at 1:20, 1:26. Sensation returned at 1:34 p.m. Duration - 10 to 15 minutes.

VI. $C_6H_5N\cdot(CH_3)\cdot C_2H_4N(C_2H_5)_2\cdot 2HCl$:

6-22-27: 0.2 cc of a 2 per cent solution instilled into left eye of white rabbit at 2:34 p.m. There was no effect at 2:35 or 2:36 p.m. The solution was irritating.

VII. $C_6H_5OC_2H_4N(C_2H_5)_2\cdot HCl$:

6-22-27: 0.2 cc. of a 2 per cent solution instilled into right eye of white rabbit at 2:29 p.m. There was no effect at 2:30, 2:32. The solution was irritating. It had a noticeable effect on the human tongue.

VIII. $p\text{-}CH_3\cdot C_6H_4SC_2H_4N(C_2H_5)_2\cdot HCl$:

6-21-27: 0.2 cc. of a 2 per cent solution instilled into eye of rabbit at 10:39 a.m. Anesthesia was complete at 10:40. Sensation had returned at 10:45 a.m. The solution was quite irritant.

6-21-27: 0.2 cc. of a 2 per cent solution instilled into left eye of rabbit at 1:56 p.m. Anesthesia was complete at 1:57, 2:02 and 2:07. Sensation had returned at 2:12 p.m. The solution was slightly irritating.

6-21-27: 0.2 cc. of a 2 per cent solution instilled into left eye of rabbit at 2:55 p.m. Anesthesia was complete at 2:56 and 3:01. Sensation had returned at 3:06. The solution

was irritant.

IX. p-$CH_3 \cdot C_6H_4 \cdot SO_2 \cdot C_2H_4N(C_2H_5)_2 \cdot HCl$:

6-22-27: 0.2 cc. of a 2 per cent solution instilled into right eye of red rabbit at 1:22 p.m. There was no effect at 1:23 and 1:26 p.m.

X. $C_6H_5 \cdot NH \cdot C(=S) \cdot OC_2H_4N(C_2H_5)_2 \cdot HCl$:

6-21-27: 0.2 cc. of a 2 per cent solution instilled into right eye of rabbit at 1:50 p.m. There was complete anesthesia at 1:51, 1:55, 2:00, 2:07 and 2:10. Sensation had returned at 2:15 p.m.

6-21-27: 0.2 cc. of a 2 per cent solution instilled into right eye of rabbit at 10:36 a.m. Anesthesia was complete at 10:37, 10:41 and 10:46. Sensation had returned at 10:51 a.m.

6-21-27: 0.2 cc. of a 2 per cent solution instilled into right eye of rabbit at 2:52 p.m. There was complete anesthesia at 2:53, 2:57, 3:02 and 3:07. Sensation had returned at 3:12 p.m. The solution was irritant.

XI. $(C_2H_5)_2NC_2H_4Br \cdot HBr$:

6-21-27: 0.2 cc. of a 2 per cent solution instilled into right eye of rabbit at 3:26. There was no effect at 3:27 and 3:28 p.m. The solution was irritant.

XII. $(C_2H_5)_2NC_2H_4Cl \cdot HCl$:

6-21-27: 0.2 cc. of a 2 per cent solution instilled into left eye of rabbit at 3:29 p.m. Slight anesthesia at 3:30. Sensation had completely returned at 3:33. The solution was irritant.

XIII. $(C_2H_5)_2NH \cdot HCl$:

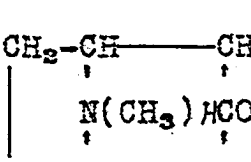
6-23-27: 0.2 cc. of a 2 per cent solution instilled into left eye of white rabbit at 4:35 p.m. There was anesthesia at 4:36. Sensation had returned at 4:41 p.m. There was no sensation on the tongue or when injected.

XIV. $(C_2H_5)_2 \cdot NC_2H_4OH \cdot HBr$:

6-24-27: 0.2 cc. of a 2 per cent solution instilled into left eye of brown rabbit at 4:32 p.m. There was complete anesthesia at 4:33, 4:38, 4:42, 4:47, 4:52 and 4:55 p.m. Sensation had not returned when test had to be ended. Duration - at least 23 minutes.

6-25-27: 0.2 cc. of a 1 per cent solution instilled into right eye of blue rabbit at 10:16 a.m. Anesthesia was complete at 10:17, 10:22 and 10:59. Sensation had returned at 11:00 a.m. Duration - 44 minutes. There was no anesthesia on the human tongue, or when injected.

TABLE I

Compound	Strength of Solution	Irritation	Duration of Anesthesia	Rating[38,4]
 Cocaine Hydrochloride	2%	none	30 min.	10
	1%	"	15-20min	
	0.5%	"	8-10 min	
I. $(C_2H_5)_2NC_2H_4 \cdot CH \cdot (COOC_2H_5)_2 \cdot HCl$	4%	none	no effect	0
$(C_2H_5)_2NC_2H_4 \cdot CH(COOC_2H_5)_2$ (Free base)	5%	marked	60 min.	Less than 10% as effective as cocaine
	2%	slight	35 "	
	1%	"	20 "	
II. $C_6H_4(CO)_2NC_2H_4N(C_2H_5)_2 \cdot HCl$	2%	very slight	no effect	0
III. $C_2H_5CH=CHCOOC_2H_4N(C_2H_5)_2HCl$	4%	none	slight anesthesia	1.0
$C_2H_5CH=CHCOOC_2H_4N(C_2H_5)_2$ (Free base)	5%	marked	60 min.	More than 10% as effective as cocaine
	2%	slight	20 "	
	1%	"	20 "	
IV. α-$C_{10}H_7 \cdot COOC_2H_4N(C_2H_5)_2 \cdot HCl$	2%	very slight	10 min.	3.33
V. β-$C_{10}H_7 \cdot COOC_2H_4N(C_2H_5)_2 \cdot HCl$	2%	very slight	10-15min	3.33-5
VI. $C_6H_5N(CH_3)C_2H_4N(C_2H_5)_2 \cdot 2HCl$	2%	rather marked	no effect	0

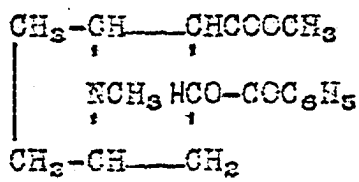
Compound	Strength of Solution	Irritation	Duration of anesthesia	Rating
VII. $C_6H_5OC_2H_4N(C_2H_5)_2 \cdot HCl$	2%	rather marked	shows action on tongue	0
VIII. $p\text{-}CH_3 \cdot C_6H_4SC_2H_4N(C_2H_5)_2 \cdot HCl$	2%	marked	10-15min	3.3-5
IX. $p\text{-}CH_3 \cdot C_6H_4 \cdot SO_2 \cdot C_2H_4N(C_2H_5)_2 \cdot HCl$	2%	very slight	no effect	0
X. $C_6H_5NHC(=S)OC_2H_4N(C_2H_5)_2 \cdot HCl$	2%	very slight	20 min.	6.66
XI. $(C_2H_5)_2NC_2H_4Br \cdot HBr$	2%	marked	no effect	0
XII. $(C_2H_5)_2NC_2H_4Cl \cdot HCl$	2%	marked	slight	0
XIII. $(C_2H_5)_2NH \cdot HCl$	2%	very slight	10 min.	3.33
XIV. $(C_2H_5)_2NC_2H_4OH \cdot HBr$	2%	very slight	25+ min.	8.33 to 13.66
	1%	"	44 "	

[38] Cocaine has been selected arbitrarily as a standard and given a value of 10. The ratings given in the last column of the preceding table were determined by comparing the duration time with that of a solution of cocaine hydrochloride of like concentration.

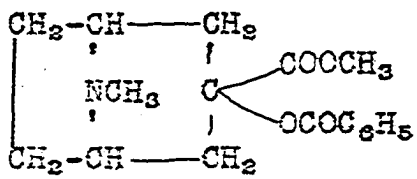
DISCUSSION OF RESULTS

Great care must be taken in a discussion of the relationship of chemical constitution to physiological action. Even more caution must be exercised in the interpretation of the results of experiments dealing with this relationship. As an illustration of the far-reaching effect that comparatively minor changes in chemical constitution may have on physiological action, the following examples are given.

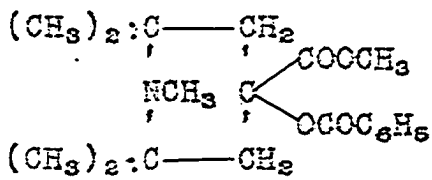
Natural cocaine has the following structure:



It has a marked local anesthetic action. ∝-Cocaine, with the following structure has no such action:



A third substance, ∝-eucaine, resembling ∝-cocaine more than it does cocaine, has marked local anesthetic action:



The Effect of Unsaturation on Local Anesthetic Action

Kamm[39] has demonstrated that compounds of the procaine type showed local anesthetic action when the carbonyl group of the ester was attached to an atom that was a member of an unsaturated group. Gilman and Pickens[4] showed that this was also true when the carbonyl group was attached to aromatic nuclei other than benzene. Gilman, Heckert and McCracken[40] have shown that local anesthetic action persisted when the carbonyl group of the ester was attached to unsaturated aliphatic radicals. Compounds containing the ethylenic linkage ($H_2C=CH-$) and the trichloromethyl (Cl_3C-) group were tested. This present work extends the investigation to other unsaturated groups, and to the unsaturated atoms, trivalent nitrogen, divalent oxygen, and divalent sulfur[41]. Unsaturated groups comprising a part of the pharmacaphore itself also caused increased local anesthetic action[42].

Use will be made later of the term 'degree of unsaturation'. Little definite information is available concerning the extent to which there is a variation in the unsaturation

[39] Kamm, J. Am. Chem. Soc., 42, 1030 (1920).
[40] Gilman, Heckert and McCracken, J. Am. Chem. Soc., 50, 437 (1928).
[41] For a comprehensive discussion of unsaturation, and types of unsaturated groups, see Stewart's "Recent Advances in Organic Chemistry" (Longmans, Green and Company, 1927) I, 307-318.
[42] See section on 'Effect of the Ethylene Group', p. 54.

of the groups called 'unsaturated' [41]. That such a variation exists is shown by the fact that certain groups react as though unsaturated toward one reagent, and quite saturated toward another[43, 41], although this second reagent may react quite readily with another 'unsaturated' group. As an illustration of this, bromine adds quite readily to the double bonds in ethylene, but not at all to those of benzene. Apparently, the degree of unsaturation of the ester group was increased by the substitution of divalent sulfur for divalent oxygen in the carbonyl group[44], because increased local anesthetic action resulted. Sulfur probably is more unsaturated when divalent, than is oxygen, for the compounds of tetravalent sulfur are more stable than those of tetravalent oxygen[45]. Compounds of hexavalent sulfur are even more stable, while hexavalent oxygen is unknown.

A discussion of the theories[46, 68] of physiological action

[43] Vorländer, Ann., 320, 66 (1902). See also Vorländer, Ber., 34, 1633 (1901).

[44] See section on "The Thion Ester Group", p. 63.

[45] Oxonium Compounds, Collie and Tickle, J. Chem. Soc., 75, 710 (1899), Baeyer and Villager, Ber., 34, 2679 (1901).

[46] A discussion of the various theories of physiological action may be found in such books as Fränkels "Die Arzneimittelsynthese" (Springer, 1921) 10-42, or Mays "Chemistry of Synthetic Drugs" (Longmans, Green and Co., 1921) 1, 16, 36. For some later developments, see also Meyer and Bullroth, Z. Phys. Chem. 112, 55-79 (1921), C.A., 15, 2925 (1921).
Yumikura, Biochem. Z., 157, 359-70 (1925).
Moreau, Chem. Reviews, 212, 190.
Traube and Klein, Biochem. Z., 120, 111-24 (1921).
Copeland and Notton, Brit. Med. J., 1925, 547.

is out of place in this dissertation. It is desirable however to call attention to one such theory which may have a direct bearing on the results of this research. Mathews[47] has suggested that a union between the nerve tissue and the molecule of a local anesthetic was brought about by means of residual valencies somewhere in the molecule of the compound.

The Effect of Unsaturated Groups

The Effect of the Ester Group:

Many of the compounds known to have local anesthetic action have somewhere in the molecule, an ester group. In compounds of the procaine type, this ester group links the pharmacaphore to the remainder of the molecule. The presence of this ester group certainly aids local anesthetic action, as a consideration of the following compounds shows.

β-Diethylaminoethyl phenyl-urethane[48] ($(C_2H_5)_2NC_2H_4OOC\cdot NH\cdot C_6H_5$) and β-diethylaminoethyl phenylmethyl-urethane[49] ($(C_2H_5)_2NC_2H_4OOC\cdot N\cdot CH_3\cdot C_6H_5$) both showed local anesthetic action. A compound corresponding to the latter, but without the ester group ($C_6H_5N\cdot CH_3\cdot C_2H_4N(C_2H_5)_2$) [14] did not show local anesthetic action.

[47]Mathews, Intern. Z. physik. chem. Biol., 1, 433-49 (1914), C.A., 9, 2940 (1915), J. Chem. Soc. 108, 106 (1915).
[48]Fromherz, Arch. Exp. Path. Pharmakol., 76, 266 (1914).
[49]Farb. Merster, Lucius and Brunning, Ges. 272529, Apr. 3 (1914), Chem. Zentr., I, 85, 1534 (1914).

On the other hand, the presence of the ester group is not essential to the property of local anesthetic action. Benzyl alcohol has local anesthetic action[13], as does holocaine[50] $(CH_3C(=N\cdot C_6H_4\cdot OC_2H_5)(-NH\cdot C_6H_4\cdot OC_2H_5))$, and certain of its derivatives. Diethylamine $((C_2H_5)_2NH)$[51], β-diethylaminoethanol $((C_2H_5)_2NC_2H_4OH)$, and β-diethylaminoethyl p-tolyl sulfide $(p\text{-}CH_3\cdot C_6H_4SC_2H_4N(C_2H_5)_2)$, prepared and tested in this research, all showed marked local anesthetic action[14].

Two explanations for the influence of the ester group on local anesthetic action may be offered. The first of these is in accord with the results obtained in investigating the effect of the other unsaturated groups[39].

The ester group $(C(:O)\cdot O\cdot R)$ contains the unsaturated carbonyl group $(C:O)$[41]. The pharmacaphore (R) is attached to the carbon atom of this group by divalent oxygen, an unsaturated atom. Taken as a whole, the ester group possesses a certain degree of unsaturation. As will be shown later, unsaturated atoms, or groups attached to the pharmacaphore increases local anesthetic action[42]. If this be strictly true, all esters containing pharmacaphore groups should show local

[50]Hill and Rabinowitz, J. Am. Chem. Soc., 48, 732-737 (1926) Hill and Cox, J. Am. Chem. Soc., 48, 3214, 1926.
[51]Phenylethylamine shows local anesthetic action. Abelin, Biochem. Z., 141, 458-70 (1923).

anesthetic action. Kamm[37] has shown this is not the case, for he found that the carbonyl group of the ester must be attached to an unsaturated atom, if the compound shows local anesthetic action. It may be that the ester group alone does not possess a sufficient degree of unsaturation to cause this effect. When attached to an unsaturated atom or group, however, this degree of unsaturation may be increased to such an intensity that local anesthetic action results. If this is the case, a part of the function of the neighboring unsaturated group may be to increase the degree of unsaturation of the ester group.

Such an action is not unknown, because various unsaturated groups in the same molecule do effect each others activity to a certain extent[52]. This is especially true when the unsaturated groups are arranged in the so-called conjugated manner. The presence of two ester groups in the same molecule might then cause an increase in local anesthetic action. This was not the case with the compounds tested[14]. The literature furnishes conflicting data[53] so a definite conclusion can hardly be drawn.

[52]Thiele, Ann., 306, 87-170 (1899); Posner, Ber., 34, 1395 (1901), 35, 799 (1902), 36, 4305 (1903), 38, 646 (1905), 39, 3515 (1906), 40, 218 (1907); Posner and Opperman, Ber., 39, 3705 (1906), Blaise, Bull. soc. chim. III, 33, 42 (1905).

[53]Pyman, J. Chem. Soc., 93, 1793-1807 (1908).

An example of the effect of increasing the degree of unsaturation of the ester group is furnished by the behavior of β-diethylaminoethyl phenylthionurethane ($C_6H_5NHC(=S)OC_2H_4N(C_2H_5)_2$) [44]. This compound shows an increase in local anesthetic action over the corresponding compound without the sulfur. Substitution of sulfur for the carbonyl oxygen should render the ester group more unsaturated, for sulfur is more unsaturated than oxygen.

The second explanation of the influence of the ester group is offered because of the surprising local anesthetic action of β-diethylaminoethanol ($(C_2H_5)_2NC_2H_4OH$)) [14]. This compound, tested as the hydrochloride salt, had a cocaine coefficient of 8.3 to 13.6 by the rabbit cornea method, although inactive when injected. The free β-diethylaminoethanol was very active.

Esters hydrolyze quite readily to give the alcohol and the acid from which they were originally formed. Since β-diethylaminoethanol was found to be so active, possibly esters and other physiologically active compounds containing the pharmacaphore ($(C_2H_5)_2NC_2H_4$-) hydrolyze to give the aminoalcohol in the free state.

Copeland and Notton[7] state that the effect of a local anesthetic is due to the selective affinity of its <u>free base</u> for nerve fibrils. They base this conclusion on the behavior of the borocaines, which are borate salts of anesthetics of

the procaine type. The conclusion is further supported by the fact that local anesthetics as free bases[14] are much more effective than the strong acid salts of the same compounds.

The idea of a hydrolysis of the ester to give free β-diethylaminoethanol which is physiologically active, seems a logical extension of this reasoning.

A comparison of the effects of di-(β-diethylaminoethyl) diphenate $(C_6H_4COOC_2H_4N(C_2H_5)_2)_2$ [54] and diethyl β-diethylaminoethyl malonate $((C_2H_5)NC_2H_4 \cdot CH \cdot (COOC_2H_5)_2)$ seems to support the theory of a hydrolysis to free β-diethylaminoethanol. The first of these compounds when injected as a 0.05 per cent solution of the hydrochloride salt produced local anesthesia for 5 to 10 minutes. The second compound, as a 4 per cent solution of the hydrochloride salt was inactive by the rabbit cornea method. The ester groups of this latter compound cannot hydrolyze to give β-diethylaminoethanol.

If hydrolysis of the ester does take place, the basicity[56] of the aminoalcohol used to esterify the carboxyl group at once becomes an important factor in that it will influence the rate of hydrolysis.

It is fully realized that there are many objections to the idea that hydrolysis of esters frees an aminoalcohol

[54]Roberts and Johnson, J. Am. Chem. Soc., 47, 1396-1402 (1925).

which has local anesthetic action. The local anesthetic action of many compounds having ester groups[15] in the molecule cannot at present be explained on this basis. On the other hand many compounds which should readily hydrolyze[53] to give β-diethylaminoethanol, show no local anesthetic action. Still other compounds showing local anesthetic action, yield only inactive products on hydrolysis[55]. However, in view of the evidence presented, partially supported as it is by the results of other investigators[55,64], it is felt that the idea is worthy of some consideration.

Whether or not the suggestion made is of value, hydrolysis of some sort probably is a factor in the local anesthetic action[55] of certain compounds. Adams and Vliet[56] found that decreasing the hydrogen ion concentration of the solution used caused an increase in local anesthetic action. Regnier and David[57] claim this increased action is not due to hydrolysis of the anesthetic, but due to the action of the hydroxyl ion

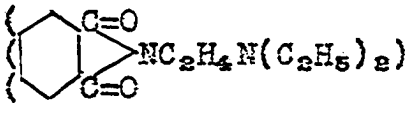
[55] Jensen and Hirschfelder, J. Pharmacol. 24, 423-48 (1925).
Nielsen and Higgins, J. Lab. Clin. Med. 7, 1 (1922).
Volwiler and Vliet, J. Am. Chem. Soc., 43, 1672 (1921).
Schonle and Row, ibid. 43, 361 (1921).
Regnier, Compt. rend. soc. biol., 92, 605-8 (1925), C.A., 19, 1904-5 (1925).

[56] Adams and Vliet, J. Am. Chem. Soc. 48, 2158 (1926).
See also, Gros. Arch. exp. Path. Pharmakol., 63, 80 (1910), ibid. 67, 127, 130 (1912).

[57] Regnier and David, Bull. sci. pharmacol., 32, 513-522 (1925), C.A., 20. 451 (1926).
See also, Regnier, Bull. sci. pharmacol., 32, 405-12 (1925), C.A., 19, 3000 (1925).

on the cell acted upon by the anesthetic. The cell is somehow made more receptive, but not necessarily by decreased surface tension.

The Effect of the Carbonyl Group:

The introduction of a carbonyl (C:O) group into the molecule of a compound showing local anesthetic action should increase this action[4] since it is an unsaturated group[41]. According to Keach and Hill[58] the ketonic carbonyl group confers hypnotic action. The carbonyl group is present in the ester group (-C:O·OR), but it is impossible to determine the extent to which local anesthetic action is influenced by the carbonyl group alone, in this connection. Undoubtedly its degree of unsaturation does determine to some extent the influence of the ester grouping previously discussed, as is shown by the substitution of a more unsaturated grouping (·C=S) for it[44]. In view of the facts shown by this research, but little light can be thrown on the subject. In β-diethylaminoethyl phthalimide[50]  two carbonyl groups are present. The compound did not show local anesthetic action. Ethyl β-diethylaminoethylaceto-acetate[15] ($CH_3C{:}OCH{\cdot}(C_2H_4N(C_2H_5)_2COOC_2H_5$) has local anesthetic action and there is one carbonyl group in its molecule, besides the one in the ester

[58] Keach and Hill, J. Am. Chem. Soc., 48, 2743-5 (1926).

group. Whether or not the physiological action of this compound is due to this carbonyl group, or to some other group, or to the general make-up of the molecule, can hardly be distinguished. The same is true of most other compounds described in the literature. Frankel and Cornelius[59] have prepared β-hydroxy-ethyl benzamid ($C_6H_5CONHCH_2CH_2OH$) and two other compounds in which the hydroxyl group formed esters with m- and p-aminobenzoic acids. None of these compounds showed local anesthetic action.

Evidence concerning the effect of carbonyl groups was found to be inconclusive. It was believed that the inactivity of β-diethylaminoethyl phthalimide was due to some factor[59] other than the presence of the two carbonyl groups. The presence of a carbonyl group attached directly to a pharmacaphore should have the same effect as the presence of any other unsaturated group or atom in a like position.

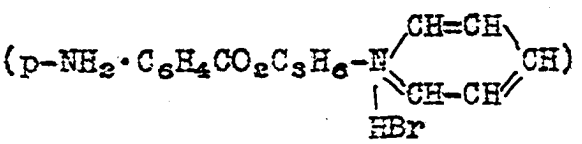
The Effect of the Ethylene Group:

The effect of unsaturation on local anesthetic action is most marked when the unsaturated linkage is made a part of the pharmacaphore[4]. This has been shown by V. Braun and Braunsdorf[61] who replaced one of the ethyl groups in the pharmacaphore of procaine with allyl and cinnamyl groups. Kamm and

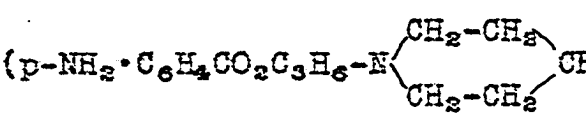
[59] Frankel and Cornelius, Ber., 51, 1654-62 (1918).
[60] See Section on "Effect of Nitrogen in Amino and Imido Groups", p.57
[61] V. Braun and Braunsdorf, Ber., 54B, 2081-88 (1921), C.A., 16, 1084 (1922). See also, V. Braun and Kohler, Ber., 51, 79-96 (1918).

Volwiler[62] have prepared the di-allyl analogues of both procaine and butyn, and have found increased local anesthetic action in both cases. A part of this increased action may be attributed to an increase in molecular weight[43].

Under certain conditions the effect of unsaturation takes a surprising turn. Adams and Barnes[63] found p-aminobenzoyl-γ-hydroxypropyl pyridonium bromide



to be physiologically inactive while the corresponding saturated compound



is 8 times as active as procaine. Gilman and Pickens[4] noticed the same sort of behavior with β-diethylaminoethyl phenylpropiolate ($C_6H_5C{\equiv}C\cdot COOC_2H_4N(C_2H_5)_2$) which should have had a strong local anesthetic action, but produced intense pain instead.

Kamm[37] has indicated the apparent necessity for the carbonyl group of an ester being attached to an unsaturated atom or group[64], if the compound is to have local anesthetic action. Gilman and Pickens[4] and later, Gilman, Heckert and McCracken[40] have shown this to be true in cases where the un-

[62] Kamm and Volwiler, U.S. 1388573, Aug. 23 (1922), C.A., 16, 990 (1922).
[63] Adams and Barnes, J. Am. Chem. Soc., 49, 1368-23 (1927).
[64] See Pyman, J. Chem. Soc., 111, 167, 1119 (1917).

saturated atom or group was attached to either an aromatic or an aliphatic radical. This work extended the investigation still further, and corroborated the results previously obtained. β-Diethylaminoethyl β-ethylacrylate ($C_2H_5CH=CHCOOC_2H_4N(C_2H_5)_2$) was prepared and found to have a cocaine coefficient of 6.6 as a free base and 1.0 as the hydrochloride salt[14].

Conclusion:

The unsaturated groups, -C(:O)·OR, =C:O, and -HC:CH-, have been studied with a view to determine the effect they have on local anesthetic action. It has been concluded that the effect of the first of these was due either to its degree of unsaturation, or to a ready hydrolysis which frees the aminoalcohol with which the group has been esterified. This aminoalcohol has been shown to have local anesthetic action to a marked degree[14].

Concerning the effect of the second group, the carbonyl, little direct evidence was available. In the compounds studied it was found impossible to reach any definite conclusions.

The third group, which contains the ethylenic linkage, was found to have an effect confirming the conclusions of Gilman and Pickens[4], Kamm[39] and Gilman, Heckert and McCracken[40]. Unsaturated groups of this type increase physiological action when a part of the pharmacaphore, or when attached to the carbonyl group of an ester group holding a pharmacaphore.

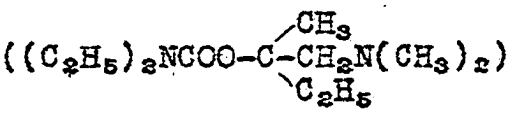
The Effect of Unsaturated Atoms

As has been indicated by the preceding discussions, local anesthetic action results when the pharmacaphore is attached to an atom which is a member of an unsaturated group. This section of the present work was an attempt to determine whether or not this property continued to exist when the pharmacaphore was attached to an atom which may be considered as unsaturated[41].

To this end, the β-diethylaminoethyl group was attached to trivalent nitrogen, divalent oxygen, and divalent and hexavalent sulfur. All these di- and trivalent atoms are capable of showing higher valences[41 45].

The Effect of Nitrogen in Amino and Imido Groups:

The presence of two nitrogen atoms in a molecule of a compound showing local anesthetic action is not at all unusual. Ordinarily one of these nitrogen atoms is present in the pharmacaphore, really being the nucleus of that group. The other nitrogen atom may be far removed from the first, as in the case of procaine, or it may be quite near, as in the case of β-diethylaminoethyl phenyl-methyl-urethane[43,49] ($C_6H_5N(CH_3)COOC_2H_4N(C_2H_5)_2$). Apparently, the presence of the second nitrogen atom which is usually trivalent, increases local anesthetic action[9]. It may serve as an anchoring group, or possibly as a secondary pharmacaphore. In the case of the

esters of diethyl carbamic acid 

prepared by Riedel[65] the second nitrogen atom undoubtedly served as the unsaturated atom to which the carbonyl group of the ester should be attached in order to show local anesthetic action[39].

In view of these facts, the action of β-diethylaminoethyl methylaniline ($C_6H_5N(CH_3)C_2H_4N(C_2H_5)_2$) was surprising. This compound showed no local anesthetic action whatever[14]. This behavior may have been due to the absence of an ester group, although this should not have been the case since β-diethylaminoethyl p-tolyl sulfide, ($p\text{-}CH_3\cdot C_6H_4SC_2H_4N(C_2H_5)_2$) and β-diethylaminoethyl phenyl ether ($C_6H_5OC_2H_4N(C_2H_5)_2$) both showed local anesthetic action[14].

A more logical conclusion would be that neither of the nitrogen atoms was unsaturated, for analysis of the hydrochloride salt of this compound (as which it was tested) showed that a di-hydrochloride[20] had been formed. If this conclusion is correct, it offers a striking example of the effect of unsaturated and saturated atoms on local anesthetic action.

A third possibility is that the relative positions of the two nitrogen atoms causes this result. This conclusion

[65]Riedel, Ger., 169787, April 2 (1906), Chem. Zentr., I, 1683 (1906).

seemed to be supported by the fact that β-diethylaminoethyl phthalimide ($C_6H_4(CO)_2NC_2H_4N(C_2H_5)_2$) was also physiologically inactive[14]. The relative positions of the nitrogen atoms were the same in both compounds.

In the case of the phthalimide derivative it might be suggested that steric hindrance played some part. A compound somewhat similar in type, di-(β-diethylaminoethyl) phthalate[58] (C_6H_4 with ortho $COOC_2H_4N(C_2H_5)_2$ and $COOC_2H_4N(C_2H_5)_2$), is without local anesthetic action.

The evidence is not conclusive enough however to prove either of the last conjectures. For some reason, attachment of the pharmacaphore to the rest of the molecule with a nitrogen atom failed to give the expected local anesthetic action.

The Effect of Oxygen in the Ether Group:

In all local anesthetics of the procaine type, the pharmacaphore is attached to the carbonyl group of the ester by a divalent oxygen. In holocaine (CH_3C with $N-C_6H_4OC_2H_5$ and $NH-C_6H_4OC_2H_5$) and its derivatives, studied by Hill and his coworkers[50], the ethyl group is attached by means of a divalent oxygen. Duliere[66] has prepared a series of compounds containing divalent oxy-

[66]Duliere, Bull. Soc. Chim. (4) 39-40, 286 (1926).

gen ($C_6H_5CH(OR)C_2H_4NR_2$), in which R means various alkyl radicals. These compounds had some local anesthetic action.

During this investigation, another type of compound containing divalent oxygen attached to the pharmacaphore, was prepared. This compound, β-diethylaminoethyl phenyl ether[14] ($C_6H_5OC_2H_4N(C_2H_5)_2$), showed no local anesthetic action when applied to the cornea of a rabbit, but did show such action on the human tongue. This places its activity as approximately that of procaine, which has no effect on the cornea until 8 per cent solutions of it are applied.

Again it is possible to suggest that the effect was due to hydrolysis of the compound, forming β-diethylaminoethanol[67]. McLeod and Robinson[68] have found that β-diethylaminoethyl ethyl ether hydrolyzed very readily. This property probably would decrease somewhat when the phenyl group was substituted for the ethyl group, which would explain the degree of local anesthetic action shown by β-diethylaminoethyl phenyl ether.

The Effect of Oxygen in Amino Alcohols:

In β-diethylaminoethanol ($(C_2H_5)_2NC_2H_4OH$), the pharmacaphore group, β-diethylaminoethyl is attached to a divalent oxygen, as was also the case with the compound just discussed. When tested on the cornea of a rabbit, as the hydrobromide salt, β-diethylaminoethanol showed surprising activity[64].

[67] See section on " The Effect of the Ester Group", p. 47.
[68] McLeod and Robinson, J. Chem. Soc. 119, 1470-6 (1921).

Its cocaine coefficient ranged from 8.33 to 13.66[14]. The factors causing this variation were not known. When injected or placed on the tongue, β-diethylaminoethanol hydrobromide produced no anesthesia. A minute quantity of the free β-diethylaminoethanol placed on the tongue, anesthetized an area of two square centimeters for over three hours.

In this connection it is interesting to note that β-diethylaminoethyl chloride ($(C_2H_5)_2NC_2H_4Cl$) [14] and the corresponding bromide were inactive, while diethylamine[51 14] had a cocaine coefficient of 3.3. The marked activity of the aminoalcohol may have been due to the degree of unsaturation of the oxygen atom. More probably it was mainly due to the anchoring[69] effect of the hydroxyl group.

The Effect of Sulfur in the Sulfide Group:

So far as can be determined, sulfides have not previously been tested for local anesthetic action, although Lawson and Reid[70] have prepared alkyl amino derivatives of diethyl sulfide by causing primary and secondary alkyl amines to react with β-dichlorodiethyl sulfide ($ClC_2H_4SC_2H_4Cl$).

During this investigation, β-diethylaminoethyl p-tolyl sulfide ($p\cdot CH_3\cdot C_6H_4SC_2H_4N(C_2H_5)_2$) was prepared and tested for

[69] Ehrlich, Deut. med. Wochschr. 1052 (1898), Proc. Roy. Soc. (London), 66, 424 (1900), Z. Physiol. Chem., 47, 173 (1906), "Studies on Immunity" (Wiley and Sons 1906), 404-442.

[70] Lawson and Reid, J. Am. Chem. Soc. 47, 2821-36 (1925).

local anesthetic action. It had a cocaine coefficient of 3.5-5 and was quite irritant as the hydrochloride salt. This last property was not surprising in view of the well known action of some organic sulfides[71]. It was not surprising that this compound should have shown local anesthetic action. The previously discussed oxygen compound showed some such action, and the two are similar in type. Neither was it surprising that it showed local anesthetic action[14] to a greater degree than the oxygen analogue, for divalent sulfur is obviously more unsaturated than divalent oxygen.

The Effect of Sulfur in the Sulfone Group:

Some sulfones have hypnotic[72] action, but so far as can be determined none has previously been tested for local anesthetic action.

β-Diethylaminoethyl p-tolyl sulfone ($p\text{-}CH_3C_6H_4\text{-}SO_2\text{-}C_2H_4N(C_2H_5)_2$) was found to have no local anesthetic action whatever, when tested on the cornea of a rabbit, or on the human tongue. This was not surprising, as oxidation of the very irritant β-chloroethyl p-tolyl sulfide to the corresponding sulfone was found to completely destroy the irritant property. Bauman and Kast[72] found that for a sulfone to exert hypnotic action, two sulfone groups must be attached to the same car-

[71]Bourne, Brit. Med. J. (1926) 778.
[72]Baumann and Kast, Zeit. physiol. Chem. 14, 52 (1890).

bon atom, which must have all of its hydrogens replaced by other groups. They found all other sulfones investigated to be inactive. Renshaw and Hotchkiss[73] have found that introduction of a sulfonic acid group into a molecule often destroys physiological action.

The explanation of this loss of local anesthetic action when a sulfone group has replaced a sulfide group may be given from the facts shown in previous discussions. Divalent, and therefore unsaturated sulfur, has been replaced by hexavalent sulfur, a saturated atom.

This behavior was in direct accord with the expected action. It is believed to offer direct confirmation of the view that unsaturated atoms increase local anesthetic action as well as unsaturated groups. Saturated atoms should not have this effect, but should behave as do saturated groups.

The Effect of Sulfur in the Thion Ester Groups:

As has been previously pointed out, the substitution of a divalent sulfur atom for a divalent oxygen atom should result in an increase in local anesthetic action because the sulfur atom has a higher degree of unsaturation. If the carbonyl group of an ester is an unsaturated group, a thion carbonyl group should be even more unsaturated, and consequently the compound should show more local anesthetic action.

[73] Renshaw and Hotchkiss, J. Am. Chem. Soc. 48, 2699 (1908).

This conclusion was verified by the behavior of β-diethylaminoethyl phenylthionurethane ($C_6H_5NHC(=S)OC_2H_4N(C_2H_5)_2$), which had a cocaine coefficient of 6.6, tested by the rabbit cornea method. Although the data were not completely comparable, this compound apparently was considerably more active than β-diethylaminoethyl phenylurethane ($C_6H_5NHCOOC_2H_4N(C_2H_5)_2$) tested by Fromherz[48].

Apparently the substitution of divalent sulfur for divalent oxygen was attended by an increase in local anesthetic action. This conclusion was further verified by the behavior of β-diethylaminoethyl p-tolyl sulfide[74] and β-diethylaminoethyl phenyl ether[75].

Conclusion:

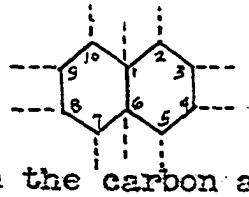
The results obtained in this section indicate that single unsaturated atoms may be substituted for unsaturated groups outside the pharmacaphore, without destroying local anesthetic action. Divalent oxygen and especially divalent sulfur had this effect. Trivalent nitrogen did not, so far as could be determined. The substitution of divalent sulfur for divalent oxygen resulted in an increase of local anesthetic action. Saturation of the unsaturated atoms resulted in a complete loss of anesthetic action.

[74] See section on "Effect of Sulfur in the Sulfide Group", p. 61.
[75] See section on "Effect of Oxygen in the Ether Group", p. 59.

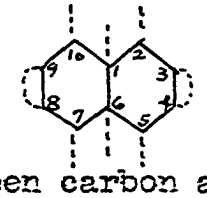
There was some indication that steric hindrance may have caused β-diethylaminoethyl phthalimide to be inactive. There was also some indication that the relative position of two nitrogen atoms in this, and a related compound, had some influence on the lack of physiological action.

The Effect of Position in the Naphthalene Nucleus. The Effect of Increased Molecular Weight.

The positions of the substituents in the naphthalene nucleus usually causes a marked difference in the physical and chemical properties of the compounds. It is possible to explain these differences, in part, if it be assumed that each carbon atom in the two benzene rings forming naphthalene possesses a certain degree of unsaturation. This may be represented by the following structural formula in which



the unsaturation components are represented by dotted lines. The components on the carbon atoms in the 3-4 and 8-9 positions (β-positions) may be assumed to neutralize each other, as shown by the following diagram[76].



The component of unsaturation of carbon atom 1, however, should be equally distributed between carbon atoms 2 and 10, and that of carbon atom 6 distributed between carbon atoms 5 and 7, leaving

[76]Thiele, Ann., 306, 125 (1899).

these carbon atoms still possessing some degree of unsaturation[76]. Naphthalene compounds having a substituent group in the α-position should most nearly resemble aromatic compounds, since the substituent is attached to a somewhat unsaturated[4] carbon atom. Those naphthalene compounds having substituents in the β-position should most nearly resemble aliphatic compounds of corresponding molecular weight, since the substituent is attached to a saturated carbon atom.

The differences, required by the above structural formula, for α- and β-monosubstituted naphthalene compounds are apparent to a certain extent. For example, the molecular refraction calculated for both mono-naphthylamines is 45.80. The experimental value for α-naphthylamine is 46.66 and for the β-naphthylamine, 45.88. Only the so-called aromatic amines show exalted molecular refraction. Other physical[77] constants vary markedly, not only in the case of the amino derivatives, but in all α- and β- monosubstitution products of naphthalene.

α-Naphthylamine has an odor closely resembling that of aniline. β-Naphthylamine has no odor. When α-naphthylamine is reduced, four hydrogen atoms attach themselves to the car-

[77] For a comparison of the physical and chemical properties of various α- and β-substitution products of naphthalene, See Meyer and Jacobson's "Lehrbuch der Organischen Chemie" (Von Veit and Co. 1903) Vol. II, part 2, pp. 295-383. In particular see pp. 323, 333, 364-6, 305, 310.
For Ionization Constants, see Scudder "Conductivity and Ionization Constants of Organic Compounds (D. Van Nostrand Company 1914) 219.

bon atoms of the ring not holding the amino group. The tetrahydride so formed behaves strictly as an aromatic amine with a saturated side chain, because the amino group can be diazotized, and does not react with carbon dioxide. β-Naphthylamine on reduction gives a tetrahydride in which the entering hydrogen atoms have attached themselves to the carbon atoms of the ring holding the amino group. This compound resembles an aliphatic amine, since the amino group cannot readily be diazotized, and reacts easily with carbon dioxide. α-Naphthylamine gives colored precipitates with ferric chloride, and potassium dichromate, while β-naphthylamine does not.

Physiologically, there is a marked difference between the two naphthylamines. α-Naphthylamine is more poisonous than β-naphthylamine, having, as does aniline, a paralyzing action on the central nervous system[78]. β-Naphthylamine causes a contraction of the pupil of the eye and is oxidized in the organism to amino naphthols[78].

α-Naphthol and β-naphthol show the usual differences in physical constants[77]. β-Naphthol readily forms ethers when treated with alcohols and hydrogen chloride. α-Naphthol reacts much less readily with these reagents, resembling phen-

[78]Fränkel, "Arzneimittel-synthese" (Springer 1921)
Physiological action of Naphthylamines, 117, 177, 295.
Physiological action of Naphthols, 117.
Physiological action of Naphthoic Acids, 103, 195.
Physiological action of Benzoic Acid, 171.

ol in this respect. It is also difficult to convert α-naphthol to the corresponding naphthylamine by treatment with ammonia, while β-naphthol is readily converted into β-naphthylamine. Physiologically, α-naphthol[79] is more poisonous than β-naphthol , having three times its toxicity and antiseptic action[78]. This shows some resemblance to phenol which is an excellent antiseptic, as well as a germicide[6].

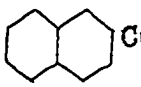
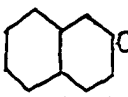
When attempts are made to nitrate or sulfonate naphthalene, only the α-positions are entered by the substituents. In the case of the sulfonic derivative, heating results in a rearrangement forming the β-derivative. When naphthalene is halogenated, the first two halogens occupy the α-positions on the same ring. Such behavior may indicate that the α-carbons are least saturated. When reduced with alcohol and sodium, hydrogen adds first to the α-positions, then to the β-positions in the same ring, only four hydrogen atoms adding to the whole molecule. This behavior indicates that the α-positions are least saturated, and furnish the initial point of attack for the entering atoms[80].

With certain reagents the halogen in the β-position seems more reactive. Loevenich and Loeser[81] secured 42.7

[79] Mays "Chemistry of Synthetic Drugs" (Longmans Green and Co., 1921) 154.
[80] Johnson and Hahn's translation of Heinrichs "Theories of Organic Chemistry" (John Wiley and Sons 1922), 67-68.
[81] Loevenich and Loeser, Ber., 60, 324 (1927), C. A., 21, 1649 (1927).

per cent yields of β-naphthol by treating β-bromonaphthalene with sodium acetate, while only 12 per cent yields of α-naphthol were secured from α-bromonaphthalene. In other reactions, however, this difference was not so apparent. Halogens attached to saturated carbon atoms are more reactive than those attached to unsaturated carbon atoms.

α-Naphthoic acid melts at 160° and has an ionization constant[77] of 2×10^{-4}. β-Naphthoic acid melts at 182° and has an ionization constant[77] of 7×10^{-5}. α-Naphthoic acid passes through the body unchanged, resembling benzoic acid in this respect. Part of the β-naphthoic acid ingested is eliminated unchanged and a part absorbed. For dogs, the toxic dose is 4 gm.[78]

In view of these facts it was surprising to find that β-diethylaminoethyl β-naphthoate ( $COOC_2H_4N(C_2H_5)_2$) was slightly more active as a local anesthetic than β-diethylaminoethyl α-naphthoate ( $COOC_2H_4N(C_2H_5)$) [14]. The opposite effect had been expected, as well as a much greater difference in activity. Apparently the correlation between unsaturation and local anesthetic action has broken down rather completely in this case.

An interesting comparison of the effect of an increase in molecular weight of the pharmacogen, outside the pharmacaphore, is possible in this case. Lynn and Lofgren[9] found β-diethylaminoethyl benzoate to have anesthetic properties. The data given were not directly comparable, but

the benzoate was less active than procaine while the naphthoates were several times as powerful as procaine.

This result was in accordance with the general conclusions reached by Kamm[39] and coworkers[82], Osterberg and Kendall[83], Braun and Braunsdorf[60], and Adams and Barnes[63], who increased the molecular weight of the pharmacaphore, usually, and found increased local anesthetic action and toxicity. Gilliard, Monnet and Cartier[11], working with alkyl esters of p-aminobenzoic acid, found that the increased molecular weight of the alkyl groups also resulted in an increased local anesthetic action.

The fact that the naphthoates prepared were not even more active was somewhat surprising. It has been shown by Madinaveitia[84] that amines containing the naphthalene nucleus were 40 times as active as those containing only the benzene nucleus. However, the physiological action so shown was not local anesthetic action, but sympathomimetic (stimulation of sympathetic nervous system) action.

Apparently, the position of the substituents in the naphthalene nucleus has very little effect on local anesthet-

[82] Adams, Kamm, and Volwiler, U.S. 1358751, Nov. 16 (1921) C.A. , 15, 412 (1921).
Kamm and Volwiler, U.S. 1388573, Aug. 23 (1922), C.A. 16, 990 (1922).
[83] Osterberg and Kendall, J. Am. Chem. Soc. 43, 1370 (1921)
[84] Madinaveitia, Anales soc. espan. fis. quim. 18, 66-78 (1920), C.A., 16, 92 (1922).

ic action, since both componunds are active to about the same degree. Substitution of the naphthalene nucleus for the benzene nucleus was attended by a marked increase in local anesthetic action.

SUMMARY

1. The effect of unsaturation on local anesthetic action has been studied with reference to unsaturated groups and unsaturated atoms. The pharmacaphore group was retained unchanged in all cases.

2. For the most part, it has been found that the presence of unsaturated groups outside the pharmacaphore, serves to increase local anesthetic action.

3. The unsaturated atoms, divalent oxygen and divalent sulfur, attaching the pharmacaphore to the remainder of the molecule, cause local anesthetic action. Trivalent nitrogen did not have this effect.

4. Substitution of divalent sulfur for divalent oxygen increased local anesthetic action.

5. Very little difference in local anesthetic action was found when the α- and β-positions in the naphthalene nucleus were studied.

6. In general, the results obtained enable the correlation between unsaturation, and physical and chemical properties, to be extended to include local anesthetic action.