Summary

It is pointed out that an examination of the physico-chemical properties of cytoplasm may help to explain the mechanism of cell permeability.

The relationship between the iso-electric point of some leaf cytoplasmic proteins and the hydrogen-ion concentration of the contents of the leaf cells has been determined and is briefly discussed.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

SOME AMIDINES OF THE HOLOCAINE TYPE. I[1]

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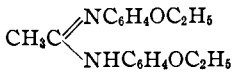
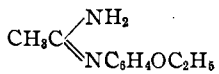
Although "Holocaine" (I) is regarded as an efficient local anesthetic



I



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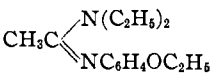


III

for ophthalmic purposes, comparatively little work has been carried out with a view to modifying its structure in order to remove the undesirable toxicity and irritability which have militated against its use.

Taube[3] has prepared a series of compounds in which methoxy and ethoxy groups occupy the *ortho* (or *para*) position in one ring, and the *para* (or *ortho*) of the other in all possible combinations, while Goldschmidt[4] has synthesized the prototype of the series in which methyl is replaced by hydrogen.

The fact that none of these compounds possesses any marked advantages over Holocaine suggests the desirability of preparing a series of amidines in which portions of the molecule are systematically replaced by groups known to exert a favorable influence on the physiological properties of local anesthetics.

An investigation has therefore been undertaken with the above-stated object in view; this paper deals with the synthesis of the following new types.

A. Compounds in which the methyl group of Holocaine is replaced by ethyl, propyl, butyl, *iso*butyl and benzyl. B. Those in which one phenetidine group is replaced by amino (II). C. Those in which one

[1] This investigation has been conducted in coöperation with the National Research Council Sub-Committee on Local Anesthetics (A. J. Hill, Chairman).

[2] This paper is constructed from the dissertation presented by Isadore Rabinowitz to the faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[3] "Chemische Technologie" (Wagner), **41**, 620, 621 (1895).

[4] Goldschmidt, Ger. pat. 97,103 (1898); 103, 982 (1899). *Chem.-Ztg.*, **26**, 743 (1902). *J. Chem. Soc.*, **82**, 785 (1902).

phenetidine group is replaced by dialkylamino (III). D. Combinations of A and B.[5]

Four methods of preparation have been employed. These are briefly outlined below.

1. The interaction of an imino-ether hydrochloride with two molecular equivalents of *p*-phenetidine in ether solution.

$$CH_3C\begin{matrix}\diagup\!\!\!=NH.HCl\\ \diagdown OC_2H_5\end{matrix} + 2\ C_6H_4(OC_2H_5)NH_2 = CH_3C\begin{matrix}\diagup\!\!\!=NC_6H_4OC_2H_5\\ \diagdown NHC_6H_4OC_2H_5\end{matrix} + C_2H_5OH + NH_4Cl$$

This method has been used for the preparation of Holocaine itself, and also the representatives of Type A, in which methyl is replaced by benzyl and *n*-butyl, both of which have frequently been shown to augment the action of local anesthetics.

2. The interaction of a *free* imino-ether with one molecular equivalent of *p*-phenetidine in ether solution.

$$RC\begin{matrix}\diagup\!\!\!=NH\\ \diagdown OC_2H_5\end{matrix} + NH_2C_6H_4OC_2H_5 = RC\begin{matrix}\diagup NH_2\\ \diagdown\!\!\!=NC_6H_4OC_2H_5\end{matrix} + C_2H_5OH$$

This method was used for the preparation of the one representative of Type B (II), and also for those of Type D, in which methyl is replaced by benzyl and *n*-butyl.

3. The action of phosphorus halides (tri- and pentachlorides) on a mixture of an *acyl* phenetidine and phenetidine.

$$RCONHC_6H_4OC_2H_5 + NH_2C_6H_4OC_2H_5 \xrightarrow{PCl_3} RC\begin{matrix}\diagup\!\!\!=NC_6H_4OC_2H_5\\ \diagdown NHC_6H_4OC_2H_5\end{matrix}$$

Method 3 was used for the preparation of representatives of Type A in which ethyl, *n*-propyl and *iso*butyl replace the methyl group of Holocaine.

4. The action of the phosphorus halides on a mixture of an acyl phenetidine and an aliphatic amine.

$$CH_3CONHC_6H_4OC_2H_5 + NH(C_2H_5)_2 \xrightarrow{PCl_3} CH_3C\begin{matrix}\diagup N(C_2H_5)_2\\ \diagdown\!\!\!=NC_6H_4OC_2H_5\end{matrix}$$

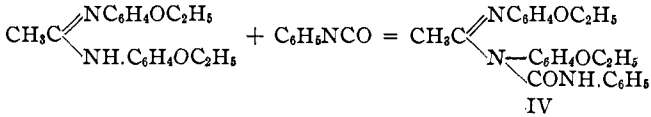
III

This has made possible the synthesis of a most interesting Holocaine derivative in which one phenetidine group has been replaced by a diethylamino radical (III). This modification should afford an interesting comparison, pharmacologically, between the aliphatic and aromatic groups.

For purposes of identification, several of the new amidines have been converted into the corresponding phenyl-ureides IV by treatment with

[5] A preliminary report concerning an additional type, in which one or both phenetidine groups have been replaced by active amino-ester groups was presented by Miss Mildred Cox and one of us, at the Washington Meeting of the American Chemical Society, 1924. That investigation will constitute Paper II of this series. A. J. H.

phenylisocyanate. It is possible that these new ureides may also possess interesting physiological properties.



IV

Experimental Part

The Hydrochlorides of the Imino-ethers, $C_2H_5OC(R)=NH.HCl$

General Procedure.—One molecular equivalent each of the appropriate nitrile and absolute alcohol[6] were dissolved in an equal weight of dry ether. The solutions were cooled in a freezing mixture and dry hydrogen chloride was passed in, until 1.25 molecular equivalents of the gas had been absorbed. After standing overnight, the precipitated hydrochlorides were filtered off and washed with ether. The substances thus obtained were used in the condensations.

TABLE I

THE IMINO-ETHER HYDROCHLORIDES

Substance	Yield, %	Analyses—Nitrogen, %—Calcd.	Found	
Ether hydrochloride				
Acetimino-ethyl[7]	83	..	..	..
Valerimino-methyl	80	9.24	9.17	9.20
Phenylacetimino-ethyl[7]	85	..	..	..

The Action of *p*-Phenetidine on the Hydrochlorides of the Imino-ethers. *sym.*-Bis-(*p*-ethoxyphenyl)-amidines, $C_2H_5OC_6H_4NHC(R)=NC_6H_4OC_2H_5$

General Procedure.—Two molecular equivalents[8] of *p*-phenetidine in 50 cc. of dry ether were slowly added during continuous stirring to 10 g. of the imino-ether hydrochloride suspended in 10 cc. of the same solvent. The mixture was allowed to stand for 21 days at room temperature and occasionally shaken. The precipitate was filtered off, and the filtrate

TABLE II

sym.-DISUBSTITUTED AMIDINES: IMINO-ETHER METHOD

	Substance	M. p., °C.	Analyses—Nitrogen, % Calcd.	Found		Yield, %	Solubilities
	Bis-(*p*-ethoxyphenyl)-						
1.	Acetamidine	117–118	9.40	9.49	9.51	12.3	Sol., alc.; insol., water.
2.	Valeramidine	96	8.23	8.41	8.34	6.7	Sol., alc., ether, benzene; insol., water.
3.	Phenylacetamidine	111	7.49	7.60	7.64	4.5	As above

[6] In the case of valeronitrile, methyl alcohol was used instead of ethyl, by reason of the difficulty of preparing the ethyl ether in crystalline condition.

[7] Compare Pinner, "Die Imidoäther," Robert Oppenheim (Gustav Schmidt), Berlin, **1892**, pp. 27 and 66.

[8] The yield is not improved by the use of more phenetidine.

placed under a bell jar in a vacuum, in order to remove the ether. After solidification had occurred, the crude material was purified by crystallization from 60% alcohol.

Preparation of the Imino-ethers from their Hydrochlorides

Acetimino-ethyl Ether,[9] Valeriminomethyl Ether and Phenylacetimino Ether

The hydrochloride was suspended in ether and a concentrated solution of potassium carbonate slowly added, during continuous shaking, until the salt was completely decomposed. The ether extract of the imino-ether was then dried over anhydrous sodium sulfate, and the material resulting from evaporation of this solution used immediately for the preparation of the amidine.

The Action of *p*-Phenetidine on the Imino-ethers. *p*-Ethoxyphenyl-amidines, $NH_2C(R)=NC_6H_4OC_2H_5$

General Procedure.—An ether solution of the imino ether was treated with one molecular equivalent of *p*-phenetidine in the same solvent. After 18 days, the solvent was removed and the residual oil kept in a vacuum until it crystallized. After washing with a little benzene to remove unaltered phenetidine, the amidine was purified by crystallization from this same solvent.

TABLE III

THE ACTION OF *p*-PHENETIDINE ON THE FREE IMINO-ETHERS

Substance	M. p., °C.	Analyses, % Calcd.	Found		Yield, %	Solubilities
p-Ethoxyphenyl-acetamidine	111–113	15.73	15.73	15.79	30	Sol., ether, alcohol, benzene; insol., water.
Phenylacetamidine	88–89	11.02	11.00	11.09	15	Same
Valeramidine	86	12.72	12.90	12.86	31	Same

Preparation of the Phenetidides

General Procedure.—A mixture of 20 g. of *p*-phenetidine and 2 molecular equivalents of the appropriate acid (propionic, butyric or *iso*valeric) was digested on a sand-bath for six hours. The reaction mixture was

TABLE IV

THE PHENETIDIDES

Crystal form: plates. All were difficultly soluble in water but soluble in alcohol

Substance	M. p., °C.	Analyses—Nitrogen, % Calcd.	Found		Yield, %
p-Phenetidine					
Propionyl	120	7.25	7.41	7.39	90
n-Butyryl	108–110	6.76	6.92	6.85	75
*iso*Valeryl	122	6.33	6.40	6.45	65

[9] Compare Ref. 7, p. 27.

poured, during stirring, into 400 cc. of cold water. The precipitated phenetidide was then filtered off, washed with cold water, and purified by crystallization from 30% alcohol.

The Action of Acyl Derivatives of *p*-Phenetidine on *p*-Phenetidine in the Presence of the Phosphorus Halides. *sym.*-Bis-(*p*-Ethoxyphenyl)-amidines,[10] $C_2H_5OC_6H_4NHC(R)=NC_6H_4OC_2H_5$.

(R = Ethyl, *n*Propyl and *iso*Butyl)

General Procedure.—One molecular equivalent of phosphorus trichloride was slowly added, during continuous shaking, to 10 g. of the acyl phenetidine suspended in 18 g. of anhydrous benzene. The mixture was cooled in an ice-bath. A solution of 1 molecular equivalent of *p*-phenetidine in 15 g. of benzene was then added, and the mixture digested on the steam-bath for five hours. There was a continuous evolution of hydrogen chloride and the colorless solution changed to a bright orange.

The benzene was removed by distillation, and the residue triturated with hot water and filtered off. The crude amidine was then precipitated from the filtrate by ammonium hydroxide, extracted with ether, and dried over anhydrous sodium sulfate. Upon evaporation of the ether, the viscous residual oil solidified in a short time. It was purified by crystallization from aqueous alcohol.

TABLE V

sym.-AMIDINES: PHOSPHORUS HALIDE METHOD

Crystal form: needles. All substances were soluble in alcohol and ether but insoluble in water.

Substance	M. p., °C.	Analyses—Nitrogen, % Calcd.	Found		Yield, %
sym.-Bis-(*p*-ethoxy-phenyl)					
-Propionamidine	84	8.97	9.10	9.14	25
-Butyramidine	106	8.59	8.43	8.48	21
-*iso*Valeramidine	108	8.23	8.41	8.38	20
p-Ethoxyphenyl-diethylacetamidine[a]	119–120	11.96	12.04	12.07	24

[a] This substance $(C_2H_5)_2N—C(CH_3)=NC_6H_4OC_2H_5$ was prepared by using diethyl amine instead of phenetidine. It is soluble in ether, alcohol, acetone and benzene, but insoluble in water.

Phenyl-ureides of the Amidines

General Procedure.—A solution of the amidine in dry ether was treated with one molecular equivalent of phenylisocyanate in the same solvent. During the addition of the latter, the solution was shaken continuously. After 24 hours the ether was removed and the residual solid purified by crystallization from acetone.

[10] The conditions contributing to a maximum yield of Holocaine and its analogs by the phosphorus halide method have been investigated by Dr. Mildred Cox, and the results will be reported in Paper II of this series.

TABLE VI

PHENYL-UREIDES

Crystal form: needles

Substance Phenylureide of Bis-(*p*-ethoxy-phenyl)	M. p., °C.	Analyses—Nitrogen, % Calcd.	Found		Yield, %	Solubilities
-acetamidine	164–165	10.07	10.11	10.18	Quant.	Sol., alcohol, acetone; insol., water, ether.
-propionamidine	101	9.74	9.69	9.60	Quant.	Sol., alcohol, ether, acetone; insol., water.
-butyramidine	105	9.44	9.54	9.58	Quant.	Same
-*n*-valeramidine	102–103	9.15	9.23	9.27	Quant.	Same
-phenylacetamidine	118	8.52	8.73	8.65	52	Same
Phenyl-ureide of *p*-Ethoxy-phenyl						
-acetamidine	164	14.14	14.33	14.28	60	Sol., acetone; insol., ether, water.
-*n*-valeramidine	158	12.39	12.54	12.48	64	Sol., alcohol, acetone; insol., ether, water.

Summary

1. Various analogs of "Holocaine" have been synthesized with a view to increasing its efficiency, and lowering its toxicity.

2. The methyl group of Holocaine has been replaced by the ethyl, propyl, butyl, *iso*butyl and benzyl radicals.

3. Analogs of substances listed in Paragraph 2, which contain but one phenetidine group, have also been prepared.

4. The above-mentioned compounds have been synthesized (a) by the action of acyl derivatives of phenetidine, and phenetidine in the presence of phosphorus trichloride, or pentachloride, and (b) by the action of imino-ether hydrochlorides (or in the case of substances given in Paragraph 3, free imino-ethers) with *p*-phenetidine.

5. Holocaine has been prepared by a new method.

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