the cut, resulted when crystallized from a mixture of ethyl alcohol and acetone.

Fruitless attempts were made to prepare fluosilicates of the following substances: (1) triphenylamine, (2) *o*-nitroaniline, (3) *p*-nitroaniline, (4) succinimide, (5) dimethyl-α-naphthylamine, (6) benzamide, (7) dimethyl-*p*-toluidine.

Benzidine fluosilicate has been prepared but will be described later.

MORGANTOWN, WEST VIRGINIA

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

LOCAL ANESTHETICS IN THE PYRROLE SERIES. II[1]

BY F. F. BLICKE AND E. S. BLAKE

RECEIVED OCTOBER 2, 1930 PUBLISHED MARCH 6, 1931

The structure of novocaine has been modified by a number of investigators in the hope that a better medicament might be obtained and also in order that more information might be acquired regarding the relationship between structure and local anesthetic action.[2] This has been accomplished by a variation in one or more of the three units A, B and C in the novocaine molecule (I).

(4) $\underset{\text{A}}{\underline{H_2N—C_6H_4—CO}}—O—\underset{\text{B}}{\underline{CH_2—CH_2}}—\underset{\text{C}}{\underline{N(C_2H_5)_2}}$

I

The primary object of our investigation was to determine, with regard to local anesthetic activity, the effect of a replacement of 4-aminobenzoyl by 2-pyrroyl and the result of a substitution of 1-pyrryl and 1-pyrrolidyl for the diethylamino group.[3] Thus in the analogs of novocaine which we obtained unit A is represented by benzoyl, 4-aminobenzoyl and 2-pyrroyl,

[1] This paper represents the second part of a dissertation submitted to the Graduate School by E. S. Blake in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan. The first part of the dissertation was published in THIS JOURNAL, **52**, 235 (1930).

This investigation was made possible by the grant of a fellowship by Frederick Stearns and Company and we wish to express our appreciation for the aid which has been given us.

[2] Fränkel, "Die Arzneimittel-synthese," J. Springer, Berlin, **1927**, p. 386–395; v. Braun and co-workers, *Ber.*, **52**, 2011 (1919); *ibid.*, **55**, 1666 (1922); McElvain and co-workers, THIS JOURNAL, **48**, 2179, 2239 (1926); *ibid.*, **49**, 2835 (1927); **51**, 887, 922 (1929); Barnes and Adams, *ibid.*, **49**, 1307 (1927); Marvel and co-workers, *ibid.*, **50**, 563 (1928); **51**, 915 (1929); Tréfuel, Tréfuel and Barbelet, *Bull. sci. pharmacol.*, **37**, 184, 240 (1930); *Chem. Abstracts*, **24**, 3502 (1930).

[3] Luft [*Ber.*, **38**, 4044 (1905)] has described the preparation of 4-(N-piperidyl)-antipyrine, while v. Braun and Lemke [*ibid.*, **55**, 3540, 3557 (1922)] prepared 4-(N-pyrrolidyl)- and 4-(N,Δ^3-pyrrolyl)-antipyrine. According to the latter investigators the pyrrolidyl is a stronger antipyretic than the piperidyl or the pyrrolyl derivative.

unit C by 1-pyrryl and 1-pyrrolidyl, respectively, and in some instances the trimethylene group has been substituted for B.

I	$C_6H_5COOCH_2CH_2NC_4H_4$	V	$C_6H_5COOCH_2CH_2CH_2NC_4H_4$
II	$H_2NC_6H_4COOCH_2CH_2NC_4H_4$	VI	$H_2NC_6H_4COOCH_2CH_2CH_2NC_4H_4$
III	$C_4H_4NCOOCH_2CH_2NC_4H_4$	VII	$C_4H_4NCOOCH_2CH_2CH_2NC_4H_4$
IV	$H_2NC_6H_4COOCH_2CH_2NC_4H_8$	VIII	$H_2NC_6H_4COOCH_2CH_2CH_2NC_4H_8$

The benzoyl (I), 4-aminobenzoyl (II) and the 2-pyrroyl (III) derivatives of β-(1-pyrryl)-ethyl alcohol, $C_4H_4NCH_2CH_2OH$, were prepared in the following manner. Potassium pyrrole was condensed with β-chloroethyl acetate with the formation of the acetyl derivative of β-(1-pyrryl)-ethyl alcohol. The latter was hydrolyzed, the alcohol converted into its potassium derivative and then allowed to react with benzoyl chloride. The 4-nitrobenzoyl and the 2-pyrroyl compounds were obtained by a similar series of reactions. Upon catalytic reduction of the 4-nitrobenzoic acid ester, $NO_2C_6H_4COOCH_2CH_2NC_4H_4$, the corresponding 4-amino derivative was formed.

4-Aminobenzoic acid was condensed with ethylene chlorohydrin with the formation of β-chloroethyl 4-aminobenzoate, $H_2NC_6H_4COOCH_2CH_2Cl$. The latter, when heated with pyrrolidine, yielded the 4-aminobenzoyl derivative of β-(1-pyrrolidyl)-ethyl alcohol (IV).

γ-(1-Pyrryl)-propyl alcohol was prepared in a manner similar to that described in the case of pyrrylethyl alcohol and the benzoyl (V), 4-aminobenzoyl (VI) and 2-pyrroyl (VII) derivatives were obtained by methods analogous to those outlined above.

γ-Chloropropyl 4-aminobenzoate, synthesized from 4-aminobenzoic acid and trimethylene chlorohydrin, was condensed with pyrrolidine to form the 4-aminobenzoyl derivative of γ-(1-pyrrolidyl)-propyl alcohol (VIII).

Stovaine (IX) is obtained by benzoylation of methylethyldimethylaminomethylcarbinol. Pyrroylation of this carbinol yielded compound XI. In order to determine the effect of the substitution of a saturated

IX	$(CH_3)(C_2H_5)[(CH_3)_2NCH_2]COCOC_6H_5$	XII	$(CH_3)(CH_3)(C_4H_4NCH_2)COH$
X	$(CH_3)(C_2H_5)(C_4H_8NCH_2)COCOC_6H_5$	XIII	$(C_2H_5)(C_2H_5)(C_4H_4NCH_2)COH$
XI	$(CH_3)(C_2H_5)[(CH_3)_2NCH_2]COCOC_4H_4N$	XIV	$(C_2H_5)(C_2H_5)(C_4H_4NCH_2CH_2)COH$

cyclic amine for the dimethylamino group, compound X was prepared by the interaction of methylethylchloromethylcarbinol with pyrrolidine and subsequent benzoylation of the reaction product.

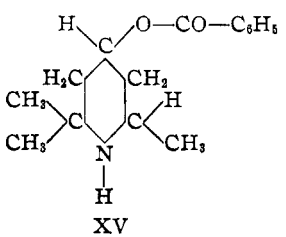
We also synthesized the three tertiary carbinols dimethyl-1-pyrrylmethylcarbinol (XII), diethyl-1-pyrrylmethylcarbinol (XIII) and diethyl β-(1-pyrryl)-ethylcarbinol (XIV). It was hoped that these compounds might be benzoylated and pyrroylated through reaction of the potassium derivatives of the carbinols with benzoyl and pyrroyl chloride, respectively, especially since it was found that stovaine can be obtained from the po-

tassium derivative of methylethyldimethylaminomethylcarbinol and benzoyl chloride. Direct interaction of the carbinols with the acid chlorides yielded only gums or resins since the hydrogen chloride formed during the reaction attacked the pyrrole nucleus. However, the products obtained from the potassium derivatives of the carbinols were oils which we were unable to purify. Although it was realized that the material may have contained a small quantity of unchanged benzoyl chloride, the benzoylation product of carbinol XIII was hydrolyzed and the benzoic acid produced was weighed. The calculated amount of acid was 1.22 g.; the quantity found was 1.18 g. In the event that the compound hydrolyzed was the benzoyl derivative of the carbinol, it seems strange that the material should have been found to be devoid of anesthetic action.

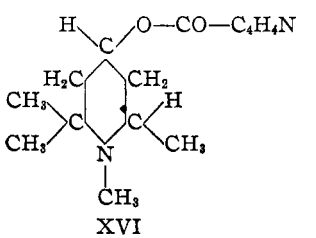
Carbinol XII was obtained by the action of potassium pyrrole on ethyl chloroacetate and subsequent treatment of the ethyl 1-pyrrylacetate with methylmagnesium iodide. When ethylmagnesium bromide was used diethyl-(1-pyrryl)-methylcarbinol (XIII) was formed.

By a similar series of reactions—interaction of potassium pyrrole with ethyl β-bromopropionate and treatment of the ethyl β-(1-pyrryl)-propionate formed with ethylmagnesium bromide—diethyl-(1-pyrryl)-ethylcarbinol (XIV) was synthesized.

In the case of β-eucaine (XV), the benzoyl derivative of the stable form of 2,2,6-trimethyl-4-hydroxypiperidine (vinyldiacetone alkamine), the molecule was modified by the substitution of a 2-pyrroyl for the benzoyl group and the replacement of the 1-hydrogen of the piperidine nucleus by a methyl group (XVI). The latter group was introduced merely in order to facilitate one stage of the synthesis.



XV



XVI

We prepared, in addition, the 4-(2-pyrroyl)-1-methyl derivative of the labile form of 2,2,6-trimethyl-4-hydroxypiperidine. The stable and labile forms of the secondary carbinol were obtained as follows. Diacetone alcohol was converted into mesityl oxide and from the latter diacetoneamine hydrogen oxalate was prepared. Reduction of the oxalate yielded a mixture of the two stereoisomeric forms of vinyldiacetone alkamine. The isomers were separated and methylated. Upon interaction of the potassium derivatives of the alcohols with 2-pyrroyl chloride the desired esters were formed.

In the novocaine series compounds I and V seemed to be inert while the other derivatives produced a distinct local anesthetic effect. The compounds were tested by the application of a concentrated alcoholic solution to the tongue and the inner side of the lips. Because of the burning and drying effect of alcohol on the mucous membrane, it is obvious that the use of this solvent is objectionable. However, in spite of these features of the alcohol the local anesthetic action produced by the compounds tested was unmistakable. The undesirable action of the alcohol is mitigated to a considerable degree by the addition of water but, unfortunately, the products tested although very soluble in alcohol are precipitated upon the addition of any appreciable quantity of water to the alcoholic solution.

Aqueous solutions of the hydrochlorides of compounds IV and VIII produced no anesthetic effect, a behavior which would be expected since novocaine (hydrochloride) is without action on the tongue but novocaine base, in alcohol, exhibits a very decided anesthesia.

Compounds X and XI, stovaine analogs, were active both as base and hydrochloride, a behavior which is consistent with that of stovaine (hydrochloride) since the latter anesthetizes the tongue.

The base of the 4-(2-pyrroyl)-1-methyl derivative of the stable form of 2,2,6-trimethyl-4-hydroxypiperidine was found to be active; the corresponding derivative of the labile form inactive.

Our investigation has shown that, in certain types of compounds at least, the following substitutions may be made in local anesthetics without loss, in a qualitative sense, of anesthetic activity—the substitution of 2-pyrroyl for benzoyl and 4-aminobenzoyl and the replacement of the dimethyl- and diethylamino by the 1-pyrryl or the 1-pyrrolidyl nucleus.

Experimental Part

β-Chloroethyl Acetate and γ-Chloropropyl Acetate.—Four hundred grams of ethylene chlorohydrin was placed in a flask fitted with a reflux condenser and a dropping funnel. The latter contained 450 g. of technical acetyl chloride which was allowed to drop into the chlorohydrin at a very slow rate. During this operation the flask was cooled with ice water and was shaken occasionally. The mixture was then heated for two hours on a steam-bath, cooled and poured into a small quantity of ice water. After the excess acetyl chloride had hydrolyzed, the oil was separated and washed with a concd. solution of sodium bicarbonate until free from hydrochloric acid. The oil was then dried with fused sodium sulfate and distilled through a fractionation column. There was obtained 500 g. of the ester which boiled at 142–145°. The yield was 82% of the calculated amount.

γ-Chloropropyl acetate was prepared from trimethylene chlorohydrin[4] and acetyl chloride in the manner described above. The ester boiled at 168–173°.[5]

[4] "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 112.

[5] Derick and Bissel [THIS JOURNAL, 38, 2483 (1916)] reported the boiling point to be 160–166°.

β-(1-Pyrryl)-ethyl Alcohol.—Potassium pyrrole was prepared by the addition of 80 g. of potassium to 300 cc. of warm pyrrole in a flask fitted with a reflux condenser. After the potassium had reacted completely, absolute ether was added to the clear solution in order to precipitate the potassium compound in the form of fine crystals. Unless ether is added the potassium pyrrole separates from the cold mixture in the form of a hard cake. The potassium derivative was filtered and washed with absolute ether. The excess pyrrole can be recovered readily from the filtrate by fractionation.

One hundred and fifteen grams of potassium pyrrole was placed in a flask fitted with a reflux condenser and 100 g. of β-chloroethyl acetate was added in small portions. The mixture was cooled thoroughly during this process. The pasty reaction mixture was heated in an oil-bath to 70° for several hours, then cooled and, after the addition of absolute ether, filtered. The ether was removed from the filtrate on a steam-bath and the residue distilled under diminished pressure. After the material had been fractionated twice there was obtained 28 g. of the acetyl derivative of β-(1-pyrryl)-ethyl alcohol which boiled at 222–225° under 740 mm. pressure. This substance seemed to possess a very slight local anesthetic action. In order to hydrolyze the ester 55 g. of the latter was heated on a steam-bath for several hours with a mixture which consisted of 40 g. of potassium hydroxide, 30 cc. of water and 50 cc. of alcohol. The alcohol and water were removed under diminished pressure and the semi-solid residue was treated with a small quantity of water. The oil which separated was extracted with ether and the ether solution dried with fused sodium sulfate. Upon fractionation 42 g. of β-(1-pyrryl)-ethyl alcohol was obtained which boiled at 110–113° under 12 mm. pressure.

Benzoyl Derivative (I).—Thirteen and two-tenths grams of β-(1-pyrryl)-ethyl alcohol, dissolved in 150 cc. of dry benzene, was heated with 4.8 g. of potassium until all of the metal had disappeared. Sixteen and eight-tenths grams of benzoyl chloride, dissolved in 100 cc. of absolute ether, was then added. A precipitate of potassium chloride formed immediately. After the mixture had been heated at 70° for several hours it was filtered from potassium chloride and the ether and benzene removed under diminished pressure. The residue, after it had been cooled, consisted of crystals contaminated by a small amount of oil. The mixture was placed on a porous plate and after some time the crystalline material was recrystallized from petroleum ether (90–120°). The yield of pure material was 20 g. or 78% of the calculated amount; m. p. 53–55°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.52; H, 6.09; N, 6.51. Found: C, 72.36; H, 6.19; N, 6.56.

4-Aminobenzoyl Derivative (II).—We prepared, first, the β-(-pyrryl)-ethyl ester of 4-nitrobenzoic acid in the following manner. Three and three-tenths grams of β-(1-pyrryl)-ethyl alcohol, dissolved in 50 cc. of dry benzene, was heated with 1.2 g. of potassium. After the metal had reacted the mixture was cooled with ice and 5.5 g. of pure 4-nitrobenzoyl chloride,[6] dissolved in 50 cc. of absolute ether, was added in small portions. The reaction mixture became intensely red but the color disappeared after all of the nitrobenzoyl chloride had been added. The mixture was heated to 60° in a bath for one hour and then filtered. The residue was washed with absolute ether and the ether added to the filtrate. After the solvents had been removed under diminished pressure, a dark brown oil was obtained which became solid when it was cooled. The material was pulverized, dissolved in ether and dark colored impurities precipitated by the addition of petroleum ether (20–40°). The solvents were then allowed to evaporate. After recrystallization from alcohol, 5 g. of slightly yellow, crystalline material was obtained which melted at 92–94°.

[6] "Organic Syntheses," John Wiley and Sons, Inc., New York, **1923**, Vol. III, p. 75.

In order to obtain the amino compound, 5.2 g. of the nitro derivative, dissolved in 190 cc. of absolute alcohol, was reduced with hydrogen in the presence of 0.3 g. of platinum oxide catalyst[7] under an initial pressure of four atmospheres. The calculated amount of hydrogen was absorbed in twenty-five minutes. After filtration the solvent was removed under diminished pressure and the solid residue recrystallized from a mixture of petroleum ether (90–120°) and benzene; m. p. 87–88°.

Anal. Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.78; H, 6.13; N, 12.17. Found: C, 67.71; H, 6.02; N, 12.25.

2-Pyrroyl Derivative (III).—In order to prepare the potassium derivative of β-(1-pyrryl)-ethyl alcohol, 6.6 g. of the alcohol, 2.4 g. of potassium and 100 cc. of dry benzene were heated to 90° in an oil-bath. Seven and seven-tenths grams of 2-pyrroyl chloride, dissolved in 100 cc. of absolute ether, was added and the mixture heated for several hours. The potassium chloride was removed by filtration and the filtrate heated under diminished pressure in order to remove the solvents. The residue was dissolved in absolute ether and low-boiling petroleum ether added to precipitate dark colored impurities. After evaporation of the solvents the colorless, crystalline material was recrystallized from a mixture of benzene and petroleum ether; m. p. 73–74°.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.67; H, 5.87; N, 13.72. Found: C, 64.72; H, 5.93; N, 13.67.

β-(1-Pyrrolidyl)-ethyl 4-Aminobenzoate (IV).[8]—Five grams of pure β-chloroethyl 4-aminobenzoate, which had been prepared from 4-aminobenzoic acid, ethylene chlorohydrin and sulfuric acid,[9] was heated in a sealed tube with 6 cc. of pyrrolidine for eight hours in a bath at 115–120°. The reaction mixture was treated with water to remove pyrrolidine hydrochloride and excess pyrrolidine and the solid material was dried and recrystallized from a mixture of benzene and petroleum ether; m. p. 98–100°.

Anal. Calcd. for $C_{15}H_{18}O_2N_2$: C, 66.62; H, 7.74; N, 11.98. Found: C, 66.67; H, 7.84; N, 12.09.

γ-(1-Pyrryl)-propyl Alcohol.—This compound was prepared in a manner similar to that described in the case of the ethyl homolog. From potassium pyrrole and γ-chloropropyl acetate the acetyl derivative of γ-(1-pyrryl)-propyl alcohol was obtained. The latter boiled at 127–135° under 13 mm. pressure and 93 g. of the material was obtained from two moles of potassium pyrrole. From 258 g. of the acetate we obtained, by hydrolysis, 150 g. of the pure alcohol. The latter boiled at 229–231° under 743 mm. pressure.

Benzoyl Derivative (V).—The material obtained from the interaction of the potassium derivative of the above alcohol and benzoyl chloride boiled at 120–170° under 5 mm. pressure and was evidently a mixture of compounds. One and eighteen-hundredths grams of the oil which boiled at 165–170° under 5 mm. pressure was hydrolyzed with alcoholic potassium hydroxide. There was obtained 0.64 g. of benzoic acid; the calculated amount of acid based on formula V is 0.61 g.

4-Aminobenzoyl Derivative (VI).—We prepared first the 4-nitrobenzoyl derivative from 7.5 g. of γ-(1-pyrryl)-propyl alcohol, 2.4 g. of potassium and 11.1 g. of 4-nitrobenzoyl chloride. The crude, solid reaction product was dissolved in alcohol and aque-

[7] "Organic Syntheses," 1928, Vol. VIII, p. 92.

[8] β-(1-Piperidyl)-ethyl 4-aminobenzoate has been described by Einhorn and Uhlfelder, *Ann.*, **371**, 140 (1909), and β-(1-piperidyl)-ethyl benzoate by Laun, *Ber.*, **17**, 680 (1884). β-(1-Pyrrolidyl)-ethyl benzoate has been obtained by v. Braun, Braunsdorf and Räth, *ibid.*, **55**, 1673 (1922).

[9] German patent 194,748.

ous sodium carbonate was added. The precipitate was removed by filtration, dried and recrystallized from alcohol; m. p. 68–70°. The yield of pure material was 5 g.

Twenty-one and five-tenths grams of the nitro compound, 250 cc. of absolute alcohol and 0.3 g. of platinum oxide catalyst were treated with hydrogen under an initial pressure of four and one-half atmospheres. The reduction required twenty minutes. The catalyst was removed and the amino compound was precipitated in crystalline form by the addition of water. After recrystallization from a mixture of benzene and petroleum ether, the compound melted at 114–116°. The yield was 17 g.; the calculated yield is 19 g.

Anal. Calcd. for $C_{14}H_{16}O_2N_2$: C, 68.81; H, 6.65; N, 11.47. Found: C, 68.74; H, 6.65; N, 11.71.

2-Pyrroyl Derivative (VII).—The potassium derivative of γ-(1-pyrryl)-propyl alcohol, obtained from 6.2 g. of the alcohol, 2 g. of potassium and 75 cc. of dry benzene, was heated for three hours with 6.4 g. of 2-pyrroyl chloride,[10] dissolved in 100 cc. of absolute ether. The potassium chloride was removed by filtration and the solvents distilled under reduced pressure. The residue was dissolved in alcohol and the pyrrole derivative precipitated by the addition of aqueous sodium carbonate. After recrystallization from a mixture of benzene and petroleum ether the product melted at 69–70°. The yield was 5 g.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.01; H, 6.46; N, 12.84. Found: C, 66.00; H, 6.48; N, 12.77.

γ-(1-Pyrrolidyl)-propyl 4-Aminobenzoate (VIII).[11]—γ-Chloropropyl 4-aminobenzoate was prepared as follows. Seventy grams of trimethylene chlorohydrin, 103 g. of 4-aminobenzoic acid and 400 g. of sulfuric acid were heated for twelve hours on a steam-bath. The mixture was treated with ice and then with sodium carbonate solution. The crude product was recrystallized from alcohol a number of times and finally from a mixture of benzene and petroleum ether; m. p. 86–87°.

γ-(1-Pyrrolidyl)-propyl 4-aminobenzoate was obtained from γ-chloropropyl 4-aminobenzoate and pyrrolidine in the same manner as compound IV. The compound melted at 84–85° after recrystallization from a mixture of benzene and petroleum ether.

Anal. Calcd. for $C_{14}H_{20}O_2N_2$: C, 67.69; H, 8.12; N, 11.29. Found: C, 67.54; H, 8.20; N, 11.80.

Benzoyl Derivative of Methylethyldimethylaminomethylcarbinol (Stovaine, IX).—Although stovaine is prepared usually by the interaction of the tertiary carbinol and benzoyl chloride[12] we found that it can be obtained in the following manner, a procedure which we used in the case of certain pyrrole derivatives in order to avoid the formation of hydrogen chloride. Three and nine-tenths grams of methylethyldimethylaminomethylcarbinol, dissolved in 50 cc. of dry benzene, was refluxed with 1.2 g. of potassium until the metal had reacted completely. Four and two-tenths grams of benzoyl chloride was then added and the mixture heated to 60–70° for one hour. The potassium chloride was removed by filtration and the filtrate treated with hydrogen chloride. The stovaine hydrochloride, after recrystallization from absolute alcohol, melted at 172–174°. The yield was 5 g.; calcd. yield, 8 g.

---

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

[11] Andrews and McElvain [THIS JOURNAL, **51**, 890 (1929)] synthesized γ-(1-pyrrolidyl)-propyl benzoate and γ-(1-piperidyl)-propyl benzoate has been prepared by Dunlop [*J. Chem. Soc.*, **101**, 2002 (1912)].

[12] Fourneau, "Organic Medicaments," P. Blakiston's Son and Co., Philadelphia, **1925**, p. 218.

Benzoyl Derivative of Methylethyl-(1-pyrrolidyl)-methylcarbinol (X).—Twelve grams of methylethylchloromethylcarbinol[13] and 20 cc. of pyrrolidine were heated in a sealed tube to 115–120° for eight hours. Upon the addition of water to the reaction mixture an oil separated. Since the latter would not solidify when cooled the mixture was made slightly acidic with hydrochloric acid, extracted with ether to remove acid-insoluble material and the aqueous, acid layer was made alkaline with sodium hydroxide. It was then subjected to steam distillation until most of the pyrrolidine had been removed.[14] The contents of the steam distillation flask were shaken with ether a number of times, the ether layer separated and dried with fused sodium sulfate. After removal of the solvent the tertiary carbinol remained in the form of an oil. The latter was benzoylated in the following manner. Five and seven-tenths grams of the carbinol, 7.1 g. of benzoyl chloride and 25 cc. of dry benzene were heated for three hours on a steam-bath. The mixture was cooled with ice, whereupon the solid, crystalline hydrochloride of the benzoylated carbinol separated. The hydrochloride was found to be very soluble in ethyl acetate and absolute alcohol. The material was recrystallized from the latter solvent but because of the hygroscopic nature of the compound it was converted into the oily base for analysis. The latter was dried for four hours at 65° under 20 mm. pressure.

Anal. Calcd. for $C_{16}H_{23}O_2N$: N, 5.36. Found: N, 5.61.

2-Pyrroyl Derivative of Methylethyldimethylaminomethylcarbinol (XI).—Five and two-tenths grams of methylethyldimethylaminomethylcarbinol[15] was dissolved in 75 cc. of absolute ether. The solution was then added, dropwise, to 5.2 g. of 2-pyrroyl chloride, dissolved in 75 cc. of absolute ether. A black, gummy precipitate formed immediately upon the addition of a small quantity of the carbinol. The solution was decanted from this material and upon the addition of more carbinol a colorless, gummy compound precipitated which after some time became partly crystalline. The material was dissolved in a small amount of hot, absolute alcohol and the solution cooled. The hydrochloride separated in crystalline form upon the addition of absolute ether. After recrystallization from absolute alcohol it melted at 194–195°.

Anal. Calcd. for $C_{12}H_{21}O_2N_2Cl$: N, 10.75; Cl, 13.60. Found: N, 10.83; Cl, 13.55.

Dimethyl-1-pyrrylmethylcarbinol (XII).—Ethyl chloroacetate was prepared from chloroacetyl chloride and absolute alcohol. One mole of potassium pyrrole was covered with absolute ether and heated with 100 g. of ethyl chloroacetate for one hour on a steam-bath. The potassium chloride was removed and the crude ethyl 1-pyrrylacetate, $C_4H_4NCH_2COOC_2H_5$, distilled. It boiled at 110–115° under 16 mm. pressure. The yield was 26 g.

A portion of the ester was warmed for several hours with aqueous sodium hydroxide. The clear, alkaline solution was boiled with charcoal, filtered, the filtrate acidified and then extracted with ether. After evaporation of the solvent the crystalline 1-pyrryl-acetic acid was recrystallized from a mixture of benzene and low boiling petroleum ether; m. p. 94–95°.

Methylmagnesium iodide was prepared from 56.4 g. of methyl iodide, 9.6 g. of magnesium and 100 cc. of ether. Twenty-three grams of the above ester was added, drop by drop, to the Grignard reagent and the mixture heated for one hour on a steam-bath. The reaction mixture was decomposed with ice and ammonium chloride and the tertiary carbinol purified by distillation; b. p. 86–88° under 2–3 mm. pressure. The yield was 18 g.

[13] Ref. 12, p. 214.

[14] After most of the pyrrolidine had distilled a colorless oil began to collect in the receiver. We did not determine whether this oil was the tertiary carbinol or some by-product of the reaction.

[15] Ref. 12, p. 215.

The carbinol was converted into its potassium derivative in the presence of benzene and then treated with the calculated amount of benzoyl chloride and 2-pyrroyl chloride, respectively. The products in both instances were oils.

Diethyl-1-pyrrylmethylcarbinol (XIII).—Forty-five grams of ethyl 1-pyrrylacetate was added to the Grignard reagent obtained from one mole of magnesium and one mole of ethyl bromide. After the mixture had been heated for several hours on a steam-bath, it was decomposed in the usual manner. The tertiary carbinol was purified by distillation; b. p. 108–110° under approximately 1 mm. pressure (bath temperature 125–130°). The yield was 38 g.

Anal. Calcd. for $C_{10}H_{17}ON$: N, 8.37. Found: N, 8.28.

In the case of this carbinol, as well as the following one, the material obtained from the interaction of the potassium derivative and benzoyl chloride was a liquid.

Diethyl-1-pyrrylethylcarbinol (XIV).—One hundred and eighty-one grams of ethyl β-bromopropionate[16] was added, drop by drop, to 126 g. of potassium pyrrole which was cooled with ice. After all of the ester had been added the mixture was heated to 140° for one hour. The potassium chloride was removed and the ethyl β-(1-pyrryl)-propionate distilled; b. p. 119–122° under 14 mm. pressure. The yield was 31 g.

A portion of the ester was hydrolyzed with aqueous sodium hydroxide. The alkaline solution was then boiled with charcoal, filtered and the filtrate concentrated. When the alkaline solution was acidified and cooled the β-(1-pyrryl)-propionic acid precipitated in the form of colorless crystals. The compound is very soluble in hot water. After recrystallization from a mixture of benzene and low-boiling petroleum ether the acid melted at 62–64°. The compound possesses a repulsive odor somewhat similar to that of butyric acid.

The tertiary carbinol was prepared from ethyl β-(1-pyrryl)-propionate and ethylmagnesium bromide. It boiled at 125–128° under 4–5 mm. pressure (bath temperature 135–140°).

Anal. Calcd. for $C_{11}H_{19}ON$: N, 7.73. Found: N, 7.88.

4-(2-Pyrroyl) 1-Methyl Derivative of the Stable and Labile Form of 2,2,6-Trimethyl-4-hydroxypiperidine (XVI).—In order to obtain these compounds it was necessary to prepare first vinyldiacetone alkamine. The latter was separated into the stable and labile modifications and these were then pyrroylated in the form of their 1-methyl derivatives.

Diacetone alcohol[17] was converted into mesityl oxide[18] and from the latter diacetoneamine hydrogen oxalate[19] was prepared. We found it unnecessary to convert the oxalate into the free amine[20] in order to reduce it to vinyldiacetone alkamine,[21] since the salt reduces in a satisfactory manner. From 50 g. of the hydrogen oxalate there was obtained 30 g. of the alkamine after the latter had been recrystallized from benzene. The separation of the alkamine into its two isomeric forms was effected by the method of Harries[22] and the latter were then methylated according to the directions given by this investigator.[23]

[16] Ref. 6, p. 51.

[17] "Organic Syntheses," John Wiley and Sons, Inc., New York, 1921, Vol. I, p. 45.

[18] Ref. 17, p. 53.

[19] "Organic Syntheses," Vol. VI, p. 28.

[20] E. Fischer, *Ber.*, **17**, 1793 (1884).

[21] E. Fischer, *ibid.*, **17**, 1794 (1884).

[22] Harries, *Ann.*, **294**, 372 (1897).

[23] Harries, *ibid.*, **417**, 178 (1918). Conversion of the mixture of the two stereoisomers into the labile form of the alkamine by means of sodium amylate in amyl alcohol is described on p. 274 of this reference. However, the amount of amyl alcohol (40 cc.) employed by Harries seems too small and we were obliged to use 100 cc. of the solvent.

The potassium derivative of the stable form of 1-methylvinyldiacetone alkamine was prepared in the following manner. Seven and eighty-five hundredths grams of the stable 1-methyl alkamine, dissolved in 50 cc. of dry xylene, was treated with 1.95 g. of potassium and the mixture refluxed for five hours. The mass should be stirred during this time to prevent the formation of a hard cake. Seven and seventy-four hundredths grams of 2-pyrroyl chloride, dissolved in 125 cc. of absolute ether, was added dropwise to the hot suspension of the potassium derivative. During this process the mixture was shaken constantly. The material was heated for ten minutes, cooled, filtered, the filtrate cooled with ice and treated with hydrogen chloride. The precipitated hydrochloride was found to be very hygroscopic, at least in the crude state. It was separated, dissolved in water and the compound precipitated as the base by the addition of ammonium hydroxide. The oily base was extracted with ether, the ether solution dried with fused sodium sulfate and the solvent removed. When the oily residue was cooled with ice and rubbed under low-boiling petroleum ether it became solid. The yield of crude product was 9 g. After recrystallization from petroleum ether the compound melted at 106–107°.

Anal. Calcd. for $C_{14}H_{22}O_2N_2$: C, 67.14; H, 8.86. Found: C, 67.14; H, 8.87.

When the base was dissolved in absolute ether and a saturated ether solution of picric acid added a yellow picrate precipitated. After recrystallization from dilute alcohol the latter melted at 192–193°.

Seven and eighty-five hundredths grams of the labile form of 1-methylvinyldiacetone alkamine was converted into the potassium derivative and pyrroylated in the manner described above. There was obtained 7 g. of the crude pyrroyl derivative. After recrystallization from petroleum ether it melted at 106–107°. Since this melting point was identical with that found in the case of the pyrroyl derivative of the stable form of 1-methylvinyldiacetone alkamine, a mixed melting point of the two compounds was determined; this was found to be 80–83°.

Anal. Calcd. for $C_{14}H_{22}O_2N_2$: C, 67.14; H, 8.86. Found: C, 67.19; H, 8.89.

Notes on the Preparation of Pyrrolidine.—This compound was prepared from adipic acid[24] according to a series of reactions described by Müller and Sauerwald[25] and by v. Braun and Lemke.[24] The methods described below were found by us to be satisfactory for the preparation of certain intermediates. Adipamide can be obtained conveniently by the following procedure. Adipic acid was treated with the amount of sodium carbonate solution required for the formation of the disodium salt and the solution evaporated to dryness. Thirty-seven grams of the oven-dried salt was placed in a round-bottomed flask, fitted with a reflux condenser, mixed thoroughly with 28 g. of pure phosphorus oxychloride and heated for five hours in an oil-bath to 50–55°. Because of the tendency of the mixture to form a hard cake, the yield of acid chloride would, undoubtedly, have been increased if the mixture had been stirred. The acid chloride was not isolated but was converted into the acid amide by the addition of the reaction mixture, in small amounts, to ten times the calculated quantity of a technical grade of ammonia water. The yield of the crude amide, based on adipic acid, was 70% of the calculated amount.

The following method for the preparation of 4-toluenesulfonamide is devoid of danger and more convenient than that described in the literature[26] since the use of a pressure bottle is avoided. Six to ten times the calculated amount of technical ammonium

[24] "Organic Syntheses," John Wiley and Sons, Inc., New York, **1925**, Vol. V, p. 9; v. Braun and Lemke, *Ber.*, **55**, 3529 (1922).

[25] Müller and Sauerwald, *Monatsh.*, **48**, 157 (1927).

[26] Inglis, *J. Soc. Chem. Ind.*, **37**, 289T (1918).

hydroxide was poured into a large beaker, heated almost to the boiling point and stirred vigorously with a mechanical stirrer. 4-Toluenesulfonechloride was then added in small portions. A vigorous reaction ensued with each addition of the chloride. After all of the material had been added the clear solution was cooled, whereupon the amide precipitated. The latter was separated, dissolved in boiling water and treated with charcoal. After filtration the sulfonamide separated from the cold, concentrated solution in the form of colorless crystals.

Summary

Eight analogs of novocaine and several compounds analogous to stovaine and β-eucaine have been prepared and tested for local anesthetic action by application to the tip of the tongue. It was found, at least as far as the compounds discussed in this paper are concerned, that the local anesthetic action of a compound can be retained by the substitution of 2-pyrroyl for the benzoyl and the 4-aminobenzoyl group and by the replacement of dimethyl- and diethylamino by the 1-pyrryl and 1-pyrrolidyl nuclei.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

DISTIBYLS. I. TETRAPHENYLDISTIBYL. ATTEMPTS TO OBTAIN TETRAPHENYLDIBISMUTHYL[1]

BY F. F. BLICKE, U. O. OAKDALE AND F. D. SMITH

RECEIVED OCTOBER 2, 1930 PUBLISHED MARCH 6, 1931

We began our present study in the hope that we might obtain tetraphenyldistibyl, $(C_6H_5)_2Sb–Sb(C_6H_5)_2$, and tetraphenyldibismuthyl, $(C_6H_5)_2Bi–Bi(C_6H_5)_2$, compounds analogous to the diarsyls[2] which have been investigated recently in this Laboratory. It was found that the first mentioned compound could be prepared from the interaction of diphenylstibyl iodide and sodium hypophosphite.[3]

Tetraphenyldistibyl, in solution, proved to be extremely reactive toward oxygen and the gas was absorbed with the same rapidity which is so characteristic of a solution of a tetra-aryldiarsyl or a triarylmethyl; hence the preparation of the distibyl was carried out in a free radical apparatus and the product isolated in an atmosphere of nitrogen or carbon dioxide.

[1] This paper represents the first part of a dissertation to be submitted to the Graduate School by U. O. Oakdale in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

This investigation was made possible by the aid of the Parke, Davis and Company Fellowship and by a grant from the Faculty Research Fund of the University of Michigan.

[2] Blicke and Smith, THIS JOURNAL, **51**, 2272 (1929); Blicke, Weinkauff and Hargreaves, *ibid.*, **52**, 780 (1930); Blicke and Smith, *ibid.*, **52**, 2937 (1930).

[3] Schmidt [*Ann.*, **421**, 235 (1920)] stated that tetraphenylstibyl oxide, $(C_6H_5)_2Sb-O-Sb(C_6H_5)_2$, when treated with hypophosphorous acid, yields a yellow compound which he thought might be tetraphenyldistibyl. However, no analysis or further description of the material was recorded.