(93) Taimni, I. K., "The reaction between thallic chloride and potassium thiocyanate," *J. chem. soc.*, 130, 2433–2435 (1931).

(94) Tananaev, N. A., "Detection of cæsium, rubidium and thallium by spot tests," *Z. anal. chem.*, 88, 343–347 (1932); *C. A.*, 26, 4271 (1932).

(95) Tanatar, S., and Petrov, S., "A new reagent for thallium," *J. Russ. Phys. Chem. Soc.*, 42, 94–95 (1910); *C. A.*, 4, 1036 (1910).

(96) Thomas, V., "Researches on thallium," *Ann. chim. phys.*, 11, 204–262 (1908).

(97) Thomas, V., "Chimie Minerale. Dosage du Thallium," *Compt. rend. acad. sci.*, 130, 1316–1319 (1900).

(98) Thomas, V., "Dosage volumetrique du thallium," *Compt. rend. acad. sci.*, 134, 655–660 (1902).

(99) Timm, *Deut. ger. med.*, 18, 73 (1932); through Reference No. 41.

(100) Troitzkii, M. V., "Argentometric determination of thallium," *J. Gen. Chem.* (U. S. S. R.), 1, 1083–1085 (1931); *C. A.*, 26, 4008 (1932).

(101) Troitzkii, M. V., "Determination of thallium with hypoiodite," *J. Gen. Chem.* (U. S. S. R.), 1, 1086–1088 (1931); *C. A.*, 26, 4008 (1932).

(102) Werther, "Thallium—quantitative analysis," *Zeit. anal. chem.*, 3, 2 (1864); 4, 113 (1865); PROC. A. PH. A., 13, 121 (1865).

(103) Willard, H. H., and Young, P., "Ceric sulphate as a volumetric oxidizing agent. X. The determination of thallium," *J. am. chem. soc.*, 52, 36–42 (1930).

(104) Willm, *Bull. soc. chim.* (Paris), 5, 352 (1863).

(105) Willm, *Ann. chim. phys.*, 5, 63 (1865).

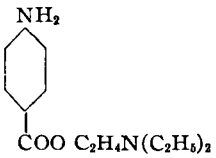
(106) Zintl, E., and Rienäcker, G., "Titrimetric determination of thallium," *Z. anorg. allgem. chem.*, 153, 276–280 (1926); *C. A.*, 20, 2631 (1926).

LOCAL ANESTHETICS—PHENYL PROCAINE.*

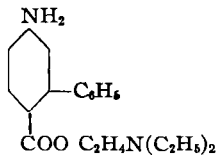
BY W. BRAKER AND W. G. CHRISTIANSEN.[1]

This investigation concerns the study of phenyl derivatives of procaine (I) and its analogues. The study was initiated by the comparatively greater activity and lesser toxicity of *o*-phenyl phenol over phenol. The substitution of a phenyl group on the benzene nucleus of procaine would yield, it was expected, a substance of greater potency and lesser toxicity than the parent substance. A summary of the biological activity of the various substances prepared is contained below.

The initial substance synthesized was phenyl procaine (II). The details of the preparation of (II) are stated in the experimental section. Essentially, the



(I)



(II)

synthesis employed was the preparation of 2-carboxy 5-amino diphenyl and the subsequent reaction of its sodium salt with β-diethylamino ethyl chloride. Phenyl procaine is an active anesthetic but due to such factors as precipitation upon the addi-

* Section on Practical Pharmacy and Dispensing, Madison meeting, 1933.

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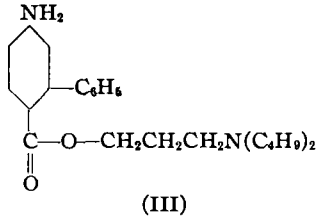
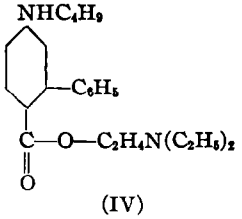
tion of buffers and irritation in corneal and intradermal tests, the compound does not appear to be of value.

Analogues of phenyl procaine were synthesized for the purpose of

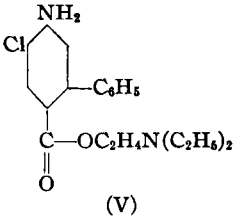
(1) Determining the effect of increasing the size of the dialkylamino alkyl group (III).
(2) Ascertaining the effect of alkylating the amino group (IV).
(3) Investigating the effect of halogenation, as depicted by (V).
(4) Observing the effect of the elimination of the amino group (VI).



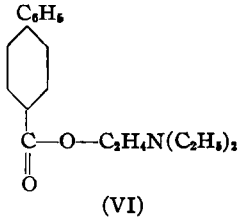
(III)



(IV)



(V)

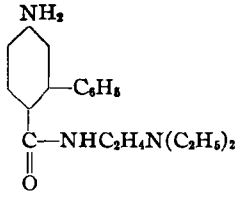


(VI)

The hydrochlorides of the above compounds were either too acid for testing (IV and VI) or too inactive (III and V) to warrant any further investigation.

A compound containing a β-diethylamino ethyl carbamido group (VII) which is present in percaine was also prepared but was comparatively inactive.

The effect of shifting the amino group from the 5- to the 4′-position was also studied. However, an aqueous solution of the hydrochloride of this substance (VIII) was comparatively inactive.



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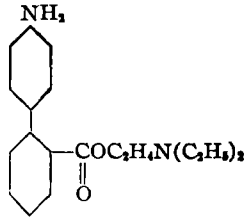

(VIII)

EXPERIMENTAL.

2-p-Toluenesulphonamidodiphenyl (*1*).—Prepared from 2-amino diphenyl and *p*-toluenesulphon chloride. M. p., 96° C.

5-Nitro 2-p-Toluenesulphonamidodiphenyl (*2*).—Prepared by nitration of 2-*p*-toluenesulphonamido diphenyl. M. p. 168–169° C.

2-Amino 5-Nitro Diphenyl (*3*).—Prepared by hydrolysis of 2-*p*-toluenesulphonamido 5-nitro diphenyl with concentrated sulphuric acid. M. p. 123–125° C.

2-Cyano 5-Nitro Diphenyl.—The best procedure for the preparation of the substance requires diazotization of 2-amino 5-nitro diphenyl in *concentrated hydrochloric acid.* Diazotization in dilute hydrochloric acid and subsequent substitution of the diazonium group leads to a reduced yield.

Fifty Gm. of 2-amino 5-nitro diphenyl was suspended in 130 cc. of concentrated hydrochloric acid and was diazotized with 21.5 Gm. of sodium nitrite contained in 70 cc. of water. The diazonium solution is then added at $-10°$ to 0° C. to a solution of potassium copper cyanide which had been prepared by adding 120 Gm. of potassium cyanide in 250 cc. of water to 100 Gm. of crystalline copper sulphate contained in 250 cc. of water. The addition of the diazonium solution was made over a period of 30 minutes using stirring. The suspension thus obtained was stirred at 0° C. for one hour when the temperature was slowly raised to 20° C. and held at the latter temperature for $^1/_2$ hour. The suspension was then slowly heated to 90° C. and kept at this temperature for 3 hours. The reaction mixture was carefully alkalinized with 150 cc. of 40% sodium hydroxide. A brown precipitate was obtained which was filtered off, washed with water and dried *in vacuo*. The substance was twice recrystallized from alcohol.

Yield, 43 Gm. of small, needle-like brown crystals -80%.
Melting point, 131–133° C.
Assay—Nitrogen found, 11.90%.
Calculated for $C_{13}H_8O_2N_2$, 12.50%.

2-Carboxy 5-Nitro Diphenyl.—This substance was obtained by hydrolysis of 2-cyano 5-nitro diphenyl.

Five and two-tenths Gm. of the cyano compound was suspended in a mixture of 75 cc. of glacial acetic acid, 60 cc. of sulphuric acid and 50 cc. of water and refluxed for 8 hours. The mixture was then cooled and diluted with an equal volume of water. The white crystals obtained were filtered, washed with water and dried *in vacuo*.

Yield, 3.5 Gm.; 62%.
Assay—Nitrogen found, 5.78%.
Calculated for $C_{13}H_9O_4N$, 5.76%.

2-Carboxy 5-Amino Diphenyl Hydrochloride.—Three Gm. of 2-carboxy 5-nitro diphenyl was reduced with 10 Gm. of tin and 50 cc. of hydrochloric acid. The reduction was carried on for 3 hours; the solution was then diluted with water and the tin precipitated with hydrogen sulphide. The sulphide was filtered off and the filtrate was concentrated. When cooled, the solution deposited 2-carboxy 5-amino diphenyl hydrochloride as silvery plates.

Yield, 1.3 Gm.
Melting point, 230° C.
Analysis—Nitrogen found, 5.42%.
Calculated for $C_{13}H_{12}O_2NCl$, 5.61%.

2-β-Diethylamino Carbethoxy 5-Amino Diphenyl.—One and two-tenths Gm. of 2-carboxy 5-amino diphenyl hydrochloride was dissolved in 20 cc. of absolute alcohol and a solution of 0.22 Gm. of sodium in 20 cc. of alcohol was added. The sodium chloride which precipitated was removed by filtration and 1.0 Gm. of β-diethylamino ethyl chloride in 10 cc. of alcohol was added to the filtrate; this alcoholic solution was refluxed for 7 hours. The solvent was then removed by distillation *in vacuo*. The residue was a light yellow oil which was converted to its dihydrochloride by passing dry hydrochloric acid gas into its ethereal solution. A yellow oil separated which, after pouring off the ether, was heated in an oven at 100° C. for 2 hours. It was then placed in a vacuum desiccator over calcium chloride and sodium hydroxide. The dihydrochloride thus obtained was a yellowish white substance which was hygroscopic.

Analysis—Nitrogen found, 7.29%.
Calculated for $C_{19}H_{26}N_2O_2Cl_2$, 7.27%.
Chlorine found, 18.34%.
Calculated for $C_{19}H_{26}N_2O_2Cl_2$, 18.44%.

The borate of the base was obtained by evaporating to dryness an aqueous solution of 1.6 Gm. boric acid and 1.1 Gm. of base. A yellowish white powder was obtained.

Analysis—Nitrogen found, 4.87%.
Calculated for $C_{19}H_{39}O_{17}B_5N_2$, 4.51%.

2-Di-n-Butylamino Carbopropoxy 5-Amino Diphenyl.—One and one-tenth Gm. of 2-carboxy 5-amino diphenyl hydrochloride was dissolved in 20 cc. of absolute alcohol and a solution of 0.2 Gm. of sodium in 20 cc. of alcohol was added. The sodium chloride formed was filtered off. The filtrate was added to a solution of 0.92 Gm. of di-*n*-butylamino propyl chloride in 30 cc. of alcohol. The solution was refluxed for 7 hours after which the sodium chloride formed was filtered off and the filtrate was distilled *in vacuo* to remove the solvent. The residue was a dark brown oil which was 2-di-*n*-butylamino carbopropoxy 5-amino diphenyl.

Analysis—Nitrogen found, 6.97%.
Calculated for $C_{24}H_{34}O_2N_2$, 7.33%.

The dihydrochloride was obtained by evaporating an alcoholic hydrochloric acid solution of the base *in vacuo*. It was a dark brown, brittle substance.

Analysis—Chlorine found, 15.94%.
Calculated for $C_{24}H_{36}O_2N_2Cl_2$, 15.71%.

2-Phenyl 4-Amino Benzoyl Chloride.—Two and seven-tenths Gm. of 2-carboxy 5-amino diphenyl was dissolved in 30 cc. of benzene and 5.0 Gm. of thionyl chloride was added. The solution was refluxed for 3 hours after which the benzene and excess thionyl chloride were removed by distillation *in vacuo*, leaving an oily residue. The latter was distilled at 2–3 mm. at which pressure 2-phenyl 4-amino benzoyl chloride distilled at 175–183° C. It was a yellow oil.

Yield, 2.5 Gm.
Analysis—Chlorine found, 15.49%.
Calculated for $C_{13}H_{10}ONCl$, 15.33%.

2-β-Diethylamino Ethyl Carbamido 5-Amino Diphenyl Hydrochloride.—Three and four-tenths Gm. of 2-phenyl 4-amino benzoyl chloride was dissolved in 30 cc. of dry benzene and reacted with 2.0 Gm. (20% excess) of unsymmetrical diethylethylene diamine contained in 25 cc. of benzene. The reaction mixture warmed up rapidly; it was refluxed for 3 hours. A solid separated out during refluxing. The isolation was made by pouring off the benzene from this solid and dissolving the latter in dilute hydrochloric acid. The acid solution was decolorized with charcoal and was evaporated to dryness *in vacuo*. The product was an extremely hygroscopic, dark brown solid.

Analysis—Nitrogen found, 12.45%.
Calculated for $C_{19}H_{26}N_3OCl$, 12.09%.
Chlorine found, 10.84%.
Calculated for $C_{19}H_{26}N_3OCl$, 10.23%.

A borate was also prepared; it also was hygroscopic and was not further investigated.

2-Carboxy 5-Butylamino Diphenyl.—Two and two-tenths Gm. of 2-carboxy 5-amino diphenyl was dissolved in 10 cc. of toluene and refluxed with 1.5 Gm. of *n*-butyl bromide. After 6 hours the toluene and excess butyl bromide were removed by distillation *in vacuo*. An alcoholic solution of the residual semi-solid substance was decolorized with charcoal and evaporated to dryness. The residue was a brown semi-solid.

Analysis—Nitrogen found, 4.96%.
Calculated for $C_{17}H_{19}O_2N$, 5.20%.

2-β-Diethylamino Carbethoxy 5-Butylamino Diphenyl.—2.35 Gm. of 2-carboxy 5-butylamino diphenyl was dissolved in 25 cc. of absolute alcohol and a solution of 0.22 Gm. of sodium in 12 cc. of alcohol was added, followed by 2 Gm. of β-diethylamino ethyl chloride in 10 cc. of alcohol. The solution was refluxed for 7 hours and then filtered from sodium chloride. The filtrate was decolorized with charcoal and 1 mol. of hydrochloric acid was added. By evaporating the solution to dryness *in vacuo* the mono-hydrochloride was obtained as a dark brown brittle substance.

Analysis—Nitrogen found, 6.56%.
Calculated for $C_{23}H_{33}N_2O_2Cl$, 6.92%.
Chlorine found, 8.90%.
Calculated for $C_{23}H_{33}N_2O_2Cl$, 8.78%.

2-Carboxy 4-Chlor 5-Amino Diphenyl Hydrochloride.—Two and two-tenths Gm. of 2-carboxy 5-amino diphenyl hydrochloride was dissolved in 25 cc. of glacial acetic acid and then 1.8 Gm. of sulphuryl chloride was added. The solution was allowed to remain at 25° C. for 2 hours after which the acetic acid was removed by distilling *in vacuo*. The last traces of acetic acid were removed by heating with alcohol and subsequently distilling. The residue was a light brown solid.

Analysis—Chlorine found, 25.39%.
Calculated for $C_{13}H_{10}O_2Cl_2N$, 25.08%.

A portion of this substance was oxidized with alkaline permanganate solution. A small quantity of benzoic acid was isolated and identified by melting point. This indicated that the position of the chlorine atom was in the substituted benzene nucleus.

2-β-Diethylamino Carbethoxy 4-Chlor 5-Amino Diphenyl Dihydrochloride.—One and three-tenths Gm. of the sodium salt of 2-carboxy 4-chlor 5-amino diphenyl was refluxed with 1.2 Gm. of β-diethylamino ethyl chloride in alcohol for 5 hours. The isolation was made as in the preparation of 2-β-diethylamino carbethoxy 5-amino diphenyl. A light yellow oil was obtained which was converted to its dihydrochloride by evaporating its alcoholic–hydrochloric acid solution to dryness *in vacuo*. A brown hygroscopic substance was obtained.

Analysis—Nitrogen found, 7.08%.
Calculated for $C_{19}H_{25}N_2O_2Cl_3$, 6.67%.
Chlorine found, 16.22%.
Hydrochloride chlorine calculated for $C_{19}H_{25}N_2O_2Cl_3$, 16.92%.

2-Cyano 4'-Nitro Diphenyl.—The substance was prepared by the same procedure used for 2-cyano 5-nitro diphenyl. A dark brown substance was obtained in a 30% yield.

Analysis—Nitrogen found, 11.93%.
Calculated for $C_{13}H_8N_2O_2$, 12.50%.

2-Carboxy 4'-Nitro Diphenyl.—This substance was prepared by the hydrolysis of 2-cyano 4'-nitro diphenyl by the same procedure used for hydrolyzing 2-cyano 5-nitro diphenyl. A dark brown substance was isolated in a 54% yield.

Analysis—Nitrogen found, 5.93%.
Calculated for $C_{13}H_9O_4N$, 5.76%.

2-Carboxy 4'-Amino Diphenyl Hydrochloride.—This was prepared by reduction of 2-carboxy 4'-nitro diphenyl by tin and hydrochloric acid. A dark brown, feathery substance was obtained.

Analysis—Nitrogen found, 5.38%.
Calculated for $C_{13}H_{12}O_2NCl$, 5.61%.

2-β-Diethylamino Carbethoxy 4'-Amino Diphenyl Dihydrochloride.—The method employed was identical with-that used in the preparation of 2-β-diethylamino carbethoxy 5-amino diphenyl dihydrochloride. A dark brown semi-solid substance was obtained.

Analysis—Nitrogen found, 7.70%.
Calculated for $C_{19}H_{26}O_2N_2Cl_2$, 7.27%.
Chlorine found, 18.48%.
Calculated for $C_{19}H_{26}O_2N_2Cl_2$, 18.44%.

4-Cyano Diphenyl (*4*).—The substance was prepared according to Kaiser's method (5). M. p. 79° C.

4-Carboxy Diphenyl (6).—The hydrolysis of 4-cyano diphenyl yielded the substance. M. p. 220° C.

4-β-Diethylamino Carbethoxy Diphenyl Hydrochloride.—This substance was obtained by refluxing sodium *p*-phenyl benzoate with diethylamino ethyl chloride and subsequently covering the base to its hydrochloride by methods mentioned above.

Analysis—Chlorine found, 10.29%.
Calculated for $C_{19}H_{24}O_2NCl$, 10.64%.

Anesthetics Tests.—The biological results have indicated that phenyl procaine is considerably more active than cocaine hydrochloride and novocaine. This fact is borne out by the following table denoting the concentrations required for equivalent duration of anesthesia by intradermal injection into guinea pigs.

TABLE I.

	Required Concentration of the Dihydrochloride.		
Duration of Anesthesia.	Phenyl Procaine.	Cocaine.	Procaine.
50 Minutes	0.73%	1.01%	2.1%
35 Minutes	0.40%	0.52%	1.0%

Phenyl procaine hydrochloride was also more active on the rabbit's cornea although it was slightly irritating.

The biological tests on compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb and Sons and we gratefully acknowledge their assistance.

SUMMARY.

In a series of phenyl derivatives of procaine the most active is the hydrochloride of β-diethylamino ethyl 2-phenyl 4-amino benzoate.

REFERENCES.

(1) Bell, *J. Chem. Soc.*, 2774 (1928).
(2) Bell, *Ibid.*
(3) Bell, *Ibid.*
(4) Kaiser, *Annalen*, 257, 100 (1890).
(5) Kaiser, *Ibid.*
(6) Kaiser, *Ibid.*

ACYL DERIVATIVES OF ORTHO-AMINOPHENOL.*

BY C. B. POLLARD AND W. T. FORSEE, JR.

When diacyl derivatives of *o*-aminophenol were prepared by the usual methods, it was found in many cases that the order of introduction of the two different acyl groups has no influence upon the formation of the diacyl, identical products being isolated from the two acylations. The formation of identical rather than isomeric products on reversing the order of acylation indicated that during acylation a rearrangement must have occurred in one of the two cases. The positions of the acyl groups of the molecule were determined by removing the group attached to the oxygen by saponification with dilute alkali, and determining from the physical constants of the remaining monoacylated product the group attached to the nitrogen. The formation of isomeric diacyls and the production of the same

* Contribution from the Chemical Laboratories, College of Pharmacy, University of Florida.