the acid chloride with thionyl chloride, and the resulting mixture of acid chlorides separated by distillation through a 12-in. column packed with 1/8-in. glass helices. After removing the phenylacetyl chloride, a sharp cut of the desired acid chloride was obtained; b. p. 115° (14 mm.), $n^{25}D$ 1.5071.

Anal. Calcd. for $C_{12}H_{15}ClO$: Cl, 16.83. Found: Cl, 16.50.

Phenyl-Δ^2-cyclohexenylacetyl Chloride.—A solution of 125.7 g. (0.615 mole) of phenyl-Δ^2-cyclohexenylacetic acid[1] in 100 ml. of dry benzene and 73 ml. of thionyl chloride was heated on a steam-bath for one hour. After removal of the solvent the product was distilled through a short column giving 111 g. (77%) of yellow product, b. p. 97° (0.04 mm.), $n^{25}D$ 1.5478.

Anal. Calcd. for $C_{14}H_{15}ClO$: Cl, 15.11. Found: Cl, 15.24.

Summary

Ten new pyrrolidylalkyl and diethylaminoethyl thiol esters of disubstituted acetic acids have been prepared.

Several new intermediate pyrrolidylalkyl chloride hydrochlorides and isothiouronium salts are reported.

KALAMAZOO, MICHIGAN RECEIVED MARCH 28, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS COLLEGE OF PHARMACY]

Methoxysubstituted Benzamidines as Local Anesthetics[1]

BY N. J. SINTOV,[2a] J. S. RODIA, J. A. TURSICH,[2b] H. L. DAVIS AND G. L. WEBSTER

The hydrochlorides of certain amidines, derived from both aliphatic and aromatic acids, have been shown to exhibit local anesthetic activity.

Most, if not all, of the fatty acid amidines fall into three categories: (1) homologs of Holocaine, $CH_3 \cdot C(NC_6H_4OC_2H_5)(NHC_6H_4OC_2H_5)$, (2) Holocaine or its homologs in which different substituents appear on the N-substituted phenyl groups, and (3) compounds of the type of Holocaine or its homologs in which one or both of the substituents on the nitrogen atoms are varied.

Taube[3] prepared a number of amidines of the Holocaine type in which the two phenyl groups were substituted with methoxy or ethoxy groups, ortho (or para) in one phenyl group and para (or ortho) in the other.

Goldschmidt[4] prepared a series of similarly substituted formamidines which showed local anesthetic activity. He also prepared formamidines in which the two N-substituted phenyl groups were substituted in the para-position with either carbethoxy or carbomethoxy groups.

Hill and Rabinowitz[5] attempted to overcome the undesirable characteristics of Holocaine by substituting for the methyl group the ethyl, propyl, butyl, isobutyl and benzyl radicals. In the amidines containing the two latter radicals one of the phenetidyl groups was replaced by an amino group and one phenetidyl radical in Holocaine was replaced by a diethylamino group. Hill and Cox[6] modified the lower homologs of Holocaine by substituting for one or both of the phenetidyl groups the *p*-carbethoxyphenyl group.

The substituted and unsubstituted benzamidines have not generally exhibited local anesthetic activity. Easson and Pyman[7] prepared and tested meta and para aminobenzamidine and 3,4-dimethoxybenzamidine, none of which showed local anesthetic properties, but they found slight anesthetic activity in both *p*-carbethoxybenzamidine and *p*-carbethoxyphenylguanidine. These authors, reasoning from the structure and properties of Holocaine, prepared and tested N-veratrylbenzamidine and found that it "had well-marked" local anesthetic character.

With the results of this previous work in mind, the purpose of these experiments was to prepare and test pharmacologically N,N'-diphenylbenzamidines in which one or more of the three phenyl groups were substituted with one or more methoxy groups.

These amidines, listed in Table I, were prepared by a modification of the method of Hill and Cox[6] in yields ranging from 32 to 62%.

In the preparation of these compounds it made no difference in the yield or purity of the product if the imidyl chloride was formed first and then it reacted with the appropriate amine or if the anilide and amine were at once added to the benzene solution of phosphorus pentachloride and the reaction completed in one operation.

The hydrochlorides of amidines numbered 1, 2, 5, 6, 8, 9 and 10 in Table I precipitated as a cream-colored powder during refluxing and no yield of hydrochloride was obtained from the benzene filtrates.

Since the disubstituted amidines are tautomeric[8] those having two different substituents on

(1) From theses presented by the first three authors in partial fulfillment of the requirements for the M.S. degree. This work was supported in part by a grant from the Lederle Laboratories, Pearl River, N. Y.

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

(4) Goldschmidt, *J. Chem. Soc.*, 785 (1902).

(5) Hill and Rabinowitz, THIS JOURNAL, **48**, 732 (1926).

(6) Hill and Cox, THIS JOURNAL, **48**, 3215 (1926).

(7) Easson and Pyman, *J. Chem. Soc.*, 2991 (1931).

(8) Burtles and Pyman, *J. Chem. Soc.*, 361 (1923).

TABLE I

	Derivative	Amidines M. p., °C.	Formula	Nitrogen, % Calcd.	Found	Amidine hydrochlorides M. p., °C.	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found	Anesthesia[a,b] Corneal[c] 2%	1%	½%	Local[d,e,f] 1/10%	1/20%	1/40%
	Benzamidines															
1	N-*p*-Anisyl-N′-phenyl	114	$C_{20}H_{18}ON_2$	9.27	9.15	205	8.27	8.02	10.48	10.32	10	28	35	65	69	26
2	N,N′-Di-*p*-anisyl	125	$C_{21}H_{20}O_2N_2$	8.49	8.30	227–228	7.64	7.53	9.68	9.58	60	26	35	51	81	34
3	N-Veratryl-N′-phenyl	125	$C_{21}H_{20}O_2N_2$	8.43	8.13	202	7.60	7.28	9.61	9.45	30	10	None	19	22	80
4	N-Veratryl-N′-phenetyl	147	$C_{23}H_{24}O_3N_2$	7.44	7.38	Could not be obtained pure										
	Anisamidines															
5	N-*p*-Anisyl-N′-phenyl	124	$C_{21}H_{20}O_2N_2$	8.43	8.12	227	7.51	7.24	9.61	9.72		35	None	16	82	60
6	N,N′-Di-*p*-anisyl	105	$C_{22}H_{22}O_3N_2$	7.73	7.50	248 dec.	7.02	6.87	8.89	8.79			38	47	28	70
7	N-Veratryl-N′-phenyl	126	$C_{23}H_{22}O_3N_2$	7.73	7.57	196					50	50				
8	N,N′-Di-veratryl	143	$C_{24}H_{26}O_6N_2$	6.63	6.47	106	6.12	5.82	7.74	7.49	61	15	5	17	24	27
	Veratramidines															
9	N-*p*-Anisyl-N′-phenyl	145	$C_{22}H_{22}O_4N_2$	7.73	7.70	238	7.03	6.86	8.90	8.72		29	15	25	34	27
10	N,N′-Di-*p*-anisyl	140	$C_{23}H_{24}O_4N_2$	7.14	7.17	234	6.44	6.54	8.28	8.04	35	24	25	38	31	15
	Cocaine hydrochloride											36	32			
	Nupercaine															62

[a] Duration in minutes. [b] The pharmacological tests were made by Mr. Rodia under the direction of Dr. C. C. Peiffer Head of the Department of Pharmacology, University of Illinois College of Medicine. [c] All solutions were in contact with the rabbit cornea for thirty seconds. [d] 0.2 ml. aqueous solution was used, at least two effective intradermal wheals were produced on the back of a guinea pig. [e] The LD. 50 dose for mice of compounds 2, 9, 6 and 10 was, respectively, in mg./kg., 153, 328, 105 and 123. [f] Compounds 1, 3, 5 and 8. produced sloughing of the skin.

the two nitrogen atoms may be made by starting with an anilide prepared from either amine. N,N′-Veratrylphenylbenzamidine was prepared from benzanilide and veratrylamine and from benzoylveratryl amide and aniline to learn if the hydrochloride of the amidine would precipitate during formation. It did not precipitate in either case. N,N′-*p*-Anisylphenylbenzamidine was prepared by starting with benzoyl-*p*-anisidide and also with benzanilide. The melting point of veratroyl anilide was found by us to be 166° but is given by Shriner and Fuson[9] to be 154°. The analysis of our anilide and of the amidine prepared from it, using *p*-anisidine, prove the composition of this anilide. The proof of the structure of this amidine was shown by the fact that the identical amidine was prepared from veratroyl-*p*-anisidide and aniline.

Preliminary experiments to determine which amine should be converted into the anilide for best results in the preparation of the amidine showed that better yields were obtained from anilides prepared from the amines which have the most substituents. It was also observed that when the more highly substituted free amine was added to the imidyl chloride a greater amount of undesirable side-reaction occurred and a considerable amount of unreacted anilide was recovered. Comparative yields are illustrated by the preparation of N,N′-veratrylphenetylbenzamidine. When prepared from benzoylveratryl anilide and phenetidine the yield of amidine was 42%, while the combination of benzoyl-*p*-phenetidide and veratrylamine yielded only 17% of theoretical.

Intradermal wheals produced by injection of 0.1 ml. of 0.025% solutions of compounds 2, 6, 9 and 10 into the human arm gave immediate anesthesia that lasted for 39, 26, 34 and twenty-eight minutes, respectively. Each of these injections produced sloughing of the skin.

Experimental

4-Aminoveratrole.—It is very important that this amine be as pure as possible. The best product was obtained in the best yields by using the directions given in "Organic Syntheses."[10]

Preparation of Monosubstituted Amides.—The procedure of Kuehn and McElvain[11] was modified for the preparation of these amides. In the preparation of the acid chlorides 5 molecular proportions of thionyl chloride were mixed with one molecular proportion of acid, the solution was refluxed for four hours and the excess thionyl chloride removed by vacuum distillation. The acid chloride was used immediately.

Veratroyl-*p*-anisidide.—Prepared by the above method in 75% yield, m. p. 173°.

Anal. Calcd. for $C_{16}H_{17}O_4N$: N, 4.88. Found: N, 4.85.

Veratroyl Anilide.[9]—Prepared by the above method in 65% yield, m. p. 166°.

Anal. Calcd. for $C_{15}H_{15}O_3N$: N, 5.45. Found: N, 5.45.

Preparation of the Amidines.—This procedure was a modification of that used by Hill and Cox.[6] Ten per cent. more than one molecular proportion (6.9 g.) of phosphorus pentachloride in 50 ml. of sodium-dried benzene was heated on a water-bath under reflux until the evolution of hydrogen chloride had ceased. The solution was then cooled. At this point the procedure was varied in two different ways with the same final result. (1) One molecular proportion of the anilide was added and the imidyl chloride formed by refluxing the mixture until no more hydrogen chloride was evolved (about thirty minutes). The solution was cooled and one molecular proportion of the amine was added. (2) One molecular proportion each of the anilide and amine were added, in this order. Following either procedure (1) or (2) the mixture was heated for six hours, or, if the amidine hydrochloride precipitated during the reaction, until no more precipitation occurred.

If the amidine hydrochloride precipitated during the re-

(9) Shriner and Fuson, "The Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd edition, 1940, p. 184.

(10) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. II, 1943, pp. 619–623.

(11) Kuehn and McElvain, THIS JOURNAL, **53**, 1173 (1931).

action the reaction mixture was worked up by cooling it and filtering off the amidine hydrochloride. The filtrates did not yield more product. The dried crude hydrochloride was stirred for fifteen minutes with 200 ml. of water, the mixture filtered and the amidine precipitated by the addition of concentrated ammonia water or solid potassium carbonate to complete precipitation. The undissolved residue from the crude hydrochloride was repeatedly extracted with water until the extracts yielded no more amidine.

The amidines numbered 3, 4 and 7 in Table I did not precipitate as the hydrochloride during refluxing, although the time of refluxing was extended to ten hours. After refluxing, the solution in each case was distilled under reduced pressure until the benzene and phosphorus oxychloride were removed. The brown, viscous residue was thoroughly stirred with 10–15 ml. of 5% hydrochloric acid and the latter decanted. The viscous paste solidified after this treatment to a soft solid. This mass was extracted, at room temperature, with 60 ml. of 5% hydrochloric acid and the amidine precipitated from the filtered extract with concentrated ammonia water. Repeated extractions were required to remove all the amidine from the residue. The first extracts yielded a brown product which became a pale ivory in color when reprecipitated from 5% hydrochloric acid. The crude amidine crystallized from 75% alcohol as a white or slightly ivory-colored, finely-divided solid.

Preparation of Amidine Hydrochlorides.—Five grams of amidine was dissolved in the least amount of ether (because of the solubility of their hydrochlorides benzene was used with the amidines numbered 3, 8, 9 and 10 in Table I) and dry hydrogen chloride gas was passed into the solution until complete precipitation of the hydrochloride, when the solution was immediately filtered by suction. The crude hydrochlorides crystallized in white needles from an alcohol–ether mixture.

Summary

Ten new amidines have been prepared and their hydrochlorides have been tested for local anesthetic activity.

All of the amidine hydrochlorides produced local anesthesia. Their solution produced sloughing of tissue at the site of injection.

CHICAGO, ILLINOIS RECEIVED MAY 28, 1949

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

N,N-Disubstituted Amidines. II. Benzamidines. The Effect of Substitution on Basicity[1]

BY EMIL LORZ AND RICHARD BALTZLY

By means of the synthetic method recently reported from these laboratories[2] a series of N,N-disubstituted benzamidines has been prepared. The primary object herein was to determine on relatively accessible compounds the effect of substitutions in the ring on the local anesthetic potency. Taken together with the benzamidines previously reported (Compounds I–VII, XIII and XXI–XXIV in our first paper)[2] the series suffices for the prediction with reasonable accuracy of the influence of convenient substitutions on the physiological properties of amidines of this type. While none of the substances reported in this paper and none of the benzamidines described earlier are of exceptional merit, the regularities observed have been found transferable to other series of greater inherent potency.

The new amidines prepared are shown together with analytical data in Table I, the numbering being consecutive with that of our earlier paper.[2] N,N-Di-*n*-butylbenzamidine (I) has a toxicity about four times that of cocaine (LD_{50} = 26.5 mg./kg. administered intraperitoneally) in mice and a potency as a surface anesthetic about one-half that of cocaine (by the method of application to the cornea of a guinea pig). Substitution of the ring by methyl, methoxyl or dimethylamino groups or by chlorine increased the potency; substitution by hydroxyl eliminated it. The most pronounced effect here was that of *p*-chlorine substitution: *p*-chloro-N,N-di-*n*-butylbenzamidine having 7.4 times the potency of cocaine. In general, the potencies run from two to five times that of cocaine.

Chlorine substitution tends to increase toxicity though not very markedly and with little selective action in respect to position. Methoxyl substitution, on the other hand, diminishes toxicity considerably in the meta and para positions and increases it markedly in the ortho: the LD_{50} for the *o*-, *m*- and *p*-methoxy-N,N-di-*n*-butylbenzamidines are 9, 30 and 36 mg./kg., respectively. This phenomenon is quite consistent, the 2,5-dimethoxy and 2,6-dimethoxy compounds (XXXI and XXXII) having LD_{50} = 13.5 and 7, respectively, while the 3,4-dimethoxy and 3,4,5-trimethoxy analogs (XXXIII and XXXV) have LD_{50} = 38 and 52.

The presence of an aromatic radical on the amidine nitrogen confers lower toxicity but increases the potency only a little.

There was a distinct possibility that these variations might be correlated with the basicity of the amidines. Since amidines have not been studied very extensively from this standpoint and amidines of the present type were formerly rather rare, a number of the hydrochlorides sufficient to indicate the effect of substitutions on basicity, were titrated in 50% methanol. Use of a partly organic solvent is necessary to prevent serious error due to precipitation of base; Hall and Sprinkle[3] showed that this device gives satis-

(1) The work here reported is part of a joint research carried out in collaboration with a Pharmacological group in these laboratories.

(2) Lorz and Baltzly, THIS JOURNAL, **70**, 1904 (1948).

(3) Hall and Sprinkle, *ibid.*, **54**, 3469 (1932).