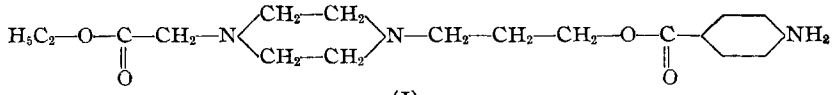
tative estimation of antipyrine in the form of its hydroferrocyanide. The method can be applied in the presence of amidopyrine.

MINNEAPOLIS, MINN.,
May 1933.

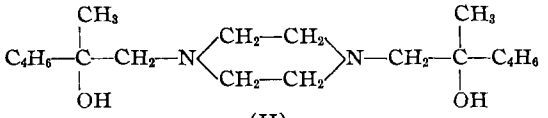
PIPERAZINE DERIVATIVES AS LOCAL ANESTHETICS.*

BY W. BRAKER AND W. G. CHRISTIANSEN.

Several piperazine derivatives have been reported in the literature (1) to possess anesthetic activity. This investigation concerns the *p*-amino benzoate of 4-(carbethoxymethyl)-1-piperazine propanol (I) and the phenyl urethane of 1,4-bis-(β-hydroxy-β-methyl hexyl) piperazine (II).



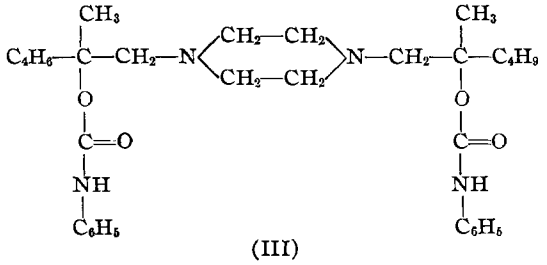
(I)



(II)

It is stated (2) that 1,4-*bis*(β-hydroxy-β-methyl hexyl)piperazine has a definite anesthetic action on the rabbit's tongue. An increase in the size of the alkyl groups was accompanied by increased activity so that the heptyl derivatives were considerably more effective than cocaine.

The method of preparation of 1,4-*bis*(β-hydroxy-β-methyl hexyl)piperazine is contained below. An effort to prepare a mono-phenyl urethane of this substance resulted in the isolation of only the diphenyl urethane derivative (III). No further attempt was made to prepare the mono-phenyl urethane.



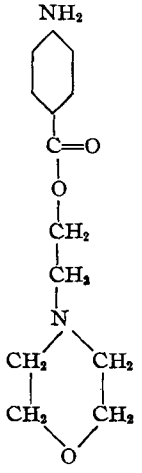
(III)

The dihydrochloride of (III) was found to be soluble to the extent of only 1.1%. The p_H of such a solution was found to be 2.2 and the solution would not permit of buffering. Consequently, it appeared impractical to further study such types of compounds.

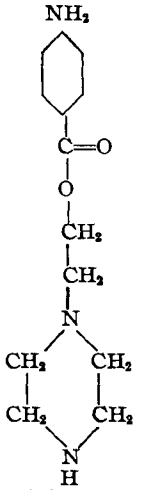
The *p*-amino benzoate of 4-(β-hydroxyethyl)morpholine (IV) has been reported to be an active anesthetic (3). A study of the substitution of the oxygen atom in

* Scientific Section, A. PH. A., Madison meeting, 1933.

the morpholine ring by a nitrogen atom was therefore commenced. The relationship between these compounds is demonstrated by their structural formulas:



(IV)



(V)

It is difficult to prepare the compound (V) with substitution on only one of the extremely basic nitrogens. As a result it was necessary to first obtain a monosubstituted piperazine. This was accomplished by preparing ethyl 1-piperazineacetate and subsequently therefrom the compound I. The synthesis is described below.

A 2% aqueous solution of the dihydrochloride of I could be effectively buffered with sodium phosphate to a p_H of 6.8. This solution was tested for anesthetic activity but it was comparatively inactive judging from the results of intradermal injections in guinea pigs.

EXPERIMENTAL.

Ethyl 1-Piperazineacetate.—The procedure followed consisted of reacting piperazine with ethyl chloracetate and subsequently fractionating the substance from 1,4-*bis*(carbethoxymethyl)piperazine.

Boiling point of ethyl 1-piperazineacetate—153–159° C. at 9–11 mm.
Yield—7.0 Gm. of a colorless oil.
Assay: N, Found 15.75%
Calculated for $C_8H_{16}O_2N_2$ 16.28%.

Ethyl-4-(γ-Hydroxy Propyl)-1-Piperazineacetate.—Seven grams of ethyl 1-piperazineacetate, 6.0 Gm. of 1-chlor 3-hydroxy propane and 7.0 Gm. of potassium carbonate were heated together in an oil-bath maintained at 155–160° C. for 7 hours. The reaction was then considered to be complete as judged from the cessation of the evolution of carbon dioxide bubbles.

The excess trimethylene chlorohydrin was removed by distillation *in vacuo*. The semi-solid residue was extracted with a mixture of alcohol and benzene. The extracts were dried over sodium sulphate. Efforts to crystallize the substance were unsuccessful. The solvents were then removed completely by vacuum distillation and a yellow, viscous oil was obtained as a residue, which was assayed.

Assay: N, Found 11.57%
Calculated for $C_{11}H_{22}N_2O_3$ 12.17%.

Ethyl-4-(γ-Chloro Fropyl)-1-Piperazineacetate.—Twelve grams of ethyl 4-(γ-hydroxy propyl)-1-piperazineacetate was refluxed with 10.0 Gm. of thionyl chloride and 6.0 Gm. of pyridine for 3 hours. An oil separated out from the benzene solution during refluxing. The benzene solution was poured off from the oil and distilled; the residue from this distillation was negligible.

The oil was treated with dilute ammonium hydroxide to liberate the base. The latter was found to be soluble in aqueous solution which effected its separation from pyridine. The latter was extracted with benzene. The aqueous solution was evaporated to dryness and the residue treated with several portions of alcohol. The alcoholic extract was evaporated, yielding 2.8 Gm. of a yellow viscous oil.

Assay: Cl, Found 14.05%
Calculated for $C_{11}H_{21}O_2N_2Cl$ 14.29%.

p-Amino Benzoate of 4-(Carbethoxymethyl)-1-Piperazinepropanol.—1.37 Gm. of *p*-amino benzoic acid was dissolved in 25 cc. of absolute alcohol. To this solution was added one of 0.23 Gm. of sodium dissolved in 20 cc. of alcohol. The resulting suspension of sodium *p*-amino benzoate was refluxed for 12 hours with an alcoholic solution of 2.5 Gm. of ethyl 4-(γ-chlor propyl)-1-piperazineacetate. The alcoholic solution was filtered from sodium chloride. The filtrate was distilled *in vacuo* which resulted in the isolation of a viscous yellow oil as the residue.

Assay: N, Found 11.62%
Calculated for $C_{18}H_{27}N_3O_4$ 12.03%.

1,4-bis(β-Hydroxy β-Methylhexyl)Piperazine.—This substance was prepared by the procedure of Fourneau and Samdahl (4).

Diphenyl Urethane of 1,4-bis(β-Hydroxy β-Methyl Hexyl)Piperazine.—Three grams (1 mole) of the carbinol and 1.1 Gm. (1 mole) of phenyl isocyanate were dissolved in 50 cc. of dry benzene. The benzene solution was refluxed for four hours. The hydrochloride of the substance was obtained by the addition of ether containing hydrochloric acid gas. The precipitate was filtered off, washed with ether and dried *in vacuo*.

It was recrystallized from alcohol.

Yield—3.4 Gm. of small, plate-like, white crystals.
Melting point—180–181° C.

Assay:	Nitrogen.	Chlorine.
Found	9.08%	10.90%
Calculated for $C_{32}H_{50}N_4O_4Cl_2$	9.12%	11.36%

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.

(1) A phenyl urethane of 1,4-*bis*(β-hydroxy β-methyl hexyl)piperazine has been prepared. This substance could not be tested biologically for anesthesia because of its acidity.

(2) The *p*-amino benzoate of 4-(carbethoxymethyl)-1-piperazineacetate has been prepared. A 2% solution of the dihydrochloride is comparatively inactive.

BIBLIOGRAPHY.

(1) Gardner and Haenni, *J. A. C. S.*, 53 (1931), 2768.
(2) Fourneau and Samdahl, *Bull. soc. chim.*, 47 (1930), 1003.
(3) Gardner and Haenni, *J. A. C. S.*, 53 (1931), 2768.
(4) *Bull. soc. chim.*, 47 (1930), 1003.

RESEARCH DEPARTMENT OF THE CHEMICAL AND PHARMACEUTICAL LABORATORIES,
E. R. SQUIBB AND SONS,
BROOKLYN, N. Y.

A MODIFIED ASSAY PROCESS FOR ALKALI BENZOATES AND SALICYLATES.*,†

BY JACOB E. SCHMIDT AND JOHN C. KRANTZ, JR.

INTRODUCTION.

The assay processes of sodium benzoate and salicylate have been the subject of much investigation during the past three decades. In 1902, Alcock (1) called attention to the simple assay process of the British Pharmacopœia. The method consisted of simple ignition and titration of the resulting carbonate. Certain difficulties in the method were enumerated. This worker suggested the conversion to chloride and argentimetric determination of the chloride. The field was reviewed and studied comprehensively by Clark (2) in 1926. This investigator concluded that the most accurate and uniform results are obtained by either weighing the metal as chloride or extracting the liberated organic acid and weighing.

In the preparation of the official monographs for the forthcoming edition of the Pharmacopœia the method of assay recently described by Henville (3) was investigated in this laboratory.

A modification of the Henville procedure was adopted and the results obtained are set forth in this communication.

EXPERIMENTAL.

In the method suggested by Henville, a weighed quantity (about 2 Gm.) of the salt is transferred with water to a cylindrical separator. A few drops of methyl orange is added and 30 cc. of neutral ether. Half-normal hydrochloric acid is run in with careful shaking until the indicator shows a distinct red color. The aqueous layer is then transferred to another separator and the water washings of the ether are added. Neutral ether is added and upon shaking the color again becomes yellow. The titration is continued until the second end-point is reached.

In an effort to simplify the method the authors have adopted the following procedure which serves as a rapid and accurate method for Pharmacopœial purposes.

---

* Scientific Section, A. PH. A., Madison meeting, 1933.

† The expense of this investigation was defrayed in part by a grant from the Research Fund of the AMERICAN PHARMACEUTICAL ASSOCIATION.