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.

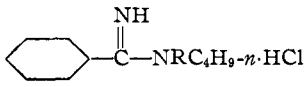
There was a distinct possibility that these variations might be correlated with the basicity of the amidines. Since amidines have not been studied very extensively from this standpoint and amidines of the present type were formerly rather rare, a number of the hydrochlorides sufficient to indicate the 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).

TABLE I

N,N-DIALKYLBENZAMIDINE HYDROCHLORIDES 

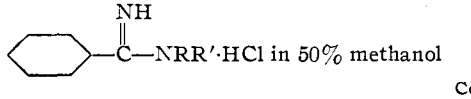
Compound no.	Ring substituents	R	Method of isolation[a] yield, %	M. p., °C.[b]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
XXV	None	4-$MeOC_6H_4$	A 67[c]	211	$C_{18}H_{23}ClN_2O$	67.80	68.09	7.27	7.17
XXVI	3-MeO	n-C_4H_9	B 70	138	$C_{16}H_{27}ClN_2O$	64.30	64.53	9.11	8.89
XXVII	3-MeO	2-$CH_3C_6H_4$	B′ 51	201–202	$C_{19}H_{25}ClN_2O$	68.55	68.55	7.57	7.43
XXVIII	4-MeO	n-C_4H_9	B 77	185	$C_{16}H_{27}ClN_2O$	64.30	64.55	9.11	9.21
XXIX	4-BzO	n-C_4H_9	C 36[d]	201	$C_{22}H_{31}ClN_2O$	70.47	70.80	8.33	8.39
XXX	4-OH	n-C_4H_9	[e]	166	$C_{15}H_{25}ClN_2O$	63.25	63.32	8.85	8.81
XXXI	2,5-$(MeO)_2$	n-C_4H_9	A′ 65	171–172	$C_{17}H_{29}ClN_2O_2$	62.08	61.79	8.89	8.80
XXXII	2,6-$(MeO)_2$	n-C_4H_9	A′ 81	196	$C_{17}H_{29}ClN_2O_2$	62.08	62.38	8.89	8.78
XXXIII	3,4-$(MeO)_2$	n-C_4H_9	B 70	194	$C_{17}H_{29}ClN_2O_2$	62.08	62.25	8.89	8.85
XXXIV	3,4-OCH_2O	n-C_4H_9	A′ 50	146	$C_{16}H_{25}ClN_2O_2$	61.43	61.50	8.06	7.76
XXXV	3,4,5-$(MeO)_3$	n-C_4H_9	A′ 54	167	$C_{18}H_{31}ClN_2O_3$	60.24	60.11	8.71	8.37

[a] Yield based on quantity of solid hydrochloride before recrystallization, except as otherwise noted. [b] All melting points are corrected. [c] Yield calculated on weight of distilled base, b. p. (1 mm.), 175–180°. [d] Based on analytically pure hydrochloride. [e] The purification was difficult and the yield hard to estimate.

factorily comparable results which vary in a consistent fashion from values obtainable in water. The dissociation constants so obtained, expressed as pK_a, are presented in Table II.

TABLE II

ACID DISSOCIATION CONSTANTS OF BENZAMIDINE HYDROCHLORIDES



Ring substituents	R	R′	pK_a[c]	Compound no.
None	n-C_4H_9	n-C_4H_9	11.27	I
None	C_6H_5	n-C_4H_9	10.40	XXII
None	$C_6H_5CH_2$	$C_6H_4CH_2$	9.98	XIII
None	4-$MeOC_6H_4$	n-C_4H_9	10.52	XXV
None	N-RR′ = N-tetrahydroquinolyl		9.79	XXIII
None	N-RR′ = N′-benzylpiperazino		10.54[a]	XXIV
2-Cl	n-C_4H_9	n-C_4H_9	10.70	IV
2-MeO	n-C_4H_9	n-C_4H_9	11.51	III
3-Cl	n-C_4H_9	n-C_4H_9	10.68	V
3-MeO	n-C_4H_9	n-C_4H_9	11.20	XXVI
3-MeO	2-$CH_3C_6H_4$	n-C_4H_9	10.28	XXVII
4-Cl	n-C_4H_9	n-C_4H_9	10.90	VI
4-MeO	n-C_4H_9	n-C_4H_9	11.50	XXVIII
4-OH	n-C_4H_9	n-C_4H_9	12.05[b]	XXX
4-NMe_2	n-C_4H_9	n-C_4H_9	11.65	VII
3,4-$(MeO)_2$	n-C_4H_9	n-C_4H_9	11.30	XXXIII
3,4,5-$(MeO)_3$	n-C_4H_9	n-C_4H_9	11.14	XXXV
2,4,6-Me_3	n-C_4H_9	n-C_4H_9	11.74	XXI

[a] Two pK_a values observed, at 4.46 and 10.54. The former must be that of the tertiary benzylamino nitrogen. [b] Two pK_a values observed, at 8.80 and 12.05. The former is obviously that of the hydroxyl group whose acidity should be increased by the presence of the cationic amidinium portion. [c] pK_a values were calculated according to the formula given in Clark, ref. 6, Chapter I, p. 16.

At first sight it appears surprising that an aromatic group on the amidine nitrogen diminishes the basicity so little (compare I with XXII and XXV also XXVI with XXVII), less than one unit in the pK scale. Actually, this corresponds very closely with the observations in the guanidine series[3,4] it having been shown that pK_a diminishes in the series: guanidine > phenylguanidine > N,N′-diphenylguanidine from 13.65 to 10.77 to 10.12. It would seem that the resonance possibilities in the benzamidinium ion are very close to those in the phenylguanidinium ion while compound XXII is comparable to *sym*-diphenylguanidine.

The influence of ring substitution on the basicity is in general consistent with theoretical expectations. The very high basicity observed with the 4-hydroxy derivative is obviously correlated with the fact that the hydroxyl group has been titrated first and the oxygen is anionic in the *p*H range involved in the titration of the amidinium moiety. It is to be noted that the three coöperative methyl groups of the mesityl derivative (XXI) exercise an influence greater than that of a para methoxyl or dimethylamino group. This may be partly due to steric inhibition of resonance between the amidine moiety and the ring which probably has an over-all tendency to diminish the basicity of the amidine. Schwarzenbach and Lutz[5] report pK_a for acetamidine hydrochloride as 12.40 (in water) which is significantly above the value for any of these aromatic amidines.

Experimental

Compound XXX, 4-hydroxy-N,N-di-*n*-butylbenzamidine hydrochloride was prepared by hydrogenolysis of its benzyl ether (XXIX) with palladized charcoal. With this exception all the amidines here reported were obtained by the addition of the appropriate bromomagnesium amide to a benzonitrile.[2] The nitriles employed are all described in the older literature. Most of the significant information is presented in Table I, the method of isolation being indicated by the letters A, A′, B, B′ and C, in the column

(4) Davis and Elderfield, THIS JOURNAL, **54**, 1499 (1932).

(5) Schwarzenbach and Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940).

headed "Method of isolation." Methods A, B and C have been described previously.[2]

Method B′ is a modification of B in which steam distillation of the basic material is omitted and the amidine is separated from secondary amine by extraction from ethereal solution by successive portions of dilute hydrochloric acid. This is to be preferred with N-arylamidines since the secondary amine is feebly basic and the amidine base may undergo some decomposition during a prolonged steam distillation.

Method A′ differs from A only in that the amidine base is not itself distilled. The secondary amine is volatilized by heating *in vacuo* to a temperature preferably not over 160°. In some cases more drastic heating (up to 200° at 1 mm.) was employed with no apparent decomposition but it is believed that the yield of pure amidine hydrochloride suffered from such treatment.

The amidine hydrochlorides were purified by crystallization from ethanol–ether mixtures.

Electrometric Titrations.—These were performed at 0.02 molar initial concentration of amidine hydrochloride in 50% methanol, adding 0.1 *N* sodium hydroxide solution. The apparatus was a Beckman *p*H meter, Model G. Determinations of the *p*H range 6–9 were accomplished with a glass electrode 960 standardized at *p*H 4 and *p*H 7 with potassium acid phthalate and phosphate buffers, respectively. Above *p*H 9 a high *p*H glass electrode 960 E standardized at *p*H 9 and *p*H 12 with sodium chloride–glycine[6] buffers was employed.

Direct comparison of titrations in water and in 50% methanol is not possible with most of these amidines. The most accurate but laborious procedure is to perform a series of titrations in diminishing concentrations of methanol so as to permit extrapolation to zero per cent.—as was done by Hall and Sprinkle.[3] From observations on certain quinoline amidines we believe that in the range 9.5–11, the pK_a observed in 50% methanol runs about 0.3 unit above that in water. Compound XXX was titrated both in 50% methanol and in water. The two curves were roughly parallel, that for methanol being above that for water except at high *p*H (at 11.9 the curves cross). The first two pK_a values, at 8.65 in water and 8.80 in 50% methanol, presumably are due to the phenolic hydroxyl group. The higher pK_a values, relating to the amidine portion were at 12.05 in 50% methanol and 12.15 in water.

Summary

1. A number of N,N-disubstituted benzamidines have been prepared.

2. The effect of substitutions upon the basicity of unsymmetrically disubstituted benzamidines is discussed.

(6) Clark, "The Determination of Hydrogen Ions," 3rd Edition, Williams and Wilkins Co., Baltimore, Md., 1928, Chapter IX.

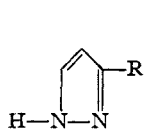
TUCKAHOE 7, N. Y. RECEIVED JUNE 11, 1949

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

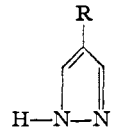
The Synthesis of Some Amines and Amino Acids Containing the Pyrazole Nucleus

BY REUBEN G. JONES

As part of a study concerned with the biological activity of certain amines and amino acids[1] the two isomeric β-aminoethylpyrazoles, I and II, and the two corresponding pyrazolealanines, III and IV, were prepared.



I, R = $CH_2CH_2NH_2$

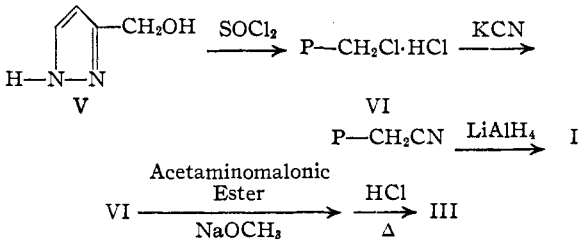


II, R = $CH_2CH_2NH_2$

III, R = $CH_2CHNH_2CO_2H$ IV, R = $CH_2CHNH_2CO_2H$

These pyrazole compounds were of particular interest because of their apparently close structural resemblance to the imidazole derivatives, histamine and histidine.

Compounds I and III were synthesized by straightforward procedures as indicated in the accompanying reactions.



Two methods were developed for the preparation of the starting material, 3-hydroxymethylpyrazole, V. Reduction of ethyl 3-pyrazolecarboxylate[2] with lithium aluminum hydride in ether gave V in 84% yield. Compound V was also prepared by the condensation of diazomethane with propargyl alcohol. It has been observed that substituted acetylenes of the type R—C≡CH undergo reaction with diazomethane to yield predominately 3-substituted pyrazoles,[3]

(1) (a) Jones, THIS JOURNAL, **71**, 383 (1949); (b) Jones, *ibid.*, **71**, 644 (1949).

(2) Knorr, *Ber.*, **37**, 3522 (1904).

(3) (a) Kuhn and Henkel, *Ann.*, **549**, 279 (1941); (b) Huttel, *Ber.*, **74**, 1680 (1941).