[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

Some N-Alkyl N′-Aryl Furamidines

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Among those compounds which exhibit local anesthetic activity, particularly upon topical application, are the N-substituted amidines RC(=NR′)NR″R‴, where R is commonly a simple alkyl group, and R′, R″, and R‴ commonly hydrogen or substituted phenyl groups. Holocaine (N,N′-di-*p*-phenetylacetamidine), and Acoine (N,N′-di-*p*-anisyl-N′-*p*-phenetylguanidine) have received some clinical attention because of their rapid onset and powerful anesthetic action, but suffer from a lack of persistence and a comparatively high toxicity.

A number of other amidines showing physiological action have been prepared by Täuber,[2] Goldschmidt,[3] Hill and Rabinowitz,[4] Hill and Cox,[5] and others.

Comparatively little attention has been devoted to the investigation of physiologically active amidines where R is aromatic or heterocyclic. Easson and Pyman[6] prepared and submitted to pharmacological evaluation several unsubstituted and substituted benzamidines, and reported the latter to be somewhat active. Boomer[7] has prepared a number of N,N′-di-aryl furamidines, which did not show great activity.

In the present investigation it was determined to hold one group (R) in the general formula R—C(=NR′)NR″R‴ constant throughout. The furyl group was chosen for this purpose. Two series of derivatives were then prepared: in the first series R′ was *p*-phenetyl and R″ any of a series of alkyl groups; in the second series R′ was *n*-butyl, R″ any of a series of aryl groups. Several amidines were prepared which do not fit into these two categories.

After some investigation it was found best to prepare the desired amidines from the alkyl furamides and the aryl amines in the presence of phosphorus pentachloride, according to the technique described by Hill and Cox.[5] After isolation, the amidines were further characterized as hydrochlorides. It was not found possible to reverse this procedure and use the aryl furamides and alkyl amines as starting materials.

TABLE I

N-ALKYL FURAMIDES

N-Alkyl group	M. p., °C.	Nitrogen, % Calcd.	Found	Yield, %
n-Propyl	39–40	9.15	8.61	80
n-Butyl	40–41	8.38	8.07	84
Butyl-2	122–123	8.38	8.52	90
(2-Methyl)-propyl-2	99	8.38	8.55	80
n-Amyl	31–32	7.73	7.57	72
Amyl-2	48–56	7.73	7.80	89
(2-Methyl)-butyl-2	68–69	7.73	7.91	93
(3-Methyl)-butyl-1	53–54	7.73	7.76	93
(4-Methyl)-amyl-2	54–55	7.18	7.22	90
Cyclohexyl	108.5–109	7.25	7.38	97
(2-Ethyl)-hexyl-1	(Oil)	6.28	5.90	93

TABLE II

N-ALKYL N′-ARYL FURAMIDINES AND THEIR HYDROCHLORIDES

Substituted furamidine	M. p., °C.	Nitrogen, % Calcd.	Found	Yield, %
N-*n*-Propyl N′-phenyl	63.5–64.0	12.28	12.10	55
Hydrochloride	139–140	10.59	10.54	90
N-*n*-Propyl N′-*p*-phenetyl	81.0–81.5	10.29	10.39	60
Hydrochloride (·1 H_2O)	78.5–79.5	8.58	8.50	80
N-*n*-Propyl N′-*p*-carbethoxyphenyl	86–87	9.33	9.17	70
Hydrochloride	167–168	8.32	8.24	91
N-*n*-Butyl N′-phenyl	67–68	11.51	11.31	60
Hydrochloride	141–142	10.06	10.12	99
N-*n*-Butyl N′-*p*-phenetyl	65.5–66.0	9.79	9.74	51
Hydrochloride (·1 H_2O)	78.5–79.5	8.22	8.23	87
Hydrochloride (anhydrous)	135–136	8.68	8.61	94
N-*n*-Butyl N′-*p*-carbethoxyphenyl	75.5–76.0	8.92	8.81	74
Hydrochloride	128–129	7.99	8.03	90
N-*n*-Butyl N′-α-naphthyl	54.5–55.5	9.59	9.54	62
Hydrochloride	99–101	8.53	8.34	100
N-*n*-Butyl N′-β-naphthyl	61.5–62.0	9.59	9.54	51
Hydrochloride	91.5–92.5	8.53	8.42	96
N-Butyl-2 N′-*p*-phenetyl	52.0–52.5	9.79	9.72	...
Hydrochloride	132–133	8.68	8.83	...
N-*n*-Amyl N′-*p*-phenetyl	61.0–61.5	9.33	9.14	63
Hydrochloride (·1 H_2O)	75–76	7.90	7.77	76
N-Amyl-2 N′-*p*-phenetyl	75–76	9.33	9.30	52
Hydrochloride	125.5–126.5	8.32	8.18	96
N-(3-Methyl)-butyl-1 N′-*p*-phenetyl	78–79	9.33	9.46	51
Hydrochloride	142–143	8.32	8.36	100
N-(4-Methyl)-amyl-2 N′-*p*-phenetyl	77	8.92	8.77	55
Hydrochloride	120–121	7.99	8.10	100
N-Cyclohexyl N′-phenyl	78.5–79.0	10.45	10.31	59
Hydrochloride	174	9.20	9.26	100
N-Cyclohexyl N′-*p*-phenetyl	108–109	8.97	8.80	64
Hydrochloride	170–171	8.04	8.21	89
N-Cyclohexyl N′-*p*-carbethoxyphenyl	114–115	8.24	8.05	73
Hydrochloride	188–189	7.44	7.64	99

(1) This paper is constructed from a thesis to be presented by Frank B. Pope to the Faculty of the Graduate School of Indiana University in June, 1940, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) E. Täuber, *Chemische Technologie* (Wagner), **41**, 620 (1895).

(3) C. Goldschmidt, *J. Chem. Soc.*, **82**, 785 (1902).

(4) A. J. Hill and I. Rabinowitz, THIS JOURNAL, **48**, 732 (1926).

(5) A. J. Hill and M. V. Cox, *ibid.*, **48**, 3214 (1926).

(6) A. P. T. Easson and F. L. Pyman, *J. Chem. Soc.*, 2991 (1931).

(7) G. L. Boomer, M.S. Thesis, Yale University, 1934.

TABLE III

PHARMACOLOGICAL RESULTS

Furamidine hydrochloride	Toxicity LD ± S. E. mg.^{50}/kg.	% Soln.	Duration of anesthesia, min. No. used	Guinea pig skin	No. used	Rabbit eyes	Irritation Rabbit eyes	Rabbit skin
N-*n*-Propyl	40.80±1.41	1.0	6	83	6	36	None	Severe
N'-*p*-phenetyl-		0.5			3	36	None	Severe
		0.1			6	0	None	
N-*n*-Propyl	77.41±4.82	1.0	3	33	3	28	Severe	
N'-*p*-carbethoxyphenyl-[a]		0.5			3	11	Severe	
N-*n*-Butyl	54.01±3.13	1.0	3	75	3	17	Slight	Severe
N'-phenyl-		0.5	3	44	3	0	None	Severe
N-*n*-Butyl	19.47±1.00	1.0	6	103	6	81	None	Severe
N'-*p*-phenetyl-		0.5	3	110	6	60	None	
		.25			3	55	None	Severe
		.125			3	29	None	Moderate
		.1			26	23	None	Mild
		.066			3	0	None	Slight
N-*n*-Butyl	87.02±3.70	1.0			3	14	Severe	
N'-*p*-carbethoxyphenyl-[a]		0.5			3	10	Severe	
N-*n*-Butyl	84.87±6.43	1.0			3	0	Severe	
N'-α-naphthyl-		0.5			3	0	Severe	
		0.1			3	0	Severe	
N-*n*-Butyl	76.86±3.07	1.0			3	78	Severe	
N'-β-naphthyl-		0.5			3	5	Severe	
		0.1			3	0	Severe	
N-Butyl-2	38.46±1.58	1.0	3	90	3	53	None	Severe
N'-*p*-phenetyl-		0.5			3	25	None	Severe
		0.1			3	0	None	1 Sev., 2 Negl.
N-*n*-Amyl	16.60±0.50	1.0	3	76	3	52	Moderate	Severe
N'-*p*-phenetyl-		0.5	3	40	3	55	Moderate	Severe
		0.1	3	48	3	15	Mild	Severe
N-Amyl-2	22.76±1.18	1.0	3	13	4	75	Severe	
N'-*p*-phenetyl-		0.1			3	0	Severe	
N-(3-Methyl)-butyl-1	18.74±0.83	1.0	3	65	3	54	Mild	Severe
N'-*p*-phenetyl-		0.5	3	33	3	64	Mild	Severe
		0.1	3	40	3	25	None	Mild
		0.066			5	2–23 3–0	None	Negl.
N-(4-Methyl)-amyl-2	21.45±0.74	1.0	3	49	4	68	Severe	
N'-*p*-phenetyl-		0.1			4	33	Moderate	
		0.066			4	7	Slight	
N-Cyclohexyl	59.33±2.15	1.0			3	17	Severe	
N'-phenyl-		0.5			3	8	Severe	
		0.1			3	0	Slight	
N-Cyclohexyl	26.69±1.24	1.0	3	120	3	67	Moderate	Severe
N'-*p*-phenetyl-		0.5	3	35	3	34	Slight	
		0.3	3	32	3	26	Slight	
		0.2	3	30	3	12	Slight	
		0.1			3	16	None	Moderate
Cocaine (for comparison)	16.38±1.72	1.0		30		25	None	None

[a] Precipitated in the eye.

The amides used have not previously been reported. They were prepared from the corresponding amines and furoyl chloride.

Experimental

Furoyl Chloride.—Furoyl chloride was prepared from a technical grade of furoic acid by the action of thionyl chloride. The fraction boiling at 172–176° was collected for use.

N-Alkyl Furamides.—The alkyl furamides were prepared by adding one molar proportion of furoyl chloride slowly to one molar proportion of the appropriate aliphatic amine[8] suspended in 15–20% molar excess of dilute potassium hydroxide solution. The reaction mix-

(8) The authors are indebted to the Research Laboratories of the Sharples Solvents Corporation, and to The Lilly Research Laboratories, for a number of the aliphatic amines used in this investigation.

ture was vigorously motor-stirred during the addition, and the temperature held below the boiling point of the amine being used. At the end of the reaction the mixture was acidified with hydrochloric acid to dissolve any unchanged amine, and the crude furamide removed by filtration if solid, and by extraction with ether if an oil. The solid amides were recrystallized from dilute alcohol. In the case of the amides which separated as oils, the ether was removed by evaporation and the residue crystallized, if possible, from acetone solution at the temperature of a dry-ice–acetone-bath. The properties of the alkyl furamides are summarized in Table I.

N-Alkyl N′-Aryl Furamidines.—One molar proportion of phosphorus pentachloride was dissolved in benzene and the solution boiled under a reflux condenser until hydrogen chloride was no longer evolved. The solution was then cooled and one molar proportion of the appropriate alkyl furamide added. There was a vigorous reaction and the evolution of considerable quantities of hydrogen chloride. The solution was now allowed to reflux for one-half hour, and then one molar proportion of the appropriate aromatic amine was added and the solution gently boiled until the evolution of hydrogen chloride had substantially ceased. The time necessary to bring this about varied widely from case to case. The benzene was removed by distillation and the residue rinsed into a beaker with alcohol. Cautious addition of concentrated aqueous ammonia liberated the free amidine, in most cases as an oil. The amidines were extracted with ether, the ether removed, and the crude products crystallized from dilute alcohol. The properties of the N-alkyl N′-aryl furamidines are summarized in Table II.

Furamidine Hydrochlorides.—The amidine hydrochlorides were prepared by passing dry hydrogen chloride into a solution of the appropriate amidine in absolute ether. Approximately 10 cc. of ether per gram of amidine was used. An excess of hydrogen chloride causes the amidine hydrochlorides to separate as oils or redissolve. The hydrochlorides were crystallized from ether–alcohol solution. The properties of the furamidine hydrochlorides are summarized in Table II.

Pharmacological Results[9]

The N-alkyl N′-aryl furamidine hydrochlorides were tested for toxicity by intravenous injection in mice; for anesthetic action by topical application to rabbits' eyes, and by intracutaneous injection in guinea pigs; for irritation by topical application to rabbits' eyes, and by intracutaneous injection in rabbits. The results are presented in Table III.

These results indicate a high persistency of action, coupled with a moderate toxicity, for the N-alkyl N′-*p*-phenetyl series, reaching a maximum with N-*n*-butyl N′-*p*-phenetylfuramidine hydrochloride. Compounds containing a carbethoxyphenyl group are not useful, since they precipitate in the eye and are highly irritating. Compounds containing the phenyl or naphthyl group are not sufficiently active to be useful.

Further pharmacological investigation of N-*n*-butyl N′-*p*-phenetylfuramidine hydrochloride is in progress.

(9) The authors are grateful to Mr. C. L. Rose of The Lilly Research Laboratories for the pharmacological data given in this section.

Summary and Conclusions

1. Eleven new N-alkyl furamides and sixteen new N-alkyl N′-aryl furamidines and their hydrochlorides have been prepared and characterized.

2. In the preparation of these amidines it was found necessary to introduce the alkyl substituent before the aryl substituent.

3. The amidine hydrochlorides show some anesthetic action, N-*n*-butyl N′-*p*-phenetylfuramidine hydrochloride being more than three times as active as cocaine, as judged from persistency of action. This compound is not irritating to the cornea of the eye.

4. The high anesthetic potency of this group of amidines, as compared to the di-aryl furamidines, demonstrates the value of introducing an alkyl group into the molecule. Investigation of the amidines of other aromatic and heterocyclic acids is being undertaken.

BLOOMINGTON, INDIANA RECEIVED APRIL 20, 1940