alkali metal after washing with ammonia, and usually only for nickel following washing with ethanol. In addition to surface area measurements, the quantities of hydrogen associated with the reduction products were determined. Catalytic activity was evaluated in terms of catalysis of the hydrogenation of allyl alcohol. The essential data are given in Table I, in which the catalytic activity of the nickel is expressed as the rate (in millimoles H_2 consumed/min./g. of catalyst) of the catalyzed hydrogenation reaction and the numerical values of which are taken from those portions of the corresponding rate curves over which the rates were substantially linear with time. In all cases this condition prevailed over at least three-fourths of the total reaction time.

Reduction Reactions Employing Calcium.—Similar reduction reactions employing excess calcium occurred at about the same rate as those involving lithium. Owing to the insolubility of calcium amide[8] and calcium bromide,[9] purification of the nickel by washing with liquid ammonia was ineffective. The composition of a typical ammonia-insoluble product was as follows: Ni, 17.4; Br, 44.0; N, 21.4; Ca, 11.7. Although 16% excess calcium was used in this particular case, unreacted hexamminenickel(II) bromide was present. Washing with ethanol was only partially effective as a means of purification and no means was found to purify the products without eliminating the catalytic activity of the elemental nickel present.

(8) F. W. Bergstrom, *Ann.*, **515**, 34 (1934).
(9) M. Linhard and M. Stephan, *Z. physik. Chem.*, **167**, 87 (1933).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TEXAS
AUSTIN 12, TEXAS

The Synthesis of Aryl and Aralkyl Amidines of Pharmacologic Interest[1]

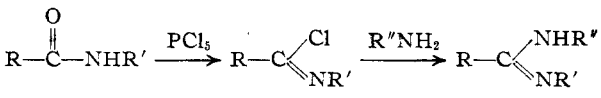
BY GEORGE L. WEBSTER AND JACOB S. RODIA[2]

RECEIVED AUGUST 14, 1952

In a previous paper from this Laboratory[3] it was shown that hydrochlorides of methoxysubstituted benzamidines possessed local anesthetic activity. The fact that all of these compounds produced sloughing of tissue at the site of injection suggested the desirability of preparing a new series of amidines in an effort to eliminate the undesirable toxicity.

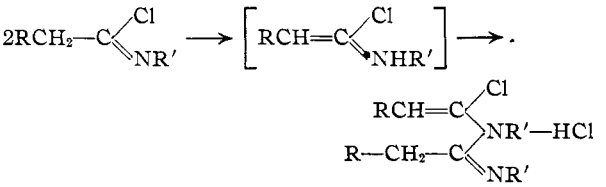
Since most local anesthetics require the use of a vasoconstrictor agent to increase the duration of anesthesia, it also appeared of interest to investigate whether the incorporation in the amidine molecule of the β-phenylethylamine skeleton would give rise to a substance having both local anesthetic and vasoconstrictor properties.

This paper deals with the synthesis of a number of new N,N′-disubstituted amidines. The amidines listed in Table I were prepared by a modification of the method of Hill and Cox[4] in yields ranging from 43 to 81%.



In the preparation of the amidines numbered 1, 2, 4, 5 and 6 in Table I, the phosphorus oxychloride formed by the interaction of the acylamino compound and phosphorus pentachloride was removed under reduced pressure prior to the addition of the amine. This procedure was found to be essential to the synthesis of the amidines (1 and 2), since their preparation required the use of an aminophenol with an unprotected phenolic group. In the other cases, this modification was adopted in order to shorten the time during which the β-phenylethylamide would be in contact with the phosphorus halide. It is known[5] that β-phenylethylamides are cyclized by phosphorus halides to the corresponding 3,4-dihydroisoquinoline derivatives.

Since the imidochlorides are very unstable and readily change into chlorovinylamidinium chlorides,[6] probably according to the reaction



it was necessary in the preparation of the disubstituted phenylacetamidines to conduct the conversion of the starting anilide into the imidochloride in the presence of the arylamine. By employing the method of Hill and Cox such a change was prevented and the expected disubstituted phenylacetamidine obtained in good yield.

In the preparation of the vanillamidines it was found that the carbethoxyl group proved to be satisfactory for the protection of the phenolic hydroxyl group. Its subsequent removal was easily accomplished with dilute alkali without affecting the amidine.

Experimental

Carbethoxyvanilloylanilide.—Vanillic acid, m.p. 207°, prepared from vanillin by the method described by Pearl,[7] was carbethoxylated according to the procedure given by Heap and Robinson.[8] A solution of 60 g. of carbethoxyvanillic acid in 150 ml. of thionyl chloride was boiled for 45 minutes or until active evolution of hydrogen chloride ceased. After removal of the excess reagent under reduced pressure, the residue was dissolved in 100 ml. of anhydrous ether, cooled and 45 ml. of aniline in 100 ml. of anhydrous ether was gradually added with stirring. The white solid which consisted of aniline hydrochloride and the desired anilide was successively washed with 100-ml. portions of water, dilute alkali, dilute acid and water. The product was recrystallized from 95% alcohol, filtered by suction and dried; yield 62.0 g., m.p. 132–133°.

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.44; N, 4.44. Found: C, 64.70; H, 5.42; N, 4.39.

Preparation of the Amidines.—One and one-tenth molecular proportion of phosphorus pentachloride in 50 ml. of sodium-dried benzene was heated on a water-bath under reflux until active evolution of hydrogen chloride ceased. The solution was cooled and 0.03–0.05 mole of the anilide was added. In the preparation of amidines numbered 5 and 6, the imidochloride was formed in the absence of the solvent using one molecular proportion of phosphorus pentachloride. The reaction mixture was then heated for two hours on a water-bath, after which the solvent and the phosphorus oxychloride formed during the reaction were removed

(1) An abstract of a thesis submitted by J. S. Rodia to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.
(2) American Foundation for Pharmaceutical Education Fellow, 1951–1952.
(3) M. J. Sintov, *et al.*, THIS JOURNAL, **71**, 3990 (1949).
(4) A. J. Hill and M. V. Cox, *ibid.*, **48**, 3215 (1926)).
(5) R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 74.
(6) J. V. Braun, F. Jostes and A. Heymons, *Ann.*, **453**, 113 (1927).
(7) I. Pearl, THIS JOURNAL, **68**, 2180 (1946).
(8) T. Heap and R. Robinson, *J. Chem. Soc.*, 2341 (1926).

TABLE I

N,N'-DISUBSTITUTED AMIDINES AND THEIR SALTS

	Benzamidines	Formula	M.p., (uncor.), °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
1	N-Phenyl-N'-*p*-hydroxyphenyl	$C_{19}H_{16}ON_2$[a]					
	hydrochloride	$C_{19}H_{17}ON_2Cl$	285	8.62	8.65	10.92	10.79
2	N-Phenyl-N'-*m*-hydroxyphenyl	$C_{19}H_{16}ON_2$	215	9.72	9.65		
	hydrochloride	$C_{19}H_{17}ON_2Cl$	271	8.62	8.58	10.92	10.86
3	N-Phenyl-N'-*p*-benzoxyphenyl	$C_{26}H_{20}O_2N_2$	131	7.14	7.08		
	hydrochloride	$C_{26}H_{21}O_2N_2Cl$	257	6.53	6.33	8.27	8.34
4	N-Phenyl-N'-homoveratryl	$C_{23}H_{24}O_2N_2$[b]	114	7.77	7.69		
	hydrochloride	$C_{23}H_{25}O_2N_2Cl$[c]					
5	N-Phenyl-N'-β-phenylethyl	$C_{21}H_{20}N_2$[d]	70	9.33	9.31		
	hydrochloride	$C_{21}H_{21}N_2Cl$	162–163	8.32	8.35	10.53	10.58
6	N,N'-Bis-β-phenylethyl	$C_{23}H_{24}N_2$	78	8.53	8.41		
	hydrochloride	$C_{23}H_{25}N_2Cl$[c]					
	sulfate	$C_{23}H_{26}O_4NS$	141	6.42	6.38		
	picrate	$C_{29}H_{27}O_7N_5$	169	12.56	12.46		
		Phenylacetamidines					
7	N-Phenyl-N'-*p*-phenetyl	$C_{22}H_{22}ON_2$	96	8.48	8.54		
	hydrochloride	$C_{22}H_{23}ON_2Cl$[c]					
8	N-Phenyl-N'-*p*-tolyl	$C_{21}H_{20}N_2$	93	9.33	9.23		
	hydrochloride	$C_{21}H_{21}N_2Cl$	155–156	8.32	8.41	10.53	10.50
		Vanillamidines					
9	N,N'-Bisphenyl 4-carbethoxy	$C_{23}H_{22}O_4N_2$[e]					
	hydrochloride	$C_{23}H_{23}O_4N_2Cl$	165	6.56	6.49	8.31	8.44
10	N-Phenyl-N'-*p*-phenetyl-4-carbethoxy	$C_{25}H_{26}O_4N_2$[e]					
	hydrochloride	$C_{25}H_{27}O_4N_2Cl$	184	6.16	6.27	7.79	7.50
11	N-Phenyl-N'-*p*-tolyl-4-carbethoxy	$C_{24}H_{24}O_4N_2$[e]					
	hydrochloride	$C_{24}H_{25}O_4N_2Cl$	167	6.36	6.42	8.04	8.15
12	N,N'-Bisphenyl	$C_{20}H_{18}O_2N$	187	8.80	8.57		
13	N-Phenyl-N'-*p*-phenetyl	$C_{22}H_{22}O_3N_2$	86	7.73	7.77		
14	N-Phenyl-N'-*p*-tolyl	$C_{21}H_{20}O_2N_2$	76	8.43	8.18		

[a] This amidine was also prepared by the method of Wagner and Holljes.[9] By both procedures the same hydrochloride and amidine were obtained. The amidine isolated in both cases possessed a melting point range 124–130°, and was found to be analytically impure. [b] Obtained in much better yield starting with N-(3,4-dimethoxyphenylethyl)-benzamide. [c] Could not be obtained pure. [d] Prepared in considerably better yield starting with N-(β-phenylethyl)-benzamide. [e] Isolated as an uncrystallizable oil.

under reduced pressure. In the preparation of the phenylacetamidines and the vanillamidines, the solvent and the phosphorus oxychloride were not removed prior to the addition of the amine. One molecular proportion of the amine (two in the cases of amidines numbered 4, 5 and 6) was added to the residue in 50 ml. of dry benzene and the mixture heated on a water-bath for three hours or until no more precipitation occurred.

When the amidine hydrochloride precipitated (compounds numbered 1, 2 and 3), it was filtered, dried and extracted with water until no more amidine could be obtained upon the addition of concentrated ammonia water to the extracts.

When the amidine did not precipitate as the hydrochloride, the solvent was removed under reduced pressure and the residue dissolved in a minimum amount of 95% alcohol. To the cooled alcoholic solution, a slight excess of strong ammonia was added slowly with stirring. When an oil was obtained, additional cooling and scratching of the sides of the vessel converted it into a crystalline material. The amidines were recrystallized from 95% alcohol.

In the cases of the 4-carbethoxyvanillamidines (compounds 9, 10 and 11) the amidine precipitated as an uncrystallizable oil which was extracted with ether and the extract dried over anhydrous sodium sulfate. After the evaporation of the ether, the residual gum was dissolved in an alcoholic hydrogen chloride solution and the hydrochloride precipitated by several additions of anhydrous ether. The gummy hydrochloride became crystalline upon cooling in an ice mixture and scratching the sides of the vessel. The hydrochloride was recrystallized from absolute methanol and anhydrous ether.

Hydrolysis of the 4-Carbethoxyvanillamidines.—One gram of the 4-carbethoxyvanillamidine hydrochloride and 10 ml. of a dilute potassium hydroxide solution were heated on a steam-bath until solution occurred (0.5 to 4 hr.). The solution was diluted, cooled and neutralized with concentrated hydrochloric acid. The yellow precipitate was filtered by suction, washed with water and dried in the air. The crude base was recrystallized from 95% alcohol with the addition of hot water. The yellow crystalline base which precipitated was filtered by suction and dried in the air.

Preparation of the Amidine Salts.—The amidine was dissolved in a minimum amount of an alcoholic hydrogen chloride solution and the hydrochloride precipitated by several small additions of anhydrous ether. The crude hydrochloride was filtered by suction, dried, and recrystallized from an absolute alcohol–anhydrous ether mixture.

The hydrochlorides of amidines numbered 1, 2 and 3 in Table I precipitated during the reaction. They were filtered by suction, dried and recrystallized from an absolute alcohol–anhydrous ether mixture.

The sulfate of N,N'-bis-β-phenylethylbenzamidine, which precipitated as an oil by the addition of a dilute solution of sulfuric acid to the pure base, was converted to a crystalline product upon cooling and scratching the sides of the vessel. It was recrystallized from an absolute alcohol–anhydrous ether mixture.

The picrate of the above amidine was obtained by warming an alcoholic solution of the base and picric acid. It was recrystallized from benzene.

DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY
UNIVERSITY OF ILLINOIS
CHICAGO 12, ILLINOIS

(9) E. C. Wagner and E. L. Holljes, *J. Org. Chem.*, **9**, 31 (1949).