would have all of the propertes found in the experimental work. Such a mixture might reasonably be expected to be formed in petroleum production.

CLEVELAND, OHIO.

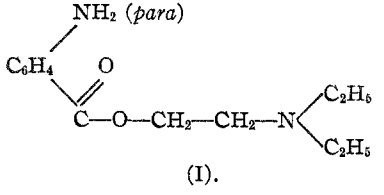
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS AND FROM THE ABBOTT LABORATORIES, OF CHICAGO, ILLINOIS.]

THE RELATIONSHIP BETWEEN CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION IN LOCAL ANESTHETICS. I. HOMOLOGS OF PROCAINE.

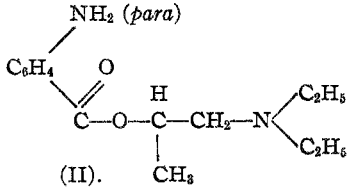
BY OLIVER KAMM.

Received February 23, 1920.

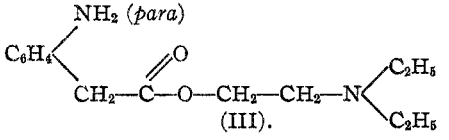
Several simple homologs of the well-known anesthetic, procaine (Formula I),[1] have been described in the literature. The formulas for compounds of this type which differ from the parent substance in that they possess one more carbon atom are represented structurally as follows:



(I).



(II).



(III).

Compound II is described in the German patent literature,[2] but the writer is not aware of published data recording the physiological action of this individual. Compound III has been synthesized more recently by Pyman[3] and has been found to be inactive as an anesthetic. It is to be noted that the latter compound is an amino-alcohol ester of an aliphatic acid (*p*-aminophenyl *acetic* acid) whereas a maximum anesthetic effect appears to develop when the carbonyl group is united directly to the aromatic nucleus. Such a type of linkage is, however, not essential, provided that the carbonyl group of the ester be united to an unsaturated carbon atom,[4] such as is illustrated by Formulas IV and V. Both of these

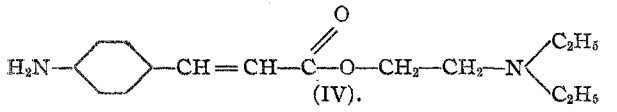
[1] This is the formula of the free base. Procaine (also called novocaine) is the monohydrochloride of this compound.

[2] Friedlaender, **8**, 995; *D. R. P.* 179,627.

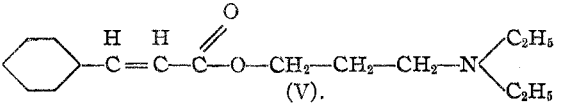
[3] *J. Chem. Soc.*, **111**, 167, 1119 (1917).

[4] For exceptions see Fourneau, *J. pharm. chim.*, [7] **2**, 337, 397 (1910).

compounds have been prepared[1] and found to possess anesthetic properties.

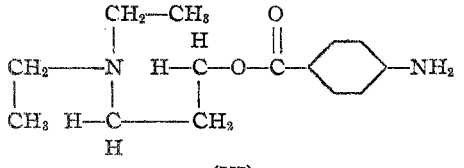


(IV).

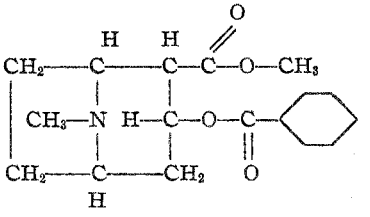


(V).

The writer has prepared a homolog of procaine possessing Structure VI. It will be noticed that this compound differs from procaine in the fact that it possesses a chain of 3 carbon atoms between the oxygen and nitrogen atoms. This variation in structure is important in the study of the relationship between chemical constitution and physiological action, because of the fact that the naturally occurring anesthetic, cocaine (VII), also possesses such a structure. The 2 formulas are here written so as to emphasize this relationship.



(VI).



(VII).

In physiological tests, cocaine, procaine, and the new compound (*p*-aminobenzoate of γ-diethylaminopropyl alcohol), have been tested side by side.

Aryl esters of γ-diethylaminopropyl alcohol have long been known. Thus the simplest aryl ester, the benzoyl derivative of the amino alcohol, was described by Gault[2] in 1908. The cinnamoyl derivative has already been referred to above (Formula V). For direct comparison with procaine it seemed advisable, however, to prepare the *p*-aminobenzoate. The method of preparation and the properties of the corresponding *m*-amino isomer are also given and a later report will deal with the study of the effects due to *ortho*-, *meta*-, and *para*-substitution.

Preparation of γ-Diethylaminopropyl Ester of *p*-Aminobenzoic Acid.

p-Nitrobenzoyl chloride (65 g.) is dissolved in 500 cc. of benzene and to this solution there is added gradually a benzene solution of 45 g. of γ-diethylaminopropyl alcohol. Reaction between the acid chloride and

[1] Friedlaender, **8**, 1007; *D. R. P.* 187,593. Wildman and Thorp, U. S. pat. 1,193,649, Aug. 8, 1916.

[2] *Bull. soc. chim.*, [4] 3, 376, (1908).

the alcohol takes place readily with the formation of a pasty cream-colored precipitate of the hydrochloride of γ-diethylaminopropyl ester of *p*-nitrobenzoic acid. In order to insure completion of the reaction, the mixture is warmed on the water bath for about one hour, after which the precipitate is filtered off. The weight of dry product is 105 g., which corresponds closely to that theoretically possible.

The hydrochloride of γ-diethylaminopropyl ester of *p*-nitrobenzoic acid is a cream-colored solid which after one recrystallization from alcohol, melts at 189–190°. The product is dissolved in water, an excess of tin is added, and the temperature controlled at about 40° by the gradual addition of hydrochloric acid. During the first stage of the reduction an oily product separates, possibly the free nitro ester, which redissolves as the reduction proceeds. After complete reduction, the solution is diluted and the tin removed by means of hydrogen sulfide. From the clear solution the γ-diethylaminopropyl ester of *p*-aminobenzoic acid is precipitated by the addition of sodium hydroxide solution and ice. The product is a white solid which, after recrystallization from petroleum ether, melts at 69°. The yield of product corresponded to 75% of that theoretically possible. The hydrochloride of γ-diethylaminopropyl ester of *p*-aminobenzoic acid crystallizes from absolute alcohol in white needles which melt at 164°.

Preparation of γ-Diethylaminopropyl Ester of *m*-Aminobenzoic Acid.

The γ-diethyl aminopropyl ester of *m*-aminobenzoic acid may be prepared in a manner exactly analogous with that described above for the *p*-amino compound, *m*-nitrobenzoyl chloride being used in place of *p*-nitrobenzoyl chloride. The intermediate product, the γ-diethyl aminopropyl ester of *m*-nitrobenzoic acid, is obtained in the form of a hydrochloride melting at 139–140°. Upon reduction, the latter yields the γ-diethylaminopropyl ester of *m*-aminobenzoic acid, a colorless oil which solidifies only at a low temperature. Its monohydrochloride is a white solid melting at 151°, which is very soluble in water, less soluble in alcohol, and only sparingly soluble in ether.

The Relationship Between Chemical Constitution and Physiological Action in the *p*-Aminobenzoates of β-Diethylaminoethyl and γ-Diethylaminopropyl Alcohols.

The results of physiological tests that will be published in detail elsewhere[1] show that the physiological action of the *p*-aminobenzoic ester of γ-diethylaminopropyl alcohol is exactly what one might predict from its slightly closer relationship to cocaine. Procaine, Formula I, contains the structure

$$—O—CH_2—CH_2—N<$$

[1] All such references will be included in later articles in this series.

whereas, as is indicated in Formula VII, cocaine possesses a chain of 3 carbon atoms between the *N* and *O* atoms in the amino alcohol. Cocaine is considerably more toxic than procaine but for certain types of anesthesia, such as surface anesthesia, it shows stronger action than procaine because of its greater powers of penetration.

The new homologue of procaine (Formula VI) which also possesses a chain of 3 carbon atoms between the *O* and the *N* atoms of the amino-alcohol, might, therefore, be predicted to fall somewhere between procaine and cocaine in its physiological behavior, although one would expect it to be considerably more closely related to the former compound. Tests show that these predictions are entirely substantiated. The new compound is slightly more toxic than procaine; on the other hand, its effectiveness for the production of surface anesthesia is considerably greater than that possessed by its lower homolog. For certain purposes, a given result may, therefore, be obtained with a considerably smaller quantity of anesthetic, increased effectiveness more than counterbalancing the effect of slightly increased toxicity.

The writer realizes the dangers of drawing broad generalizations upon observations gathered from the testing of a small number of individual compounds, although in the present example a prediction of physiological action of a new compound predicted by analogy to structures of previously known compounds has been completely substantiated. No attempt is made, therefore, to present broader generalizations or to indulge in further speculation until a larger amount of additional experimental data is available.

URBANA, ILLINOIS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF WISCONSIN AND OF VANDERBILT UNIVERSITY.]

THE PREPARATION OF *p*-PHENYLENEDIAMINE AND ANILINE FROM THEIR CORRESPONDING CHLOROBENZENES.[1]

BY ARMAND J. QUICK.

Received February 23, 1920.

The stability of the halogen atom attached to the benzene ring has been of considerable interest because it has prevented until recently, the direct synthesis of phenols and aromatic amino compounds from the halogen derivatives of the aromatic hydrocarbons. The early investigators[2] failed entirely in their efforts to replace the halogen by other groups. It was not until 1914 that Meyer and Bergious[3] reported that

[1] This paper represents a part of a thesis presented by A. J. Quick to the Graduate School of the University of Wisconsin in partial fulfilment of the requirements for the Degree of Master of Science, June, 1919.

[2] *Ann.*, 104, 225 (1857); 121, 358, 362 (1862).

[3] *Ber.*, 47, 3165 (1914).