ing several days, these were not examined. The crude reaction product was evaporated repeatedly with hydrochloric acid. A good yield of 2-thiohydantoin-3-acetic acid was obtained. However, the material was discolored even after recrystallization from acetic acid containing Norite and blackened at 208°, melting at 210–212°.

## Summary

1. A practical method for preparing ethyl isothiocyano-acetate is described.
2. Ethyl isothiocyano-acetate interacts smoothly with glycine or its ethyl ester giving the corresponding symmetrically substituted thio-ureas. The latter compounds undergo a cyclic condensation by digestion with hydrochloric acid giving 2-thiohydantoin-3-acetic acid.
3. Desulfurization of this 2-thiohydantoin compound leads to the formation of hydantoin-3-acetic acid, the simplest representative of a polypeptide-hydantoin.

NEW HAVEN, CONNECTICUT

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# THE CORRELATION OF SOME AROMATIC TYPES WITH PHYSIOLOGICAL ACTION. LOCAL ANESTHETICS CONTAINING THE FURAN, THIOPHENE AND PYRROLE NUCLEI[1]

BY HENRY GILMAN AND RUSSELL M. PICKENS

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## Introduction

Strictly speaking, there are probably no rigidly exclusive aromatic characteristics. Aromatic compounds are accorded generally a formal classification which serves to set them apart from aliphatic compounds, and the basis of such a differentiation is found in a number of essentially distinctive properties. However, such differences from what might be called corresponding aliphatic compounds are largely of degree and not of kind. Notwithstanding, the differentiation is retained. This is so partly for the convenience of such a classification, and partly because the differences, under corresponding conditions, are rather noteworthy when one considers series of compounds in the aggregate.

Aromatic properties are observed with a number of heterocyclic compounds. Some of the more important 5-membered rings are furan (I), thiophene (II) and pyrrole (III). The structural similarities of these types to benzene become apparent when they are written arbitrarily according to the Armstrong-Baeyer centric formulas.[2]

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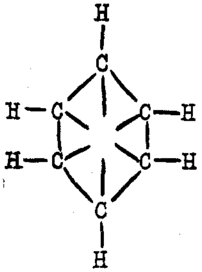
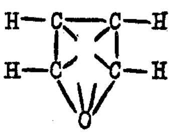
[1] A preliminary report of this work was made at the Spring Meeting of the American Chemical Society held at Birmingham, Alabama, in April, 1922.

[2] Meyer and Jacobson, "Lehrbuch der Organischen Chemie," Vol. II, part 3, section I, pp. 12–17, contains a general critical account of the formulas of these compounds.

These heterocyclic types and many of their derivatives enjoy a number of unusually marked resemblances to benzene and its corresponding derivatives. Such similarities are strikingly apparent in numerous physical and chemical properties. Comparatively little work has been done on the correlation of such related types with another property, namely, physiological action.[3] The basic assumption underlying the rather considerable amount of work done on synthetic drugs is a relationship between physiological action and chemical constitution. The present study was undertaken partly with a view to the extension of the known correlation of aromatic types with physical and chemical properties to physiological action. The derivatives have been patterned after some local anesthetics because the extent of recent work in this field of drugs assured reasonably accurate quantitative measurements of the effectiveness of such compounds.





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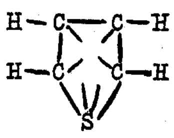

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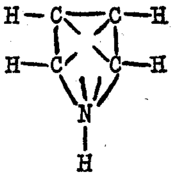
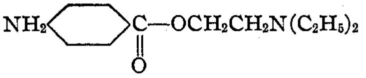
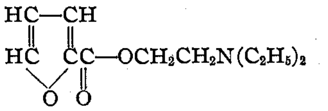


III

One of the most widely known local anesthetics is procaine, also called novocaine.[4] This is the monohydrochloride of the β-diethylamino-ethyl ester of *p*-aminobenzoic acid (IV).[5] Because the related compound without the *p*-amino grouping has marked local anesthetic action, and because of known inherent difficulties in the introduction of amino groups into the nucleus of furan, thiophene and pyrrole, the compounds studied are those without an amino group in the ring, such as β-diethylamino-ethyl 2-furancarboxylate (V).



IV



V

In addition to the β-diethylamino-ethyl esters of 2-furan-, 2-thiophene-, and 2-pyrrole-carboxylic acids, the study includes the corresponding

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[3] Steinkopf and Ochse [*Ann.*, **437**, 14 (1924)] have described recently the thiophene isolog of cocaine which has properties very similar to those of cocaine.

[4] For a review of some recent work on local anesthetics see Gilman, *J. Ind. Eng. Chem.*, **14**, 812 (1922).

[5] The salts, generally the hydrochlorides, are used in practice, but for the sake of convenience the formulas of the free bases will be used here.

esters of 2-furanacrylic acid ($C_4H_3O—CH{=}CHCOO(CH_2)_2N(C_2H_5)_2$) and phenylpropiolic acid ($C_6H_5C{\equiv}CCOO(CH_2)_2N(C_2H_5)_2$). Also, because the benzyl esters of many acids have a related physiological action[4] some of these have been prepared. Unsuccessful attempts were made to prepare the diethylamino-ethyl esters of benzenesulfonic and -sulfinic acids. However, for comparison with the physiologically active ethyl benzoate, the ethyl esters of the sulfonic and sulfinic acids were also studied.

The results, in general, are in reasonable agreement with what might have been predicted: the known correlation with physical and chemical properties can be extended to include physiological action. However, the dangers of drawing broad generalizations in studies on physiological action and chemical constitution are emphasized strongly in a few cases, particularly with diethylamino-ethyl phenylpropiolate.

A later work will contain the results of studies with several diethylamino-ethyl esters of substituted aliphatic acids.

## Discussion of Syntheses

The hydrochlorides of the diethylamino-ethyl esters of the several acids were prepared in the usual manner by adding a benzene solution of the acid chloride to a cool, well-stirred benzene solution of $\beta$-diethylamino-ethyl alcohol. All of the acid chlorides were made by treating the corresponding acid with thionyl chloride. The acids, in turn, were synthesized by known methods with only minor variations excepting in the preparation of 2-pyrrole-carboxylic acid.

Because the yield of 2-pyrrolecarboxylic acid prepared according to the method of Oddo[6] was rather low, the conditions were varied in several experiments. First, ethylmagnesium bromide instead of methylmagnesium iodide was used in the preparation of the pyrrolemagnesium halide from pyrrole. Second, the organometallic halide so prepared was sprayed into an atmosphere of carbon dioxide, instead of bubbling the carbon dioxide into an ether solution as is customary. It is probable that both these factors contributed to the 7.5–12.5% improvement in yield that was noted. Apparently, ethylmagnesium bromide is better suited than ethylmagnesium iodide or methylmagnesium iodide for the replacement of so-called active hydrogens by an —MgX group. Attention was called to this by Gilman and Hoyle[7] in connection with the acidic hydrogen of phenyl-acetylene. A more complete account of the spraying method for the preparation of carboxylic acids from organomagnesium halides has been reported recently.[8]

Considerable difficulty was experienced in the preparation of the hy-

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[6] Oddo, *Gazz. chim. ital.*, **39**, I, 649 (1909).

[7] Gilman and Hoyle, This Journal, **44**, 2621 (1922).

[8] Gilman and Parker, *ibid.*, **46**, 2816 (1924).

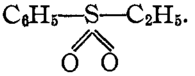
drochloride of diethylamino-ethyl 2-pyrrole-carboxylate. The somewhat tarry compounds which are present generally with pyrrole derivatives, and the highly hygroscopic nature of the ester-hydrochloride made purification by crystallization almost impossible. This trouble was circumvented by liberating the free ester-base from the hydrochloride and then distilling it under reduced pressure. In this manner a pure compound was obtained from which the hydrochloride is readily prepared in a form that lends itself to easy purification by crystallization.

Several unsuccessful experiments under varying conditions were carried out in an effort to prepare the diethylamino-ethyl esters of benzenesulfinic and benzenesulfonic acids. Some of the results appear quite unusual, and no plausible mechanism is offered for the formation of several compounds in the work with benzenesulfinic acid.

The reaction of benzenesulfinic chloride with diethylamino-ethyl alcohol gave the customary pasty precipitate that accompanies the formation of the ester-hydrochlorides of corresponding carboxylic acids. After several attempted crystallizations, it was hoped that the alteration in procedure used in the preparation of the pyrrole ester would give better results. Accordingly, the cold aqueous solution was made alkaline with dil. sodium hydroxide, extracted with ether and the ether layer separated, dried and vacuum-distilled.

At 40° and 2 mm. about 1 g. of an amine came over. Its hydrochloride melted at 185°, but a mixed melting point with the hydrochloride of *sym*-tetraethyldiamino-ethane which melts at 187° showed that it was not this compound. When the temperature of the distillate rose to 70°, the contents of the flask partly solidified. An alcoholic extract of this residue removed the liquid part. This extract was found to consist largely of phenyl disulfide, $C_6H_5SSC_6H_5$. The solid remaining after extraction with alcohol was identified as *sym*-ethylene-diphenyldisulfone, $C_6H_5SO_2CH_2CH_2SO_2C_6H_5$.

It is believed that the desired sulfinic ester, $C_6H_5SO_2CH_2CH_2N(C_2H_5)_2$, was first formed. A tentative explanation that suggests itself for the formation of the disulfone is the conversion of a sulfinic ester to the isomeric sulfone. However, although a reasonable basis exists for the two tautomeric forms of a sulfinic acid ($R-\underset{\underset{O}{\|}}{S}-OH$ and $R-\underset{O\ \ O}{S}-H$), the work of Otto and Rössing[9] makes it improbable that the sulfinic ester has undergone rearrangement. They tried, without success, to convert the ethyl ester of benzenesulfinic acid to the isomeric phenylethyl sulfone, $C_6H_5-\underset{O\ \ O}{S}-C_2H_5$.



$C_6H_5-\underset{O\ \ O}{S}-C_2H_5$

[9] Otto and Rössing, *J. prakt. Chem.*, **47**, 152 (1893).

The reaction between benzenesulfochloride and diethylamino-ethyl alcohol did not give the desired ester. From several experiments made under various conditions there was obtained a solid melting at 276°, soluble in water, and containing nitrogen and sulfur but no chlorine. This compound was not identified.

Other attempts were made to prepare the sulfonic ester by treating β-chloro-ethylbenzene-sulfonate ($C_6H_5SO_2OCH_2CH_2Cl$) with diethylamine. The main product obtained was *sym*-tetra-ethyldiamino-ethane, $(C_2H_5)_2NCH_2CH_2N(C_2H_5)_2$. Clemo and Perkin[10] have described recently a similar reaction in which aromatic amines were used.

## Experimental Part

**The Hydrochloride of β-Diethylamino-ethyl 2-Furancarboxylate (V).**—A solution of 11.4 g. or 0.1 mole of freshly distilled pyromucyl chloride (prepared according to the method of Baum[11]) in 25 cc. of benzene was added slowly to 0.11 mole of β-diethylamino-ethyl alcohol in 75 cc. of benzene while the mixture was stirred. A pasty precipitate formed at once. In order to insure completion of reaction, the mixture was warmed for about an hour on a water-bath. The cooled reaction product was filtered, the solid washed several times with benzene and dried; yield, 77%. Crystallization from hot, absolute alcohol gave prismatic crystals that melted[12] at 127°.

*Anal.* Calcd. for $C_{11}H_{18}O_3NCl$: N, 5.66; Cl, 14.3. Found: N, 6.16; Cl, 14.4.

**The Hydrochloride of β-Diethylamino-ethyl 2-Thiophenecarboxylate.**—The α-thenoyl chloride was prepared from 2-thiophenecarboxylic acid[13] by the method of Jones and Hurd;[14] 3.2 g. of the acid chloride was added to 2.8 g. of the amino alcohol and the reaction mixture was worked up in a manner identical with that described in the preparation of the furan ester. The thiophene ester-hydrochloride, melting at 106°, was obtained in 61% yield.

*Anal.* Calcd. for $C_{11}H_{18}O_2NSCl$: Cl, 13.47. Found: Cl, 14.01.

**The Hydrochloride of β-Diethylamino-ethyl 2-Pyrrole-carboxylate.**—The acid chloride was prepared according to the method of Oddo and Moschini.[15] After the removal of the excess of thionyl chloride, by heating below 60° in a vacuum, the residue was dissolved in dry ether, and to the solution was then added an equal volume of petroleum ether. This formed an amorphous precipitate. The filtrate, when concentrated by evaporation in a vacuum, gave a crystal mass of the acid chloride which was only slightly contaminated by dark colored impurities.

The addition, in the customary manner, of the acid chloride to the amino alcohol, gave a tarry, highly hygroscopic paste that could not be crystallized. From this unpromising hydrochloride, the free base was prepared by adding sufficient sodium hydroxide to the aqueous solution. This alkaline solution was extracted thrice with ether, and after drying with sodium sulfate the solution was distilled in a vacuum. A small

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[10] Clemo and Perkin, *J. Chem. Soc.*, **121,** 648 (1922). Also, Brit. pat. 193,618 (Jan. 19, 1922).

[11] Baum, *Ber.*, **37,** 2949 (1904).

[12] The temperatures recorded in this paper are uncorrected.

[13] The authors wish to express their thanks to Dr. Hurd for the preparation of some of this acid.

[14] Jones and Hurd, THIS JOURNAL, **43,** 2444 (1921).

[15] Oddo and Moschini, *Gazz. chim. ital.*, **42,** II, 244 (1912).

fraction consisting of β-diethylamino-ethyl alcohol distilled at 56° (9 mm). The free amino ester distilled at 165–167° (9 mm.). It is a light yellow oil with a faint amine-like odor and turns red on standing.

The hydrochloride was prepared from the amino ester by passing dry hydrogen chloride into an ether solution until precipitation was complete. The white solid on crystallization from hot, absolute alcohol gave crystals with a slight pinkish tinge; m. p., 129°.

*Anal.* Calcd. for $C_{11}H_{19}O_2N_2Cl$: Cl, 14.4. Found: 14.49.

**The Hydrochloride of β-Diethylamino-ethyl 2-Furanacrylate.**—The 2-furanacrylic acid was prepared according to the method of Gibson and Kahnweiler[16] in a yield less than they report. However, a good yield (88%) of acid chloride was obtained by the method of Sasaki.[17]

The hydrochloride of the amino ester was prepared from the acid chloride and β-diethylamino-ethyl alcohol in a 78% yield. It was crystallized from hot absolute alcohol in needle-like clusters that were slightly yellow; m. p., 137–138°.

*Anal.* Calcd. for $C_{13}H_{20}O_3NCl$: N, 5.12; Cl, 13.0. Found: N, 5.82; Cl, 13.3.

**The Hydrochloride of β-Diethylamino-ethyl Phenyl Propiolate.**—Phenylpropiolic acid was prepared according to the method of Perkin,[18] and the corresponding acid chloride according to the method described by Watson.[19]

The ester-hydrochloride was obtained in an 86% yield from the acid chloride and the amino alcohol. It was purified by crystallization from hot, absolute alcohol; m. p., 163°.

*Anal.* Calcd. for $C_{15}H_{20}O_2NCl$: Cl, 12.59. Found: 12.31.

**The Reaction between Benzenesulfinyl Chloride and β-Diethylamino-ethyl Alcohol.**—The acid chloride of benzenesulfinic acid was prepared according to the method of Hilditch and Smiles.[20] When 17.6 g. of the acid chloride in 50 cc. of benzene was added to 14.9 g. of the amino alcohol in the same volume of benzene, 16.6 g. of an oily paste was obtained. Attempts to crystallize this from absolute alcohol were unsuccessful, the solution yielding only 2 g. of the hydrochloride of β-diethylamino-ethyl alcohol.

The reaction product of a second run was treated with cold dil. sodium hydroxide in an effort to obtain the pure ester-amine by distillation in a vacuum. As already mentioned in the section headed, "Discussion of Syntheses," the only compounds obtained and identified by mixed melting points were phenyl disulfide and ethylene-diphenyldisulfone.[21]

In a third run, a 10% excess of the acid chloride was added. The foreruns of the distillate, prior to the change of the contents of the flask to a solid consistency, gave 1 g. of a compound that boiled at 40° (2 mm.). This formed a hydrochloride that melted at 185°, and was shown not to be the hydrochloride of *sym*-tetra-ethyldiamino-ethane obtained elsewhere. The residue in the flask contained some β-diethylamino-ethyl alcohol in addition to phenyl disulfide and ethylene-diphenyldisulfone.

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[16] Gibson and Kahnweiler, *Am. Chem. Soc.*, **12,** 314 (1890).

[17] Sasaki, *Biochem. Z.*, **25,** 272 (1910).

[18] Perkin, *J. Chem. Soc.*, **45,** 172 (1884).

[19] Watson, *ibid.*, **85,** 1319 (1904).

[20] Hilditch and Smiles, *Ber.*, **41,** 4113 (1908). Also, v. Braun and Kaiser, *ibid.*, **56,** 549 (1923).

[21] The ethylene-diphenyldisulfone used as a check was prepared according to the method of Otto, *Ber.*, **13,** 1272 (1880).

**The Reaction between Benzenesulfonyl Chloride and β-Diethylamino-ethyl Alcohol.**—In one experiment the acid chloride was added in slight excess to the amino alcohol, and in another the amino alcohol was added in slight excess to the acid chloride. The reaction appeared to take place in the same manner in both runs, and the yields were 60% and 61%, respectively. In both reactions the precipitate formed at a slower rate than was observed with all carboxylic acid chloride experiments. The compound was soluble with difficulty in absolute alcohol, and the only product obtained was a solid melting at 275°. It crystallizes in small white scales from alcohol, is very soluble in water, and contains nitrogen and sulfur but no chlorine. The compound was not further studied.

In a third experiment, the reaction was carried out essentially like that described by Földi[22] for the preparation of sulfonic esters. From the ether solution which was not allowed to evaporate, about 8 g. of a solid precipitated during two hours. It melted over a wide range (250–265°), and most of it was insoluble in water and the ordinary organic solvents. The water extract gave a small quantity of the 275° compound obtained in the previous runs.

A fourth experiment was made under the conditions of the first and second runs. The solid material that first formed was filtered from the benzene, dissolved in water, the solution made alkaline, and the ether extract of this solution dried and subjected to a vacuum distillation. Considerable decomposition set in during distillation and no definite compound was obtained.

When the benzene solution from which the solid had been removed was allowed to stand for several hours, an insoluble oil separated. This was removed, and from the benzene solution about 25% of the original acid chloride was obtained by vacuum distillation. The oil was dissolved in sodium hydroxide, and the solution extracted with ether. After part of the ether from the ether extract of this alkaline solution was removed by distillation, a solid started to form. This was identified as the 275° compound obtained in the three other runs. Further concentration of the ether solution in the cold gave an oil which underwent complete decomposition in an attempted distillation at 3-mm. pressure. It is probable that this oil might have given more of the 275° compound if moderately warmed.

**The Reaction between β-Chloro-ethylbenzenesulfonate and Diethylamine.**—The β-chloro-ethylbenzenesulfonate was prepared according to the method of Clemo and Perkin and the yield[23] was 68%. Crystals commenced to form soon after a mixture containing 44 g. of the chloro-ethyl ester and 29.2 g. of the amine was heated to boiling. The reaction mixture was stirred for 30 minutes after removing the burner and to the crystal paste was added sufficient water for complete solution. This solution was then extracted with ether to remove any unchanged ester and the water layer was made alkaline with sodium hydroxide. The ether extracts of the alkaline solution were dried and distilled. When the ether and unused diethylamine had been removed by distillation, 13 g. of an oil distilled at 65° (8 mm.). This was subsequently identified as *sym*-tetra-ethyldiamino-ethane; yield, 38%.

In another experiment, 13.2 g. of diethylamine was added to 44 g. of the chloro-ethyl ester heated on a water-bath. Although the amine was slowly added over a five-hour period to an excess of the well-stirred ester, the only product obtained was the *sym*-tetra-ethyldiamino-ethane in a yield of 20%. In this experiment it was collected at 70–72° (10 mm.).

The identity of the *sym*-tetra-ethyldiamino-ethane was confirmed by synthesizing

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[22] Földi, *Ber.*, **53,** 1836 (1920).

[23] Ref. 10. See also, Gilman and Beaber, THIS JOURNAL, **45,** 839 (1923).

it from ethylene bromide and diethylamine. Apparently the physical constants of this diamine have not been published.[24] The hydrochloride melts at 187°.

*Anal.* Calcd. for $C_{10}H_{26}N_2Cl_2$: Cl, 28.93. Found: 28.94.

The chloroplatinate melts at 234°.

*Anal.* Calcd. for $C_{10}H_{26}N_2PtCl_6$: Pt, 33.53. Found: 33.31.

The chloro-aurate melts at 198°. It was not analyzed.

**Benzyl 2-Furancarboxylate.**—Benzyl 2-furancarboxylate was prepared from benzyl alcohol and the acid chloride of 2-furancarboxylic acid.

It is a pale yellow, oily liquid; b. p., 179–181° (18 mm.); $n^{20}$, 1.5550; $d_4^{20}$, 1.1632.

*Anal.* Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.95. Found: C, 71.55; H, 5.22.

**Benzyl 2-Furanacrylate.**—This substance was prepared from benzyl alcohol and the acid chloride of 2-furanacrylic acid. It is a pale yellow compound soluble in ether, benzene, acetone and hot ethyl alcohol; b. p., 201–203° (12 mm.); m. p., 42–43°.

*Anal.* Calcd. for $C_{14}H_{12}O_3$: C, 73.68; H, 5.26. Found: C, 73.61; H, 5.35.

## Discussion of Pharmacological Tests

The authors are indebted to Dr. Oliver Kamm of Parke, Davis and Company of Detroit, for the results of the pharmacological tests.

Three of the most general methods of testing local anesthetics are: (1) surface anesthesia as, for example on the cornea, or the frog's foot; (2) nerve trunk anesthesia; and (3) intracutaneous injection, corresponding with infiltration anesthesia. The order of effectiveness of a group of compounds differs according to the particular test. Because the compounds studied here are too feeble for surface anesthesia (even procaine is of little value as a surface anesthetic), this method was not used.

The data are based on comparative tests made by intracutaneous injections with human beings. This test is perhaps nearest to the actual requirements of surgical local anesthesia. The dilutions used were usually 1:200, 1:500, 1:750, 1:1000, 1:1500, 1:2000, 1:3000, etc., the compounds being dissolved in physiological salt solution.

Cocaine has been selected arbitrarily as a standard and given a weight of 10. It is possible to prepare anesthetics that lie higher in the scale than cocaine, but unfortunately these compounds are also comparatively quite toxic. On a scale of this kind, the relative and rather approximate ratings of two known compounds, procaine and the diethylamino-ethyl ester of benzoic acid, and the new compounds are as follows: procaine is approximately 6; diethylamino-ethyl benzoate is 4; diethylamino-ethyl 2-furanacrylate is 3; diethylamino-ethyl 2-pyrrole-carboxylate is 2; diethylamino-ethyl 2-thiophene-carboxylate is 1; diethylamino-ethyl 2-furancarboxylate has only a perceptible action; and, diethylamino-ethyl acetate, prepared for a later study, is zero.

The weakness of effect of diethylamino-ethyl 2-furancarboxylate is somewhat surprising. An earlier, independent observation by Dr. Kamm

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[24] Ladenburg, *Ber.*, **15**, 1143 (1882). The compound described by Ladenburg has been questioned in Beilstein, vol. I, p. 1172.

of the simple ethyl ester of 2-furancarboxylic acid showed that this compound had a very noticeable action. By comparison, the effect of diethylamino-ethyl benzoate exceeds that of ethyl benzoate.

The most unusual result was observed with the diethylamino-ethyl ester of phenylpropiolic acid. A rather large number of classes of physiologically active compounds show a general increase in effect on the introduction of an ethylenic group, particularly when this unsaturated linkage is made a part of the so-called pharmacophore group which is a kind of nucleus for physiological action. More particularly, Kamm[25] has reemphasized the apparent necessity for a related type of linkage with local anesthetics of the amino-ester class: that is, the carbonyl group of the ester should be united to an unsaturated atom.

Pyman[26] synthesized diethylamino-ethyl *p*-aminophenyl-acetate (*p*-$NH_2C_6H_4CH_2COOCH_2CH_2N(C_2H_5)_2$) and found it to be inactive as an anesthetic. However, when the carbonyl group is united to an unsaturated carbon atom as in diethylamino-ethyl *p*-aminocinnamate (*p*-$NH_2C_6H_4CH{=}CHCOOCH_2CH_2N(C_2H_5)_2$), local anesthetic action appears. This is observed more strikingly when comparison is made between diethylamino-ethyl cinnamate ($C_6H_5CH{=}CHCOOCH_2CH_2N(C_2H_5)_2$) and the same ester of hydrocinnamic acid ($C_6H_5CH_2CH_2COOCH_2CH_2N(C_2H_5)_2$). The former is active whereas the latter is reported as inactive.

Possibly the same kind of evidence may be used to account for the weak action of our diethylamino-ethyl 2-furancarboxylate (V) and the pronounced activity of the corresponding ester of 2-furanacrylic acid ($C_4H_3OCH{=}CHCOOCH_2CH_2N(C_2H_5)_2$). With the former compound the carbonyl group is attached to an unsaturated carbon, it is true, but to an unsaturated carbon which may have some of its so-called partial valence used up in a centric bond or in a conjugated system with the ring. However, too little is known with definiteness concerning such linkages to warrant much speculation.

Returning to compounds of the procaine type (IV), we find other evidences for the helpful effect of an unsaturated linkage. Kamm and Volwiler[27] prepared the diallyl analogs of procaine and butyn[4] and found these compounds to be quite effective. Here the ethyl groups in the diethylamino grouping have been replaced by the unsaturated allyl group. Also, v. Braun and Braunsdorf,[28] in a rather elaborate series of studies on the effect of unsaturated groups on physiological action, found a decided increase in anesthetic action when one of the ethyl groups of procaine is replaced by an allyl or cinnamyl group. They found that a similar replace-

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[25] Kamm, This Journal, **42**, 1030 (1920).

[26] Pyman, *J. Chem. Soc.*, **111**, 167, 1119 (1917).

[27] Kamm and Volwiler, U. S. pat. 1,388,573.

[28] v. Braun and Braunsdorf, *Ber.*, **54**, 2081 (1921).

ment by the 2-furomethyl group ($C_4H_3OCH_2$—) had little extra effect. Adams and Volwiler[29] have noted an increased effect in the simple allyl-*p*-aminobenzoate, $NH_2C_6H_4COOCH_2CH{=}CH_2$.

These comparatively recent studies in this field emphasize sufficiently the increase in action due to an ethylenic linkage. By analogy, therefore, one might expect that inasmuch as diethylamino-ethyl hydrocinnamate is without action and the correspounding ester of cinnamic acid is active, the corresponding ester of phenylpropiolic acid ($C_6H_5C{\equiv}CCOOCH_2CH_2N(C_2H_5)_2$) ought to have a decided local anesthetic action. Analogy, however, appears to break down rather completely here. The phenylpropiolic ester instead of being an anesthetic produces intense pain. The injection of even 0.0001 g. under the skin gives a smart similar to that caused by the sting of a bee and lasts for about 15 minutes. After all, this may not be too startling, for there are several classes of drugs which show a sudden change in comparative effectiveness with an undue accumulation of pharmacophore groups.

The two benzyl esters described are very insoluble in water. Superficial tests showed them to be apparently without action.

All that can be said for ethyl benzenesulfonate is that it has a slight, positive action. Ethyl benzene sulfinate produces a stinging sensation.

The authors wish to express their appreciation to Dr. Oliver Kamm and to Dr. Roger Adams for helpful criticisms.

## Summary

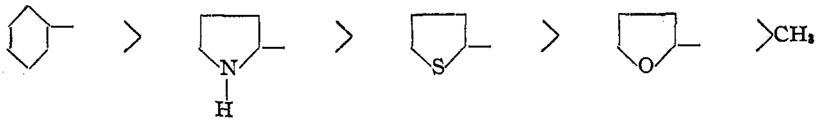
1. The diethylamino-ethyl esters and the benzyl esters of several hererocyclic carboxylic acids have been prepared and tested pharmacologically for their relative local anesthetic action.

2. In a reaction between benzenesulfinyl chloride and β-diethylamino-ethyl alcohol, phenyl disulfide and *sym*-ethylene-diphenyldisulfone were obtained.

3. It is shown that the correlation now known to exist between the physical and chemical properties of aromatic types can be extended to include physiological action.

4. Diethylamino-ethyl phenylpropiolate has a marked irritant action instead of the expected anesthetic action.

5. In their effect upon local anesthesia in the group of compounds studied, the relative values of the various radicals are as follows.



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[29] Adams and Volwiler, U. S. pat. 1,360,994.