The substance, which is isomeric with cinnamyl-hydroxynaphthoquinone, is insoluble in cold sodium hydroxide solution and is dissolved with change on boiling. The red color indicates an *o*-quinonoid structure, though the compound does not dissolve to an appreciable extent in bisulfite solution. The above structure is provisionally assigned to the compound on the basis of the analogy between cinnamyl-hydroxynaphthoquinone and lapachol.

Summary

1. 2-Alkyl-3-hydroxy-1,4-naphthoquinones are formed, in yields varying with the nature of the alkyl halide employed, in the reaction of the silver salt of hydroxynaphthoquinone with allyl, cinnamyl, benzyl, diphenylmethyl, and triphenylmethyl halides. In some cases isomeric *p*-quinone and *o*-quinone O-ethers are also formed. In general, the amount of the C-alkylation product increases with increasing reactivity of the alkyl halide.

2. Allyl-hydroxynaphthoquinone is very similar in properties and reactions to lapachol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

SOME AMIDINES OF THE HOLOCAINE TYPE
II. ESTER-SUBSTITUTED AMIDINES[1]

BY ARTHUR J. HILL AND MILDRED V. COX[2]

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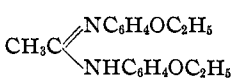
The first paper[3] of this series dealt with the synthesis of homologs of the local anesthetic "Holocaine I," in which the methyl group of this compound was replaced by other alkyl radicals. The object of the present investigation has been to replace certain portions of the holocaine molecule with amino ester groups,[4] taking cognizance of the fact that most important local anesthetics are amino esters. Theoretically, this type of replacement should decrease the characteristic toxicity and irritability of holocaine and yet maintain its anesthetic efficiency.



I

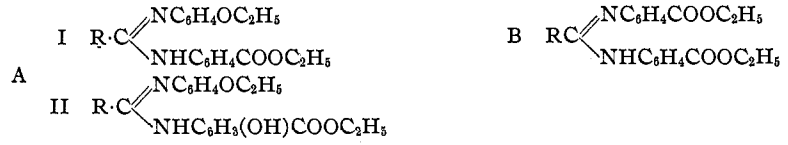
To this end, two types of ester-substituted amidines have been prepared, the type formulas of which are given below.

[1] This investigation has been conducted in coöperation with the National Research Council Sub-Committee on Local Anesthetics. It was presented in part before the Medicinal Product Section of the American Chemical Society at the Washington meeting, April, 1924.

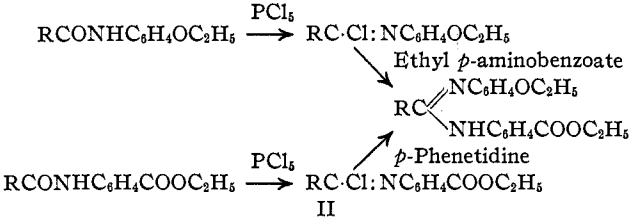
[2] This paper is constructed from the dissertation presented by Mildred V. Cox to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, **1925**.

[3] Hill and Rabinowitz, THIS JOURNAL, **48**, 732 (1926).

[4] Ester-substituted derivatives of diphenyl formamidine, possessing local anesthetic properties, have been described by Goldschmidt [*Chem.-Ztg.*, **26**, 743 (1902)].

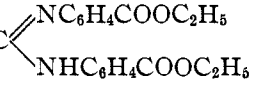


They have all been prepared by the interaction of the appropriate acylamino compound and an amine in the presence of phosphorus pentachloride.[5] Thus, the preparation of Type A compounds may be represented as follows:



The success of this method is due to the comparative inactivity of the ester group towards phosphorus pentachloride at temperatures below 100°, and in benzene solution. Indeed its inertness is interestingly shown by the fact that Type A compounds were also prepared by a reversal of the procedure, that is, by the action of the phosphorus halide on the acyl derivatives of ethyl *p*-aminobenzoate, and subsequent reaction of the intermediate imidochloride, II, with *p*-phenetidine. This procedure also confirmed the structure of these amidines. Furthermore, the chloride II also combined readily with ethyl *p*-aminobenzoate, giving the Type B amidines.

It is well known that the yields of holocaine resulting from the interaction of phenacetin and phenetidine in the presence of phosphorus pentachloride are not satisfactory on account of the difficulty, among others, of separating the pure substance from associated impurities. The success attendant upon the preparation of the new amidines led the writers to apply the same method of procedure to holocaine and certain of its derivatives, namely, the ethyl, propyl and *iso*butyl homologs.[3] The new procedure gave 70–95% yields. Explanation of these increased yields lies in the method of extraction of the final product, and in strict maintenance of anhydrous conditions during the reaction. With regard to the former, the precipitation of the free amidine, with concd. ammonium hydroxide, from an alcohol solution of the residue, resulting from evaporation of the reaction diluent, gave an oil-free, nicely granular product.

It is interesting to note that the amidine 

[5] This halide was found to be superior to either phosphorus trichloride or oxychloride as a condensing agent.

could not be prepared by the reaction of the hydrochloride of acetiminoethyl ether on ethyl *p*-aminobenzoate.[3] This is possibly due to the insufficient basicity of the latter. The phosphorus pentachloride method, on the other hand, worked very satisfactorily.

Experimental Part

General Procedure for the Preparation of the Amidines (See Tables I, II, III and IV).—Slightly more than one molecular proportion of phosphorus pentachloride was first digested in 50 cc. of the diluent (benzene dried over sodium) until evolution of hydrogen chloride had ceased. One molecular proportion of the acylamino compound was then added to the cooled solution, and the mixture shaken thoroughly. As soon as the acylamino compound had dissolved, one molecular proportion (unless otherwise stated) of the amine was added and the mixture digested on the steam-bath for three hours.

The yield of the amidine was greatly affected by the procedure used in extracting it from the reaction mixture. The best method was found to be the following. The solvent was evaporated and sufficient alcohol (10–15 cc.) added to dissolve the residue. The amidine was then precipitated by the addition of an excess of concd. ammonium hydroxide.

TABLE I

PREPARATION OF THE AMIDINES FROM THE ACYL PHENETIDINES AND ETHYL *p*-AMINOBENZOATE[a]

	Substance Ethyl ester of (phenyl-4-acid)-(phenyl-4-ethoxy)-	Reagents in benzene solution: Acyl phenetidine, g.	Ethyl *p*-amino-benzoate, g.	PCl_5, g.	Yield, %	M. p., °C.	Solubilities	N, % Calcd.	Found	
1.	-acetamidine	(Acetyl) 10	8.1	12.5	98	142	Sol. in benzene, alcohol Diff. sol. in ether Insol. in water	8.58	8.61	8.45
2.	-propionamidine	(Propionyl) 10	8.2	10.3	93	146	Same as above	8.23	8.06	..
3.	-butyramidine	(Butyryl) 10	7.6	10	50	97	Sol. in alcohol, acetone Diff. sol. in benzene, hot water	7.91	8.10	7.83
4.	-*iso*valeramidine	(*iso*Valeryl) 10	8.5	11	47	106	Sol. in alcohol, acetone Diff. sol. in hot water	7.60	7.51	7.55
5.	-*n*-valeramidine	(*n*-Valeryl) 10	8.5	11	51	91	Same as above	7.60	7.58	7.56
6.	-benzamidine	(Benzoyl) 5	4	4	81	117	Sol. in alcohol, acetone Insol. in water	7.21	7.20	7.26
7.	Ethyl ester of -(phenyl-4-oxy-3-acid) (phenyl-4-ethoxy) acetamidine	(Acetyl) 10	Ethyl amino-salicylate 10.5	10.5	29	103	Sol. in alcohol, benzene	8.18	8.11	7.99

[a] The amidines crystallize in characteristic burrs from aqueous alcoholic solutions.

TABLE II

PREPARATION OF THE AMIDINES FROM THE ACYL *p*-AMINOBENZOATES AND *p*-PHENETIDINE

Substance	Acyl *p*-aminobenzoate, g.	Phenetidine, g.	PCl_5, g.	Yield, %
1	(Acetyl) 3.5	4.5 (2 mol. propns.)	3.5	55
2	(Propionyl) 5	6.2	6	52
3	(Butyryl) 10	11.6	10	43
6	(Benzoyl) 5	5	6.6	56

TABLE III

DI(ESTER-SUBSTITUTED) AMIDINES, TYPE II[a]

	Substance Diethyl-ester of *sym.*-bis(phenyl-4-acid)	—Reagents in benzene solution— Acyl amino-benzoate, g.	Ethyl *p*-aminoben-zoate, g.	PCl_5, g.	Yield, %	M. p., °C.	N, % Calcd.	Found	
9.	-acetamidine[b]	(Acetyl) 10	8.7	11	60	156	7.90	7.84	7.79
10.	-propionami-dine	(Propionyl) 10	7.4	10.3	60	135	7.58	7.60	7.59

[a] The amidines crystallize in characteristic burrs from aqueous alcohol, are soluble in alcohol and warm benzene and slightly soluble in hot water.

[b] An attempt to prepare this amidine by the imino-ether method, Ref. 3, gave no positive results after 30 days' standing.

TABLE IV

PREPARATION OF HOLOCAINE AND CERTAIN HIGHER HOMOLOGS

Amidine *sym.*-bis(-phenyl-4-ethoxy)-	—Reagents in benzene solution— Acyl phenetidine, g.	Phenetidine, g.	PCl_5, g.	Yield, %	M. p., °C.
Acetamidine[a]	(Acetyl) 10	(2 mol. propns.) 14.8	12	96	117–118
	10	7.4	12	94.5	117–118
Propionamidine	(Propionyl) 10	13.2 (1.5 mol. propns.)	11.3	86.9	84
Butyramidine	(Butyryl) 10	10	11.7	75	106
iso-Valeramidine	(*iso*Valeryl) 10	10 (1.5 mol. propns.)	11.7	70	108

[a] Phosphorus trichloride was also used with one and two molecular proportions of phenetidine, but less successfully, the yields being 63.8 and 56.8%, respectively.

Precipitation of the amidine from either an aqueous extract of the residue or from an aqueous extract of the benzene reaction mixture proved less efficient. Indeed, in the case of the ethyl ester of (phenyl-4-ethoxy)-(phenyl-4-acid) acetamidine the yields were, respectively, 12 and 18%, compared to 98% by the best method.

Hydrochlorides of the Amidines.—The hydrochlorides (Table V) were prepared by dissolving the free base in as little ether as possible and then saturating the solution with hydrogen chloride. In the cases shown, the hydrochlorides precipitated in good crystalline condition and analyzed satisfactorily after washing with ether. Certain of the others did not come down in a granular condition and on this account are not described.

TABLE V

HYDROCHLORIDES OF THE AMIDINES

All are soluble in water and alcohol and insoluble in ether

Amidine hydrochloride	Yield, %	M. p., °C.	N, % Calcd.	Found	
1	Quant.	182–183	7.72	7.69	7.68
2	Quant.	147–148	7.41	7.42	7.52
6	Quant.	220	6.59	6.50	6.48
7		152	7.39	7.21	7.24
9	98	214–215	7.17	6.98	6.96
10	98	184–185	6.92	6.80	6.82

Ethyl *p*-Aminobenzoate.—Although the preparation of this ester has frequently been described in the literature, the writers have given below a variation of one of the usual procedures, which has proved very convenient and efficient.

Twelve and one-half g. of *p*-nitrobenzoic acid was dissolved in 75 cc. of absolute alcohol, and dry hydrogen chloride was passed into the solution until it was saturated. The mixture was digested on a steam-bath, cooled and resaturated with the gas, and again heated in order to effect complete esterification. Three molecular proportions of tin were then added slowly to the saturated alcoholic solution, the temperature being maintained at 35–40°. The mixture was allowed to stand three to four hours. Water was added and the tin completely precipitated as sulfide. The ethyl *p*-aminobenzoate was then liberated from its hydrochloride and precipitated by the addition of a large excess of sodium carbonate. It was recrystallized from alcohol; m. p., 92°; yield, 98%. This yield has been repeatedly duplicated. There is, however, an undetermined factor which occasionally reduces the yield to 70%.

The Acyl Aminobenzoates.—*Propionyl* and *butyryl* *p*-aminobenzoates (see Table VI) were prepared by heating equal parts of the appropriate acid chloride[6] and ethyl *p*-aminobenzoate until evolution of hydrogen chloride had ceased. This required approximately two hours. The reaction product was then dissolved in warm alcohol, from which the acyl derivative separated upon cooling.

[6] The writers are indebted to Drs. Hibbert and Montonna for the acid chlorides. These compounds were prepared from the corresponding acids by means of silicon chloride instead of the phosphorus halides, and they were therefore free from the impurities introduced by the use of these latter reagents.

TABLE VI

ACYL AMINOBENZOATES[a]

Substance *p*-Amino-ethylbenzoate	Yield, %	M. p., °C.	N, % Calcd.		Found
1. Propionyl	90	111	6.33		6.01
2. Butyryl	89	87	5.97	5.83	5.87

[a] These compounds are soluble in alcohol and benzene and slightly soluble in hot water. The acetyl compound has previously been described.

Acetyl *p*-Aminobenzoate.—Although acetyl chloride was also used for the preparation of this substance, the yields were not so satisfactory as those resulting from the use of acetic anhydride. The procedure employed was as follows. Equal parts of ethyl *p*-aminobenzoate (10 g.) and acetic anhydride were heated on a water-bath until crystals separated profusely upon cooling. This required approximately eight hours. After the addition of water, the precipitated acyl derivative was filtered and then purified by crystallization from water. The yield was nearly quantitative. It is soluble in alcohol, benzene and hot water and insoluble in carbon tetrachloride; m. p., 104°.

***n*-Valeryl-phenetidine.**—Equal parts of *n*-valeric acid (b. p., 181–185°—Eastman) and *p*-phenetidine (50 g.) were gently boiled for eight hours in an oil-bath. The reaction mixture was then poured into ice water, the phenetidine was filtered and washed thoroughly with water; yield, 69%.

It crystallizes from hot water in plates which melt at 92°; it is soluble in hot water, alcohol and benzene.

Anal. Calcd. for $C_{13}H_{19}O_2N$: N, 6.33. Found: 6.21, 6.26.

Summary

1. Mono ester-substituted amidines of the Holocaine type have been prepared by the interaction of certain acyl phenetidines and ethyl *p*-aminobenzoate in the presence of phosphorus pentachloride.

2. The same amidines may be obtained by reversing the above procedure and condensing the acyl derivatives of ethyl *p*-aminobenzoate with *p*-phenetidine.

3. Di ester-substituted amidines have been synthesized by condensing acyl aminobenzoates with ethyl *p*-aminobenzoate.

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