INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

UMI[®]

THE RICE INSTITUTE

The Synthesis of Esters of 2,6-Dimethyl-4-Aminobenzoic Acid

by

Isaac Dvoretzky

A THESIS

SUBMITTED TO THE FACULTY

IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
Doctor of Philosophy

G. H. Richter

Houston, Texas
May, 1952

UMI Number: 3079684

UMI[®]

UMI Microform 3079684

Copyright 2003 by ProQuest Information and Learning Company.
All rights reserved. This microform edition is protected against
unauthorized copying under Title 17, United States Code.

ProQuest Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

Dedicated to my wife, Anny

Acknowledgment

I wish to express my appreciation to Professor G. H. Richter, who conceived the problem and directed with patience and understanding the devious approach to its solution.

I wish to acknowledge also the stimulating ideas and numerous practical suggestions of Dr. E. S. Lewis, and the technical advice of Dr. Richard B. Turner.

Finally, I wish to thank the Humble Oil and Refining Company for the grant of a fellowship for the academic year 1951-52.

Isaac D. Matzky

Table of Contents

I.	Introduction	1
II.	Synthesis of Esters of 2,6-Dimethyl-4-Aminobenzoic Acid	
	A. General Discussion	10
	B. Ethyl 2,6-Dimethyl-4-Aminobenzoate	19
	C. <u>n</u> -Propyl 2,6-Dimethyl-4-Aminobenzoate	31
III.	Experimental Part	34
IV.	Pharmacological Data	54
V.	Summary	56
VI.	References	57

I. Introduction

Introduction

The obscure relationship between chemical structure and physiological activity constitutes the most profound incentive, and, simultaneously, perhaps the most severe limitation of the modern science of chemotherapy. In the absence of an infallible guiding principle, the synthesis of compounds of pharmacological interest is necessarily based largely on empirical generalization. Such an approach has been particularly evident in the synthesis of local anesthetics.

An early "law" stated by Einhorn may be considered the stimulus for the intense activity which has been directed toward the preparation of substituted aromatic esters, the most significant group of substances possessing local anesthetic activity. On the basis of observations with numerous compounds, of which novocaine (I) has

become the most illustrious example, Einhorn was led in 1909 to the conclusion "... ein physiologisches Gesetz herrscht, welches lautet: „Alle aromatischen Ester besitzen

die Fähigkeit, locale Anästhesie zu erzeugen" (1). The original validity of Einhorn's statement has since been confirmed and extended by the investigation of an even longer series of compounds, the majority of which obey the law rather closely. A number of exceptions have been encountered, however, several of which appear to merit separate discussion.

The limitations of a structural criterion for local anesthetic activity are most strikingly demonstrated by considering cocaine (II), the classical prototype of

local anesthetics, as a model for comparison. Einhorn's generalization, coupled with the subsequently discovered influence of a basic nitrogen atom in the alcoholic portion of the ester, has led pharmacologists to regard the structural element $\text{Ar-CO-O-(C)}_n\text{-N}$ as the "anesthesiophoric" group in cocaine (2). Among the analogues of cocaine, all of which contain such a group, are the closely related tropacocaine (III) of Liebermann (3) and α -cocaine (IV) of Willstätter (4). It is perhaps remarkable that while tropacocaine is even more active than cocaine as a

III

IV

local anesthetic, α -cocaine is completely inactive; in fact, α -cocaine was the only exception known to Einhorn at the time his generalization was formulated (5).

Another significant pair of cocaine relatives consists of α -eucaine (V) (6) and β -eucaine (VI) (7), both of

V

VI

which are indeed very active. It was in an attempt to emulate the structure of cocaine even more closely that McElvain (8) prepared 1-methyl-3-carbethoxy-4-piperidyl benzoate (VII) and its open-chain analogue γ -(methyl- β -carbethoxy-ethyl)-aminopropyl benzoate (VIII). Again the pharmacological data are striking—the cyclic compound is considerably less active than cocaine, and the open-chain derivative is completely inactive. Although other structural considerations, such as the problem of stereochemical

VII

VIII

configuration, also enter into the argument, it is evident from the above discussion that the simple modification of a parent active substance is not a reliable basis for the synthesis of local anesthetics.

An approach based on one of the various aspects of the physiological mechanism of local anesthetic action would appear to be more rational. The major portion of the effort directed along such mechanistic lines has resulted in the rather large number of physico-chemical theories of narcosis, all aimed toward an understanding of the anesthetizing process itself. Unfortunately, however, even the most plausible of these theories (9), by virtue of its very generality, does not suggest a connection between chemical structure and local anesthetic activity; it is indeed consistent with Einhorn's observation "... unter den organischen Verbindungen überhaupt keine physiologische Eigenschaft so sehr verbreitet ist wie die, locale Anästhesie zu bewirken" (10).

Among the more detailed elements of the gross problem of physiological mechanism, that of the metabolic

fate of the anesthetizing molecule should bear some relation to chemical constitution. Apparently the metabolism of local anesthetics has not been extensively investigated; most of the work has been limited to observations with novocaine on experimental animals. These studies have indicated that novocaine is rather rapidly broken down to *p*-aminobenzoic acid and β -diethylaminoethanol (11), and that the liver is the principal site of detoxication (12, 13, 14). A more recent discovery by Hazard (15, 14, 12), however, has significantly altered the interpretation of the metabolic process. Hazard observed the presence in plasma of an enzyme which catalyzes the hydrolysis of novocaine to *p*-aminobenzoic acid and β -diethylaminoethanol. Physiological doses of novocaine were found to disappear from plasma both in vitro and in vivo within twenty minutes, and an accompanying increase in the amount of the resulting acid and alcohol was noted. Presumably the esterase is formed in the liver—hence the role of the liver in the detoxication process.

The overall significance of the above discovery is the fact that detoxication occurs almost immediately and at the site of application. The extension of this principle to the problem of synthesis of local anesthetics seems obvious: a molecule of the novocaine type in which the ester linkage is more difficultly hydrolyzed should exhibit a more prolonged anesthetic effect. On the basis

of common laboratory experience, such a requirement immediately suggests a structure in which the ester portion of the molecule is sterically hindered.

The element of steric hindrance among previously synthesized local anesthetics is, of course, not entirely lacking; in fact, several examples of such compounds may be cited to justify somewhat the relation between steric hindrance and anesthetic activity predicated above. The amide nupercaine (IX), which is the most potent local anesthetic known (16), and the highly active corresponding ester (X) (17), may be regarded as hindered aromatic ester

IX

X

derivatives of a sort. In another series of anesthetics, that of the anilides, the substance xylocaine (XI), recently synthesized by Löfgren (18), is an outstanding ex-

XI

ample of an effective anesthetic containing a hindered functional group. It has been claimed that xylocaine is the most ideal local anesthetic hitherto known (19).

A survey of the numerous substituted benzoic acid esters reveals that in this series also many examples of a sterically hindered ester group are to be found; most of these are embraced within the following general structures (20):

None of these compounds, however, has achieved prominence as a local anesthetic. Although the distinction may be of little significance, it is perhaps noteworthy that in all of the above esters the hindrance is located in the alcoholic rather than in the acidic portion of the molecule.

Despite the occurrence of many sterically hindered esters among those compounds which have been investigated

as local anesthetics, there is no indication that the property of steric hindrance has been systematically introduced on a mechanistic basis. Furthermore, no hindered benzoic ester of the classical type studied by Victor Meyer (21), namely one in which the hindrance is effected by two ortho substituents, appears to have been examined for anesthetic activity. (The substance XII is listed as having been

XII

tested for local anesthetic action (22); however, the accompanying pharmacological data are limited, and a systematic search of the literature reveals no mention of the compound.) In view of the enzymatic hydrolysis of novocaine encountered by Hazard, and because of the prominent position among local anesthetics occupied by esters of *p*-aminobenzoic acid, a study of the anesthetic properties of esters of a *p*-aminobenzoic acid hindered by two ortho substituents would be of some importance. Accordingly, the present investigation had as its immediate objective the synthesis of the simplest series of compounds of this type, the esters of 2,6-dimethyl-4-aminobenzoic acid (XIII).

XIII

II. Synthesis of Esters of 2,6-Dimethyl-
4-Aminobenzoic Acid

Synthesis of Esters of 2,6-Dimethyl-4-Aminobenzoic Acid

Among the conceivable methods for the synthesis of an ester of 2,6-dimethyl-4-aminobenzoic acid, a procedure similar to the one most commonly employed in the preparation of the analogous novocaine would attract immediate consideration. In the case of the sterically hindered compounds, such an approach would involve esterification of the nitro acid XIV by way of the corresponding acid chloride and subsequent reduction of the resulting nitro ester to the desired amino derivative. The requisite nitro acid, however, has not previously been synthesized, and its preparation from accessible starting materials would be prohibitively complex; furthermore, the substance would probably exhibit a pronounced tendency to undergo decarboxylation. Synthesis by the above series of reactions was therefore not attempted.

Another obvious attack on the synthetic problem at hand is one which requires direct esterification of the parent 2,6-dimethyl-4-aminobenzoic acid (XV). Of the clas-

sical methods available for the esterification of ster-

ically hindered acids, only two appear to be unlimited with respect to the alcoholic portion of the ester (23). One of these involves treatment of the acid chloride with the alcohol, a procedure obviously inapplicable to the above amino acid. The other method depends upon the reaction of a salt of the acid with an alkyl halide. When applied to an amino acid of the type under consideration, however, such a reaction may result in extensive alkylation of the amino group. It was observed by Taggart (24), for example, that sodium *p*-aminobenzoate and 4-chloromethylimidazole yield the *N*-substituted acid rather than the expected ester. It follows that neither of the above two classical procedures is suited to the esterification of the hindered *p*-aminobenzoic acid.

The method developed by Newman (25) specifically for the esterification of certain sterically hindered acids would appear to be more promising. Newman's procedure consists in pouring a 100 % sulfuric acid solution of the acid to be esterified into an excess of the alcohol; the desired ester is formed rapidly and in excellent yield. The theoretical basis for this method stems from the ionization behavior of organic compounds in solvent sulfuric acid (25, 26).

All carboxylic acids in concentrated sulfuric acid solutions appear to be involved in the following equilibria:

The basic ionization of most carboxylic acids does not proceed beyond the formation of the conjugate acid RCO_2H_2^+ indicated by equation (1). In the case of some acids, however, the relative stabilities of the conjugate acid and the oxocarbonium ion RCO^+ are such that the equilibrium of equation (2), and consequently that of equation (3), lie far to the right, the overall condition being represented by equation (4). Those acids which lead to extensive oxocarbonium-ion formation undergo the esterification described above, the reaction occurring according to the equation

Experimentally, the two extreme types of basic ionization represented by equations (1) and (4) are reflected in the van't Hoff $\underline{i}$ -factors of the acids in question, the former giving rise to a value of two and the latter to a value of four.

The combination of steric and resonance effects which influence the rather critical position of the equilibrium (2) has been determined largely from observations with relatively simple carboxylic acids. For example, the

behavior of 2,4,6-trimethylbenzoic acid, which exhibits an i-factor of four (27) and readily undergoes the sulfuric acid esterification (25), appears to be well understood. The more complex polyfunctional compounds, such as amino acids, have not been so extensively investigated; it is therefore difficult to predict the facility with which 2,6-dimethyl-4-aminobenzoic acid would be esterified by the sulfuric acid procedure. However, the recent determination of the i-factors of the three isomeric aminobenzoic acids indicates that the process of multiple protonation in these compounds is appreciable—the values are 2.3, 2.7, and 2.8 for the ortho, meta, and para isomers, respectively (28). Furthermore, preliminary experiments carried out during the course of the present investigation revealed that anthranilic and p-aminobenzoic acids can both be esterified by the sulfuric acid method to a significant extent. It was therefore decided to attempt a similar reaction with the 2,6-dimethyl-4-aminobenzoic acid, and attention was directed toward the preparation of this substance.

Only one synthesis of the sterically hindered p-aminobenzoic acid has been reported. Noyes (29) in 1898 described the preparation of the compound by application of the Hofmann hypobromite reaction to the unhindered carboxyl group of 2,6-dimethylterephthalic acid (XVI). The following series of reactions was employed:

Newman (30) has adapted the above procedure to the preparation of the methyl ester of the series XIII; esterification of the hindered carboxyl group was effected by diazomethane:

The initial step of the present investigation involved an unsuccessful attempt to repeat the work of Noyes. Although a sufficient amount of each of the intermediates was obtained, especially by the somewhat modified procedure of Hufferd and Noyes (31), none of the final product could be isolated. These results are perhaps consistent with the fact that Noyes describes the yields in all except the last of the above reactions.

More recently, Newman and Gildenhorn (32) have attempted to degrade 2,6-dimethylterephthalic acid to the desired amino derivative by means of the Schmidt reaction. These workers treated a solution of the dicarboxylic acid in 100 % sulfuric acid with sodium azide. The product of the reaction was not the expected 2,6-dimethyl-4-amino-benzoic acid but the isomeric 3,5-dimethyl-4-aminobenzoic acid (XVII), which resulted from reaction of the hindered

carboxyl group. On the basis of this experiment, the authors postulated the corresponding oxocarbonium ion as an intermediate in the reaction. This conclusion was strengthened by their further observation that mesitoic acid, the prime example of a compound which yields a stable oxocarbonium ion, is readily converted to mesidine under similar conditions.

Usually, however, the Schmidt reaction is carried out not in 100 % sulfuric acid but in ordinary 96 % acid. Also, hindered aromatic dibasic acids like tetrachlorophthalic acid and naphthalene-1,8-dicarboxylic acid fail to undergo the Schmidt reaction (33). It therefore appeared reasonable that in 96 % sulfuric acid, in which oxocarbonium-ion formation would not be expected to be very appreciable, the Schmidt reaction of 2,6-dimethylterephthalic acid should yield some of the desired amino compound. As a second attempt to obtain this substance, such a reaction was carried out. Even in this case, however, the product was not the 2,6-dimethyl derivative but the isomeric 3,5-dimethyl compound. Presumably, formation of the oxocarbonium ion of 2,6-dimethylterephthalic acid is significant even in 96 % sulfuric acid. This conclusion finds support in the evidence obtained by Schubert (34) that the corresponding ion of mesitoic acid exists to a large extent in 97 % as well as in 100 % sulfuric acid.

No further attempt was made to prepare the free

2,6-dimethyl-4-aminobenzoic acid, and the possibility of synthesizing its esters by direct esterification had to be abandoned. Instead, a more indirect method of synthesis involving 2,6-dimethylterephthalic acid as the starting material was considered. It was decided to esterify the hindered carboxyl group of this substance as the initial step in the preparation, and to degrade the unhindered carboxyl to an amino group in order to complete the synthesis.

Of the three classical methods for converting a carboxyl group to an amino group, namely the Hofmann, Schmidt, and Curtius reactions, it seemed inadvisable to employ either of the first two. The Hofmann degradation was excluded because of the poor yield which it offered in the Noyes synthesis described above, and because of the additional possibility of halogenation of the aromatic ring (35). The Schmidt reaction, in the light of the results obtained with 2,6-dimethylterephthalic acid, was clearly to be avoided. The mild and flexible Curtius degradation, however, was considered to be a satisfactory method for effecting the desired transformation.

The most commonly employed variation of the Curtius reaction involves the synthetic sequence ester→hydrazide→azide→isocyanate→urethane→amine. This series of reactions requires esterification as the first step in the degradation of the unhindered carboxyl of 2,6-dimethylterephthalic acid. Since the hindered carboxyl group was

to have been esterified at an earlier stage of the synthesis, the corresponding diester became a necessary intermediate. Accordingly, the overall scheme of the proposed synthesis involved preparation of the diester followed by application of the Curtius reaction. This method of attack was applied to the synthesis of the ethyl and n-propyl esters of 2,6-dimethyl-4-aminobenzoic acid.

Ethyl 2,6-Dimethyl-4-Aminobenzoate

The diethyl ester of 2,6-dimethylterephthalic acid (XVIII) was prepared by several methods. What appeared superficially to be the most attractive of these was suggested by the course of the Schmidt reaction of the parent acid. Since the behavior of this substance in concentrated sulfuric acid indicated a high degree of activity in the hindered position, it was decided to attempt esterification by the Newman procedure. A preliminary experiment was carried out in which 2,6-dimethylterephthalic acid alone was allowed to stand in 100 % sulfuric acid solution to determine whether the acid would suffer a rearrangement of the Jacobsen type under the conditions of the esterification. The acid was recovered unchanged, so the esterification itself was attempted.

The main product of the sulfuric acid esterification of 2,6-dimethylterephthalic acid with ethanol was indeed the desired diethyl ester, obtained in a yield of 27 %. The remainder of the product consisted of a mixture of 4-carbethoxy-2,6-dimethylbenzoic acid (XIX), which apparently

resulted from ordinary acid-catalyzed esterification of the unhindered carboxyl, and unchanged starting material. This result suggested that sulfuric acid esterification of the monoester XIX rather than of the dicarboxylic acid would probably lead to a much higher yield of the diester.

The requisite monoester was then prepared in 87 % yield by means of the Fischer esterification of 2,6-dimethylterephthalic acid. Subsequent esterification of the half ester by the sulfuric acid technique followed a strikingly erratic course. In some cases the yield of the diester was as high as 67 %, while in other attempts the original acid ester was quantitatively recovered. Presumably the success of the reaction depends upon a rather fine adjustment of the obvious variables involved, namely the concentration of the sulfuric acid and the water content of the ethanol. Of these two factors, the exact concentration of the acid is probably the more critical; even the use of strictly anhydrous ethanol, for example, led to complete recovery of the starting material when no attempt was made to fix accurately the concentration of the acid.

Notwithstanding the apparently unpredictable nature of the reaction, the above results indicate that 2,6-dimethylterephthalic acid, or its monoethyl ester XIX, is capable of significant oxocarbonium-ion formation. The previously discussed behavior of the dicarboxylic acid in the Schmidt reaction leads to the same conclusion. It is

remarkable that the experimentally determined $\underline{i}$ -factor of the dimethylterephthalic acid is only 2.1 (36) — a value closer to four would be more reasonable. The discrepancy may perhaps be resolved by a more profound theoretical interpretation of the problem.

The sulfuric acid esterification of the monoester was evidently not a dependable route to the diester. Two alternative methods of synthesis which also employed the half ester as starting material were then investigated. The first of these involved treatment of the silver salt of the 4-carbethoxy-2,6-dimethylbenzoic acid with ethyl iodide. The maximum overall yield of the diethyl ester from the half ester in this reaction was 63 %. A considerable amount of the original acid ester was also obtained from the reaction mixture. This regeneration of a parent acid by the reaction of its silver salt with an alkyl halide has been encountered by other workers (37).

Still another conversion of the acid ester XIX to the desired neutral ester was effected by way of the intermediate acid chloride (XXI). This compound, which was not

actually isolated, was prepared from the acid ester by treatment with thionyl chloride; the crude acid chloride was in turn esterified with ethanol.

The ease with which the above hindered acid chloride reacted with ethanol suggested that 2,6-dimethylterephthalyl dichloride (XXII) would offer a more direct path to the diester. Bull and Fuson (38) have prepared the dichloride in a yield of 75 % by the reaction of 2,6-dimethylterephthalic acid with phosphorus pentachloride. The work of these authors was repeated during the present investigation, and the diacid chloride obtained was converted to the diethyl ester by reaction with ethanol in 83 % yield.

An improvement in the above diethyl ester synthesis was effected by substitution of thionyl chloride for phosphorus pentachloride in the preparation of the intermediate diacid chloride. As a result of this change in the reagent, isolation of the acid chloride was no longer necessary; the crude material underwent smooth conversion to the neutral ester on treatment with ethanol. Although the yield of diacid chloride obtained by the use of thionyl chloride was only 61 % as compared with the 75 % yield afforded by phosphorus pentachloride, the procedure involving the former reagent was considered preferable because of the greater experimental convenience. The fact that 2,6-dimethylterephthalic acid reacts readily with thionyl chloride may be noteworthy in view of the complete inertness of

unsubstituted terephthalic acid to the same reagent (39).

The identical nature of the products of the above diethyl ester syntheses was demonstrated by conversion of each diester to a common ester hydrazide described below. Further evidence for the structure of the diethyl 2,6-dimethylterephthalate was obtained by alkaline hydrolysis of the substance; the product was 4-carbethoxy-3,5-dimethylbenzoic acid (XX), the isomer of the monoester obtained by Fischer esterification of the parent acid.

Once the intermediate diethyl ester had been prepared, it was allowed to react with hydrazine as the first step in the Curtius degradation. Reaction of the hindered carbethoxy group under these conditions was considered highly improbable, since it is generally true that hydrazide formation is retarded in sterically hindered esters (40); also, Curtius and Davidis (41) found that the unhindered diethyl terephthalate forms a dihydrazide only with the greatest difficulty. The above expectation was indeed realized in the high yield of the desired 4-carbethoxy-3,5-dimethylbenzhydrazide (XXIII) which was obtained. This substance was observed to exhibit the properties characteristic

XXIII

XXIV

of hydrazides. For example, it forms a crystalline hydrochloride and yields the benzal derivative XXIV with benzaldehyde.

Of the remaining intermediates in the Curtius route to the final amine, no attempt was made to isolate the azide or the isocyanate. Since the urethane was to be the first stopping point, the rearrangement of the azide was carried out in refluxing ethanol so that the latter would react with the isocyanate as soon as it formed. Decomposition of the azide under these conditions, however, was so slow that acylation of the alcohol by unchanged azide yielded an appreciable amount of diethyl-2,6-dimethylterephthalate. In subsequent experiments the decomposition and rearrangement of the azide were carried out in toluene on the steam bath; this method possessed the advantages of a higher decomposition temperature and of visible evolution of nitrogen as an indication of the course of the reaction. The urethane was then obtained by addition of ethanol to the toluene solution of the isocyanate.

Three definite products other than the diester were isolated at the urethane stage of the sequence. Although conclusive analytical data were not obtained, these were considered to be the desired urethane (XXV), the corresponding allophanate (XXVI), and the symmetrically substituted urea (XXVII). The urea, because of its physical

properties, was readily separated from the mixture. The other two substances were employed either separately or as a crude mixture in the subsequent hydrolysis to the desired amine.

The most commonly employed procedure for converting a urethane to the corresponding amine is by hydrolysis with concentrated hydrochloric acid (42). This method offers the advantages that the course of the reaction can be followed by the gradual disappearance of the originally insoluble urethane and that the product can be isolated directly as the crystalline amine hydrochloride. A rather unattractive feature of the method is that the hydrolysis is very slow.

It was decided to employ hydrochloric acid hydrolysis in the initial attempt to convert the above urethane to its amine; a reflux period of forty-five hours was neces-

sary to effect solution of the substance. The product of this drastic hydrolysis was an amine hydrochloride which exhibited no local anesthetic activity. The properties of the hydrochloride itself and of its acetyl and benzoyl derivatives demonstrated that the substance was 5-amino-1,3-dimethylbenzene (XXVIII) rather than the desired ethyl 2,6-dimethyl-4-aminobenzoate (XXIX).

Apparently the sym-m-xylidine resulted from attack on the hindered carbethoxy group under the severe conditions of the reaction. Although the elimination of this group can be visualized in a number of ways, a mechanism involving actual hydrolysis of the ester to the hindered p-aminobenzoic acid and subsequent decarboxylation of the latter substance would seem very probable. This interpretation is supported by the recent demonstration that the decarboxylation of methyl mesitoate in strong sulfuric acid proceeds by way of intermediate hydrolysis (34). The facility with which 2,6-dimethyl-4-aminobenzoic acid undergoes decarboxylation in hydrochloric acid has been pointed out by Noyes (29).

The hydrochloric acid hydrolysis was repeated under

somewhat milder conditions. The course of the reaction was followed by periodic diazotization and coupling with β -naphthol-3,6-disulfonic acid of a drop of the aqueous phase of the reaction mixture. When the color test indicated the formation of a considerable amount of amine, the acidic layer of the mixture was withdrawn and a fresh portion of acid added. A total of three successive portions of hydrochloric acid was employed. This procedure was intended to decrease the extent of reaction of the hindered ester group.

Significantly, the first portion of crystalline amine hydrochloride obtained from each of the three acidic mother liquors exhibited anesthetic activity. Combustion analysis of this substance, however, indicated that it was probably largely contaminated with some of the xylidine hydrochloride. The result of a platinum determination on a chloroplatinate derivative precipitated from one of the above filtrates, on the other hand, was in rather close agreement with the theoretical value for an acid salt of the desired amino ester. Further concentration of the above acidic solutions resulted in crystallization of an amine hydrochloride which had no anesthetic action at all. This substance, as well as the remainder of the amine still in solution, was found by way of its acetyl derivative to be the sym-m-xylidine. Even the initial crystalline product, which did possess some anesthetic activity, yielded the acetyl xylidine.

Acid hydrolysis of the urethane was clearly an unsatisfactory route to the corresponding amine. Alternative methods for the conversion of either an isocyanate or a urethane to an amine were therefore investigated. A number of experiments were carried out in which α -naphthyl isocyanate and ethyl and benzyl α -naphthyl urethanes were employed as model compounds. Reaction of the isocyanate with dilute or concentrated hydrochloric acid was extremely slow, the main product being the substituted urea. Treatment of the isocyanate with hydrogen chloride gas and subsequent hydrolysis of the expected carbamyl chloride was similarly ineffective. The variation of the Gabriel amine synthesis which makes use of hydrazine as a reagent for the cleavage of substituted phthalimides suggested that the same reagent might split urethanes in the manner

Such an attempt with ethyl α -naphthyl urethane, however, was unsuccessful.

A device employed by Hans Fischer (43) to overcome the difficulty of hydrolyzing a urethane of the pyrrole series which also contained an ester group in the molecule seemed attractive. Fischer's method consisted in hydrogenolysis of the benzyl urethane of the compound over palladium to the amine, carbon dioxide, and toluene. This non-hydrolytic procedure was attempted with benzyl

α -naphthyl urethane. Although α -naphthylamine was formed, the reaction appeared to be extremely slow. Substitution of the catalyst by sodium amalgam resulted in no reaction at all. Since benzyl urethanes are apparently more readily hydrolyzed by usual methods than are ethyl urethanes (44), hydrochloric acid hydrolysis of the benzyl α -naphthyl urethane was also investigated. A quantitative yield of α -naphthylamine was obtained after a two-hour period of reflux.

The procedure which finally appeared to be the most satisfactory involved alkaline alcoholic hydrolysis. Preliminary experiments with ethyl α -naphthyl urethane in aqueous methanolic sodium hydroxide indicated that although the hydrolysis proceeds more slowly than with ordinary esters, a smooth conversion to the amine is possible. In the case of the urethane of the present investigation, it was decided to employ ethanolic rather than methanolic alkali in order to avoid the possibility of an ester interchange of the solvent with the hindered functional group of the molecule. Subsequent experiments, however, revealed that such a precaution was probably not necessary. Hydrolysis of the above substances assumed to be the urethane and allophanate in a 0.25 N solution of potassium hydroxide in 90 % ethanol actually yielded the desired amino ester XXIX. Although hydrolysis was not quantitative within a reflux period of three hours, the unchanged starting material

could be recovered and hydrolyzed further. The final product, isolated as the hydrochloride, exhibited very pronounced local anesthetic activity; it was characterized by its acetyl derivative.

n-Propyl 2,6-Dimethyl-4-Aminobenzoate

The overall sequence of reactions employed in the synthesis of the n-propyl ester of the series XIII was quite similar to that described above for the preparation of the ethyl ester. The intermediate di-n-propyl ester of 2,6-dimethylterephthalic acid (XXX) was obtained by two methods. One procedure involved preliminary Fischer esterification of the parent dicarboxylic acid to 4-carbopropoxy-2,6-dimethylbenzoic acid (XXXI), and subsequent reaction of the

silver salt of the half ester with n-propyl bromide. Esterification of 2,6-dimethylterephthalyl dichloride with n-propyl alcohol provided a more convenient route to the di-ester.

Treatment of the di-n-propyl ester with hydrazine yielded 4-carbopropoxy-3,5-dimethylbenzhydrazide (XXXIII); this substance, like the corresponding ethyl hydrazide, was observed to exhibit basic properties and to form a benzal derivative. The intermediate azide obtained from the reaction of the hydrazide with nitrous acid was not

isolated, although the substance crystallized from its ether solution during the course of the reaction. Decomposition and rearrangement of the azide was carried out in toluene, and the urethane XXXIV prepared by addition of ethanol to the toluene solution of the isocyanate; neither the isocyanate nor the urethane was isolated. In addition to the urethane, two other products were obtained, one assumed to be the allophanate and the other the urea analogous to the corresponding substances XXVI and XXVII of the ethyl series.

XXXIII

XXXIV

XXXV

The crude product of the Curtius reaction was hydrolyzed without further purification. As in the case of the ethyl ester, controlled hydrochloric acid hydrolysis involving the naphthol-sulfonic acid coupling test was first attempted. Although the initial portion of crystalline amine hydrochloride which was formed exhibited some degree of anesthetic action, the bulk of the product did not; furthermore, no definite acetyl derivative could be obtained from the mixture. Hydrolysis in ethanolic potassium hydroxide, however, yielded an amine hydrochloride

possessing very marked anesthetic activity; this substance, assumed to be the desired n-propyl ester XXXV, was characterized by its acetyl derivative. A by-product of both the acid and basic hydrolyses was 4-carbopropoxy-3,5-dimethylbenzoic acid (XXXII), which apparently resulted from hydrolysis of the di-n-propyl ester. The presence of the latter substance in the crude urethane would be expected if acylation of the n-propyl alcohol by undecomposed azide occurred during the alcohol-isocyanate reaction.

III. Experimental Part

Experimental Part

Preparation of 2,6-Dimethylterephthalic Acid

The method of Hufferd and Noyes (31) was followed in the preparation of the dicarboxylic acid by alkaline permanganate oxidation of acetomesitylene. The requisite ketone was obtained by Friedel-Crafts acetylation of mesitylene, b. p. 162-163°, with acetyl chloride and aluminum chloride according to the procedure of Meyer and Molz (45). The crude acetomesitylene, which distilled at 232-239° at atmospheric pressure, darkened on standing; redistillation at 4-5 mm. resulted in a clear pale-yellow oil, b. p. 92-105°, in a yield of 80 %. Oxidation of this purified material gave a 78 % yield of 2,6-dimethylterephthalic acid, m. p. 292-294°. The acid prepared by the above procedure was invariably contaminated with some of its ammonium salt; in subsequent experiments in which the acid came in contact with hydrogen chloride, a precipitate of ammonium chloride was consequently produced. Also, considerable amounts of 3,5-dimethylphthalic acid always resulted as a by-product of the oxidation.

Schmidt Reaction of 2,6-Dimethylterephthalic Acid:

A procedure similar to that of Newman and Gildenhorn (32) was employed. To a stirred mixture of 15 ml. of chlo-

roform and a solution of 4.7 g. (0.024 mole) of 2,6-dimethylterephthalic acid in 20 ml. of 96 % sulfuric acid there was added over a period of two and one-half hours 1.05 g. (0.016 mole) of sodium azide; the temperature did not rise above 35°. Stirring was continued for another two hours, after which time the mixture was poured onto 100 g. of ice. After separation of the chloroform layer the aqueous phase was partially neutralized by addition of 20 % sodium hydroxide; just before neutralization was complete, an amorphous white solid precipitated. This substance was collected on a filter, dried, and found to weigh 2.8 g. . Recrystallization from 5 N hydrochloric acid yielded 1.7 g. (64 %) of long white needles of 3,5-dimethyl-4-aminobenzoic acid; an additional 0.2 g. (8 %) was obtained by neutralization of the acidic mother liquor. The substance melted with decomposition at 248-255° when heated from 30° to 200° in ten minutes and at 8° per minute thereafter. Previously reported melting points vary; 235° (46), 242° (47), and 251-252° (32), all with decomposition, have been reported. The isomeric 2,6-dimethyl-4-aminobenzoic acid melts with decomposition at 194-195° and is readily decarboxylated when warmed with hydrochloric acid (29).

The product was further characterized by diazotization and coupling with *p*-naphthol; recrystallization of the azo derivative from ethanol furnished orange-red

feathery needles, m. p. 270-272° with decomposition (m. p. procedure same as above), as compared with m. p. 285-288° reported earlier (32). Warming of the diazonium solution with a little copper sulfate resulted in precipitation of 3,5-dimethyl-4-hydroxybenzoic acid, which after recrystallization from benzene took the form of off-white needles, m. p. 190-215°; melting points of 218° (48) and 223° (49) have been reported. The isomeric 2,6-dimethyl-4-hydroxybenzoic acid melts at 185° with decomposition (50). Finally, the amino acid was converted to its ethyl ester. A solution of 0.78 g. (0.0047 mole) of the acid in 15 ml. of ethanol was saturated with hydrogen chloride and the resulting mixture heated under reflux for three hours. After standing overnight in the refrigerator, the solution developed a growth of large white prisms; the weight of this crude product was 0.80 g. . The hydrochloride was then treated with 20 ml. of 20 % sodium hydroxide and the resulting suspension extracted with ether. Bubbling of hydrogen chloride into the ether extract resulted in precipitation of 0.72 g. (66 %) of snow-white crystals of ethyl 3,5-dimethyl-4-aminobenzoate hydrochloride, m. p. 190-205° with decomposition. A little of the free base, when recrystallized from petroleum ether, yielded white platelets melting at 66-67° (47).

Sulfuric Acid Esterification of 2,6-Dimethylterephthalic Acid

The method of Newman (25) was followed. A solution of 1.30 g. (0.0067 mole) of 2,6-dimethylterephthalic acid in 10 ml. of 100 % sulfuric acid (prepared by mixing 50 g. of 96 % acid with 59 g. of 15 % oleum), after standing for several minutes, was poured into 5 ml. of cold ethanol. To the resulting mixture 25 ml. of cold water was added slowly with stirring, and the suspension of solid, oil, and aqueous acid filtered with suction. The cloudy filtrate was extracted with an equal volume of ether; to this ether extract was added the precipitate, and the entire mixture shaken with 20 ml. of 10 % sodium carbonate. The ether layer was separated and the solvent evaporated; the residue, 0.45 g. (27 %) of crude diethyl 2,6-dimethylterephthalate, was not further purified, but was employed in the diethyl ester-hydrazine reaction described below. Acidification of the carbonate solution resulted in precipitation of 0.43 g. of a white solid which melted over the range 110-260° and which was almost completely soluble in ether. Alkaline hydrolysis of the crude substance yielded an acid, m. p. 295-300°; the mixed-melting point of this product with 2,6-dimethylterephthalic acid was 295-298°. On the basis of this hydrolysis and of the physical properties of the crude material, the acidic product of the esterification was considered to be a mixture of 4-carbethoxy-2,6-dimethylbenzoic acid and unchanged starting material.

whereupon a yellow-brown oil separated to the top. The mixture was extracted with two 50-ml. portions of ether, and the ether extracts washed twice with 20 % sodium carbonate and dried over magnesium sulfate. Distillation of the solvent from the dried ether extract left 1.8 g. (67 %) of a yellow-brown oil assumed to be diethyl 2,6-dimethylterephthalate; this product was used in the diethyl esterhydrazine reaction without further purification. Acidification of the sodium carbonate washings of the ether extract resulted in precipitation of 0.7 g. (29 %) of unchanged monomer.

Silver Salt-Ethyl Iodide Esterification of
4-Carbethoxy-2,6-Dimethylbenzoic Acid

To a solution of 1.7 g. (0.0076 mole) of the acid ester in dilute ethanol, 10 % sodium hydroxide was added until the phenolphthalein end point was reached. Addition of 5 % silver nitrate to this solution of the sodium salt resulted in precipitation of the curdy, gray-white silver salt; the weight of the vacuum-dried product was 1.8 g. (71 %). This silver salt was suspended in 20 ml. of benzene, and 10 ml. of freshly distilled ethyl iodide added. The mixture was heated under reflux on the steam bath for three hours; formation of the yellow silver iodide began almost immediately. The clear supernatant solution was decanted from the silver iodide, the precipitate washed

with 5 ml. of ethanol, and most of the solvent distilled from the combined solutions. The residue was extracted with 10 % sodium carbonate and ether. Evaporation of the solvent from the ether extract left 1.2 g. (88 %) of a clear light-yellow oil; this substance, assumed to be crude diethyl 2,6-dimethylterephthalate, was employed without further purification in the diester-hydrazine reaction. Acidification of the carbonate solution yielded 0.16 g. (13 %) of the original acid ester. The overall yield of crude diester from monoester was 63 %.

Preparation of Diethyl 2,6-Dimethylterephthalate
from 2,6-Dimethylterephthalyl Dichloride

A. Phosphorus pentachloride procedure:

The procedure of Bull and Fuson (38) was followed in the preparation of the diacid chloride from 2,6-dimethylterephthalic acid and phosphorus pentachloride in phosphorus oxychloride solution. The dichloride was obtained in 26 % yield as a clear pale-yellow liquid which distilled over the range 165-170° at 33 mm.. A solution of 1.0 g. (0.0043 mole) of 2,6-dimethylterephthalyl dichloride, 50 ml. of ethanol, and 10 ml. of benzene was heated under reflux for sixteen hours. The bulk of the solvent was distilled at atmospheric pressure, and the residue, which had a volume of about 15 ml., transferred to a Claisen flask. After the remaining low-boiling material had been removed at aspirator

pressure, there was obtained 0.9 g. (83 %) of diethyl 2,6-dimethylterephthalate, which took the form of a colorless oil, b. p. 151-155° at 4 mm..

B. Thionyl chloride procedure:

In a flask fitted with a reflux condenser, calcium chloride tube, and hydrogen chloride trap were placed 6.4 g. (0.033 mole) of 2,6-dimethylterephthalic acid and 75 ml. of Eastman practical-grade thionyl chloride; the violent reaction which occurred immediately after mixing soon subsided. The mixture was heated under reflux for eight hours, after which time the excess thionyl chloride was removed by distillation at the aspirator. No attempt was made to isolate the diacid chloride. To the residue, a yellow-white solid, was added 125 ml. of ethanol, and the resulting suspension heated under reflux for four hours. Most of the ethanol was then removed by distillation; addition of 60 ml. of water to the residue resulted in solution of the ammonium chloride and the appearance of a yellow-brown oil suspended in the milky aqueous phase. The mixture was extracted twice with an equal volume of ether, and the combined ether extracts washed with 10 % sodium carbonate. Acidification of the alkaline extract resulted in precipitation of only an insignificant amount of acidic material. Distillation of the solvent from the neutralized ether solution left 4.1 g. of a clear oily residue. The crude diester was converted to the ester hydrazide without further purification.

On the assumption that all of the 2,6-dimethylterephthalyl dichloride present in the crude product of the thionyl chloride reaction gave the same 83 % yield of diethyl ester afforded by the pure diacid chloride of the phosphorus pentachloride reaction, the yield of diacid chloride in the above preparation was 61 %.

A completely analogous procedure was followed in the esterification with ethanol of 4-carbethoxy-2,6-dimethylbenzoic acid through its acid chloride.

Hydrolysis of Diethyl 2,6-Dimethylterephthalate

A solution of 0.50 g. (0.0020 mole) of the diethyl ester and 0.50 g. (0.0089 mole) of potassium hydroxide in 25 ml. of ethanol and 5 ml. of water was heated under reflux for two hours, after which time most of the solvent was removed by distillation. The basic residue was acidified with 40 % sulfuric acid, and the cheesy tan precipitate collected on a filter. The crude product was redissolved in 20 % sodium carbonate and the resulting solution decolorized with Norite; acidification of the clarified solution furnished 0.44 g. (99 %) of 4-carbethoxy-3,5-dimethylbenzoic acid. Recrystallization of this product from cyclohexane yielded fluffy white needles, m. p. 129-130°.

Analysis: Calculated for $C_{12}H_{14}O_4$: neut. equiv., 222.

Found: neut. equiv., 221.

Preparation of 4-Carbethoxy-3,5-Dimethylbenzhydrazide

A procedure similar to that of Curtius and Davidis (41) was followed. To a mixture of 0.80 g. (0.0032 mole) of vacuum-distilled diethyl-2,6-dimethylterephthalate and 0.7 ml. of 85 % hydrazine hydrate, enough ethanol was added to effect complete solution. The mixture was heated under reflux for eight hours, then cooled, and the crystalline hydrazide collected on a filter. The crude product was washed with ether, and the combined filtrate and residue from the ether washings heated under reflux for four hours more after an additional 0.5 ml. of hydrazine solution had been added. Cooling of the reaction mixture and dilution with 20 ml. of water yielded a second crop of crystalline material. The weight of the combined ether-washed product, m. p. 168-171°, was 0.60 g. (80 %). Recrystallization of the crude material from dilute ethanol yielded clusters of white needles, m. p. 174-175°. Analytically pure 4-carbethoxy-3,5-dimethylbenzhydrazide, m. p. 175-176°, was obtained by an additional recrystallization from benzene.

Analysis: Calculated for $C_{12}H_{16}O_3N_2$: C, 61.00; H, 6.83.

Found: C, 60.87; H, 6.58.

Treatment of an ethanolic solution of the hydrazide with hydrogen chloride gas resulted in precipitation of fine white needles which melted over the range 185-195°. This substance, which was soluble in water and insoluble in ether,

was considered to be the hydrazide hydrochloride.

A saturated aqueous solution of the hydrazide was mixed with a saturated aqueous solution of sodium carbonate-washed benzaldehyde on the steam bath; almost immediately there developed a flocculent white precipitate. This substance, assumed to be the benzal hydrazide, was collected on a filter; recrystallization from ethanol yielded fluffy white needles, m. p. 185-188°.

Conversion of Ethyl Ester Hydrazide to Ethyl Ester Urethane

The generalized procedure of Organic Reactions (51) was employed with slight modification. A solution of 1.95 g. (0.0083 mole) of 4-carbethoxy-3,5-dimethylbenzhydrazide in 18 ml. of water and 2 ml. of 6 N hydrochloric acid was covered with 20 ml. of peroxide-free ether, and the mixture cooled to 0° in an ice-salt bath. To the stirred cold mixture was added dropwise a solution of 0.57 g. (0.0083 mole) of sodium nitrite in 1.6 ml. of water; each drop of nitrite produced a cloudy suspension in the aqueous phase which was removed by the ether. After the presence of nitrous acid was indicated by a starch-iodide test, the ether layer was separated and the aqueous phase extracted with two 10-ml. portions of ether. The combined ether extracts were washed with 5 ml. of 10 % sodium bicarbonate and dried for twenty minutes over magnesium sulfate.

The dried ether solution of the azide was decanted

into 10 ml. of toluene, and the resulting mixture warmed on the steam bath at such a rate that the ether slowly distilled. After the ether had been removed, the solution was heated strongly on the steam bath until the evolution of nitrogen ceased; this decomposition required about one hour. To the toluene solution of the isocyanate was added 20 ml. of ethanol, and the resulting mixture heated under reflux for fifteen hours. The excess ethanol was distilled from the steam bath and the yellow-brown toluene solution cooled overnight in the refrigerator; the crystals which had formed were collected on a filter and washed with ether. This substance consisted of 0.225 g. (13 %) of glistening white needles, m. p. 202-204°, considered to be the symmetrical-urea derivative; recrystallization from ethanol yielded material melting at 203-204°.

Analysis: Calculated for $C_{23}H_{28}O_5N_2$: C, 66.97; H, 6.84.

Found: C, 65.41; H, 6.23.

The toluene filtrate was evaporated under aspirator pressure until the bulk of the solvent had been removed. The residue, a yellow-brown oil, was cooled at 0° for four hours, and the white crystals which had formed collected on a filter and washed with cold toluene. Concentration and cooling of the filtrate a second time resulted in further crystallization. The total weight of this crystalline material, assumed to be the allophanate derivative, was 1.02 g. (51 %). The crude substance, m. p. 152-154°, yielded

on recrystallization from dilute ethanol fluffy white needles, m. p. 155 -155.5°.

Analysis: Calculated for $C_{26}H_{32}O_7N_2$: C, 64.44; H, 6.66.

Found: C, 65.19; H, 6.86.

Finally, complete evaporation of the solvent from the remaining filtrate left an oily residue which did not crystallize. The weight of this crude substance, assumed to be the desired urethane, was 0.8 g. (36 %). During the acid hydrolysis of this material described below, there appeared on the walls of the condenser a white crystalline substance, m. p. 73-74°, which was assumed to be pure urethane derived from steamdistillation of the crude oil.

Acid Hydrolysis of Ethyl Ester Urethane

Approximately 1 g. of the crude oily urethane was treated with 5 ml. of conc. hydrochloric acid and the mixture heated under reflux in an oil bath. After two hours, another 5 ml. of acid was added, and after an additional twenty-two hours of reflux, a third 5-ml. portion of acid was introduced. Reflux was continued for another twenty-one hours. At this point most of the original oil had dissolved, and the mixture consisted of a clear aqueous solution with some suspended white solid; white crystals, m. p. 73-74°, assumed to be pure urethane, adhered to the walls of the condenser. The aqueous suspension was extracted with an equal volume of ether, whereupon the solid

material dissolved. The aqueous layer was separated and filtered, and the filtrate saturated with hydrogen chloride. Cooling of this acidic solution resulted in precipitation of clusters of white needles which were insoluble in ether and soluble in water. This amine hydrochloride, which had no anesthetic activity, did not melt below 300°, and on ignition it resembled ammonium chloride. These properties are similar to those of sym-m-xylidine hydrochloride (52). Acetylation of the substance by the Schotten-Baumann procedure (53) yielded an acetyl derivative, m. p. 140-141°; a benzoyl derivative, m. p. 142-145°, was similarly prepared. The melting point of the acetyl derivative thus obtained is the same as that of acetyl sym-m-xylidine (52,54, 55).

Authentic samples of the acetyl and benzoyl derivatives of the xylidine were prepared from Eastman 5-amino-1,3-dimethylbenzene. An acetyl derivative of m. p. 141-142° and a benzoyl derivative of m. p. 144-145° were obtained; both compounds were purified by recrystallization from dilute ethanol. The benzoyl sym-m-xylidine has not been reported in the literature. The mixed melting points of the authentic samples with the corresponding derivatives of the acid-hydrolysis product were 140-142° and 142-145° for the acetyl and benzoyl compounds, respectively. The identity of the above product with the xylidine was thus established.

Alkaline Hydrolysis of Ethyl Ester Urethane

In 100 ml. of a 0.25 N solution of potassium hydroxide in 90 % ethanol was dissolved 1.02 g. (0.0021 mole) of the ethyl ester allophanate, m. p. 152-154°. The resulting solution was heated under reflux for one hour, after which time the condenser was turned downward and 90 ml. of distillate collected. Most of the remaining solvent was evaporated under reduced pressure, until the volume of the residue was about 5 ml.. To this was added 25 ml. of water, and the turbid suspension extracted with two 30-ml. portions of peroxide-free ether. The combined ether extracts were dried for twenty minutes over magnesium sulfate. Passage of hydrogen chloride into the dried ether solution resulted in precipitation of glistening, minute, white needles and of a dark lower oily layer. The mixture was filtered with suction and the crystalline material washed with ether; the weight of the solid material was 0.2 g., and the volume of the oily phase was about 1 ml.. A solution of the liquid material in dilute ethanol soon developed a growth of white needles melting at 151-154°; The precipitated oil therefore consisted of unchanged starting material, and could be subjected to further hydrolysis.

The crystalline hydrochloride, which exhibited very intense anesthetic activity, did not melt below 300°. Acetylation of a 0.130-g. portion of the substance by the

Schotten-Baumann method (53) yielded 0.120 g. of an acetyl derivative. Recrystallization of this substance from toluene gave white needles, m. p. 140-141°. The mixed melting point of this derivative with an authentic sample of acetyl sym-m-xylidine occupied the range 110-138°; the two were therefore different. Further recrystallization of the above acetyl derivative from water yielded crystals, m. p. 140°, the analysis of which indicated the substance to be the acetyl derivative of the desired amino ester.

Analysis: Calculated for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28.

Found: C, 66.19, 66.32; H, 7.38, 7.22.

Hydrolysis of 0.8 g. (0.003 mole) of the crude oily material assumed to be the ethyl ester urethane by the above procedure yielded 0.5 g. (72 %) of the same ethyl 2,6-dimethyl-4-aminobenzoate hydrochloride; a reflux period of three and one-half hours rather than of one hour was employed. Acidification of the ether-extracted aqueous alkaline solution resulted in precipitation of 0.065 g. (6 %) of a substance which after recrystallization from cyclohexane consisted of fluffy white needles, m. p. 124-126°. This 4-carbethoxy-3,5-dimethylbenzoic acid, and the identical product of the acid hydrolysis, resulted from hydrolysis of the diethyl 2,6-dimethylterephthalate which was a by-product of the ethanol-isocyanate reaction.

Substitution of the ethanolic potassium hydroxide by methanolic sodium hydroxide had no effect on the product of the hydrolysis.

Note: The procedures employed in the preparation of the compounds of the n-propyl series were similar in detail to those described above for the reactions of the ethyl series.

Synthesis of 4-Carbopropoxy-2,6-Dimethylbenzoic Acid

Fischer esterification of 2,6-dimethylterephthalic acid with n-propyl alcohol gave a 29 % yield of the half n-propyl ester. The product, after successive recrystallization from dilute n-propyl alcohol, cyclohexane, and carbon tetrachloride, consisted of small white granular crystals, m. p. 115-119°; the main impurity in the substance appeared to be the parent dibasic acid.

Analysis: Calculated for $C_{13}H_{16}O_4$: neut. equiv., 236.

Found: neut. equiv., 230.

Silver Salt-n-Propyl Bromide Esterification of 4-Carbopropoxy-2,6-Dimethylbenzoic Acid

The silver salt of the monoester was obtained in 80 % yield. Esterification of the salt with n-propyl bromide gave a 65 % yield of crude di-n-propyl 2,6-dimethylterephthalate; an 11 % yield of the original acid ester was recovered.

Preparation of Di-n-Propyl 2,6-Dimethylterephthalate from 2,6-Dimethylterephthalyl Dichloride

The reaction of n-propyl alcohol with 2,6-dimethylterephthalyl dichloride which was obtained from

the parent acid and thionyl chloride gave the crude di-n-propyl ester in a yield of 49 %.

Preparation of 4-Carbopropoxy-3,5-Dimethylbenzhydrazide

Treatment of the diester with hydrazine resulted in the formation of the n-propyl ester hydrazide, m. p. 150-152°, in 95 % yield. Recrystallization of the crude product from benzene yielded fluffy white needles, m. p. 150-151°.

Conversion of Propyl Ester Hydrazide to Propyl Ester Urethane

The azide formed by the reaction of nitrous acid with the hydrazide crystallized from its ether solution, but the substance was not investigated. Addition of ethanol to the toluene solution of the isocyanate yielded several products. From the crude mixture of crystals and oil there was obtained an ether-insoluble substance consisting of white prisms, m. p. 192-194°, which was assumed to be the symmetrical-urea derivative. Another crystalline product, possibly the allophanate derivative, consisted of white needles, m. p. 172-175°. The remaining oily material was considered to be a mixture of the urethane and di-n-propyl ester.

Hydrolysis of Propyl Ester Urethane

The only definite product of the hydrochloric acid

hydrolysis of the above crude urethane was 4-carbopropoxy-3,5-dimethylbenzoic acid, which after successive recrystallization from benzene and dilute ethanol took the form of white prisms, m. p. 110-111°.

Analysis: Calculated for $C_{13}H_{16}O_4$: neut. equiv., 236.

Found: neut. equiv., 238.

Hydrolysis of the crude urethane in ethanolic potassium hydroxide yielded an amine hydrochloride possessing a high degree of anesthetic activity. This substance formed an acetyl derivative which crystallized from toluene in clusters of white needles, m. p. 128-129°. Unchanged urethane was recovered as an oily hydrochloride. Acidification of the ether-extracted alkaline solution yielded a small amount of 4-carbopropoxy-3,5-dimethylbenzoic acid.

IV. Pharmacological Data

Pharmacological Data

The structural similarity of the esters of 2,6-dimethyl-4-aminobenzoic acid to the corresponding esters of unsubstituted *p*-aminobenzoic acid suggests that anesthesine (XXXVI), the simplest effective local anesthetic of the latter series of compounds, be considered as a pharmacological standard of comparison. Since ethyl *p*-aminobenzoate is employed primarily as a surface anesthetic, the compounds prepared as the objective of the present investigation were compared with anesthesine for local anesthetic action on the tongue. Ethyl 3,5-dimethyl-4-aminobenzoate (XXXVII), prepared by Fischer esterification of the product of the Schmidt reaction of 2,6-dimethylterephthalic acid, was also investigated.

XXXVI

XXXVII

One drop of a 5 % aqueous solution of ethyl *p*-aminobenzoate hydrochloride was applied to the tongue as a standard, and the characteristics of the anesthesia thus produced were observed. In a similar manner, a drop of a solution of the same molar concentration of each of the other amino ester hydrochlorides was investigated.

The induction period, relative depth of anesthesia, duration of anesthesia, and relative degree of irritation were noted for each compound; the results are tabulated below.

<u>Compound</u>	<u>Induction Period</u>	<u>Depth</u>	<u>Duration</u>	<u>Irritation</u>
XXXVI	10 seconds	moderate	3 minutes	none
XXIX	40 seconds	intense	8 minutes	intense
XXXV	45 seconds	intense	16 minutes	moderate
XXXVII	45 seconds	weak	3 minutes	none

Note: The concentration of the saturated solution of the hydrochloride XXXVII was somewhat less than the requisite concentration equivalent to the 5 % anesthesine solution.

Apparently both the ethyl and n-propyl esters of the series XIII exhibit significantly more powerful local anesthetic properties than does anesthesine; the rather pronounced degree of irritation of these two hindered esters is also to be noted, however.

V. Summary

Summary

The recent discovery in plasma of an enzyme which catalyzes the hydrolysis of novocaine to *p*-aminobenzoic acid and β -diethylaminoethanol suggests that esters of *p*-aminobenzoic acid which are more difficultly hydrolyzed should exhibit a more prolonged local anesthetic effect. Such a requirement would most obviously be satisfied by *p*-aminobenzoic esters in which the ester group is sterically hindered by two ortho substituents. The present investigation was concerned with the synthesis of the simplest series of compounds of this type, the esters of 2,6-dimethyl-4-amino-benzoic acid.

The preparation of the ethyl ester is illustrative of the synthetic sequence employed. Introduction of the hindered carbethoxy group was accomplished by conversion of 2,6-dimethylterephthalic acid to its diethyl ester; this transformation was effected by several methods, the simplest involving the intermediate diacid chloride. The unhindered carbethoxy group of the diester was converted to the hydrazide, which in turn was degraded to the corresponding ethyl urethane by means of the Curtius reaction. Alkaline hydrolysis of the urethane yielded the desired amino ester.

Preliminary tests indicate that ethyl and n-propyl 2,6-dimethyl-4-aminobenzoates exhibit a significantly more prolonged local anesthetic action than does anesthesine, the related unhindered compound.

VI. References

References

1. Einhorn, Ann., 371, 125 (1909).
2. Jenkins and Hartung, The Chemistry of Organic Medicinal Products, John Wiley and Sons, Inc., New York, second edition, 1943, p. 336.
3. Liebermann, Ber., 24, 2336 (1891).
4. Willstätter, ibid., 29, 2216 (1896).
5. Einhorn, op. cit., p. 126.
6. D. R. P. 90245; Friedländer, Fortschritte der Theerfarbenfabrikation, Julius Springer, Berlin, 1899, Vol. IV, p. 1223.
7. D. R. P. 97672; Friedländer, ibid., 1901, vol. V, p. 787.
8. McElvain, J. Am. Chem. Soc., 46, 1721 (1924).
9. Bancroft and Richter, J. Phys. Chem., 35, 115 (1931).
10. Einhorn, op. cit., p. 128.
11. Williams, Detoxication Mechanisms, John Wiley and Sons, Inc., New York, 1947, p. 107.
12. Research Today (Lilly Research Laboratories), vol. VI (spring, 1950), p. 24.
13. Adriani, The Pharmacology of Anesthetic Drugs, Charles C. Thomas, Springfield, 1942, p. 48.
14. Sollmann, A Manual of Pharmacology, W. B. Saunders Company, Philadelphia, seventh edition, 1948, p. 274.
15. Hazard, Rev. med. de la Suisse Rom., 66, 617 (1946).
16. Löfgren, Inaugural Dissertation, University of Stockholm, (1948), p. 41.
17. Ibid., p. 11.
18. Ibid., p. 28.
19. Ibid., p. 67.

20. Carney, "Benzoates and Substituted Benzoates as Local Anesthetics", chapter 4 in Medicinal Chemistry, John Wiley and Sons, Inc., New York, 1951, vol. I, p. 280.
21. V. Meyer, Gumbel, and Sudborough, Ber., 27, 510 (1894).
22. Carney, op. cit., p. 373.
23. Houben, Die Methoden der Organischen Chemie, Georg Thieme Verlag, Leipzig, 1925, vol. 2, p. 640 ff..
24. Taggart, M. A. Thesis, the Rice Institute, 1932, p. 57.
25. Newman, J. Am. Chem. Soc., 63, 2431 (1941).
26. Hammett, Physical Organic Chemistry, McGraw-Hill Book Company, Inc., New York, 1940, pp. 45-48, 278-281.
27. Hammett and Treffers, J. Am. Chem. Soc., 59, 1708 (1937).
28. O'Brien and Niemann, ibid., 73, 4264 (1951).
29. Noyes, Am. Chem. J., 20, 789 (1898).
30. Newman, private communication to the author.
31. Hufferd and Noyes, J. Am. Chem. Soc., 43, 925 (1921).
32. Newman and Gildenhorn, ibid., 70, 317 (1948).
33. Caronna, Gazz. chim. ital., 71, 475 (1941).
34. Schubert, J. Am. Chem. Soc., 71, 2639 (1949).
35. Wallis and Lane, Organic Reactions, John Wiley and Sons, Inc., New York, 1946, vol. III, Chapter 7.
36. Newman and Deno, J. Am. Chem. Soc., 73, 3651 (1951).
37. Cohen and Schneider, ibid., 63, 3382 (1941).
38. Bull and Fuson, ibid., 55, 3424 (1933).
39. McMaster and Ahmann, ibid., 50, 145 (1928).
40. Smith, Organic Reactions, John Wiley and Sons, Inc., New York, 1946, vol. III, Chapter 9, p. 341.
41. Curtius and Davidis, J. prakt. Chem., (2) 54, 66 (1896).
42. Smith, op. cit., p. 380.

43. Fischer and Waibel, Ann., 512, 195 (1934).
44. Smith, op. cit., p. 381.
45. Meyer and Molz, Ber., 30, 1270 (1897).
46. Fittig and Brueckner, Ann., 147, 42 (1868).
47. Wheeler and Hoffman, Am. Chem. J., 44, 113 (1910).
48. Thiele and Eichwede, Ann., 311, 363 (1900).
49. Jacobsen, Ber., 12, 604 (1879).
50. Rabe and Spence, Ann., 342, 328 (1905).
51. Smith, op. cit., p. 382.
52. Wroblewsky, Ann., 207, 91 (1881).
53. Shriner and Fuson, The Systematic Identification of Organic Compounds, John Wiley and Sons, Inc., New York, third edition, 1948, p. 177.
54. Thöl, Ber., 18, 359 (1885).
55. Nölting and Forel, ibid., 18, 2668 (1885).