enzyme was inactivated and the digest prepared for electrophoretic analysis as with the amyloheptaose digest.

The rate of glucose formation on digestion of maltose with *macerans* amylase was determined by analysis of aliquots removed at varying time intervals from a digest of a 3% maltose substrate with the filtrate from a pure culture of *Bacillus macerans*. Incubation was at 37 to 40° for intervals up to 800 fifteen-minute conversion periods. Glucose was determined by the micro colorimetric method of Tauber and Kleiner.[12,13]

Fractionation of the products of a similar digest was effected by precipitating with 90% ethanol and seeding with crystalline maltose hydrate. The precipitate was not crystalline and showed an average DP of approximately 4, based on reducing value. About 0.2 g. of this precipitate was dissolved in 25 ml. of water and the solution was divided into two portions. One fraction of the solution was pretreated with salivary amylase and exhibited a doubling of reducing value, and a drop in observed rotation from +1.27 to +1.16° (sodium light, 2-dm. tube). The remaining fraction was not hydrolyzed. Aliquots of both fractions were then treated with *macerans* amylase for five conversion periods. The untreated solution showed pronounced Schardinger dextrin formation, while the predigested fraction showed no conversion to Schardinger dextrins.

Electrophoretic Analyses.—The Schardinger dextrin mixtures were resolved in solution in 0.087 *M* potassium iodide against 0.087 *M* potassium iodide electrolyte, at 190 volts and 32 m. a. for four to five hours.

Oligosaccharide acid mixtures were resolved in 1 to 2% solution in 0.1 *M* potassium acetate against 0.1 *M* potassium acetate electrolyte, at 190 volts for one to three hours.

Ascending and descending mobilities calculated under the above conditions for a synthetic mixture of alpha, beta and gamma Schardinger dextrins were α = 3.9, 3.1; β = 2.8, 2.4; and γ = 2.3, 2.2 cm.^{2} sec.$^{-1}$ v.$^{-1}$ × 10^5. Ascending mobilities calculated under the above conditions for an oxidized synthetic mixture of reducing oligosaccharides were glucose = 11.4; maltose = 8.6; amyloheptaose = 4.8 cm.^{2} sec.$^{-1}$ v.$^{-1}$ × 10^5.

(12) Tauber and Kleiner, *J. Biol. Chem.*, **99**, 249 (1932).

(13) The experimental work of this paragraph was carried out by Mrs. Doris W. Knapp.

Summary

1. Electrophoretic procedures have been developed for qualitative analysis of mixtures of Schardinger dextrins and mixtures of reducing oligosaccharides.

2. These electrophoretic procedures have been used to follow the course of action of *macerans* amylase on the homogeneous substrates, amyloheptaose and maltose.

3. *Macerans* amylase has been shown to be capable of effecting redistribution reactions among linear amylooligosaccharides concurrently with reactions involving the cyclic Schardinger dextrins.

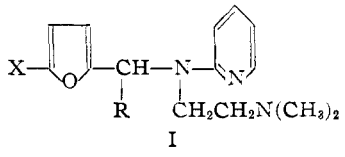
AMES, IOWA RECEIVED AUGUST 8, 1949

[A CONTRIBUTION FROM EATON LABORATORIES, INC., NORWICH, N. Y.]

Some Furan Antihistaminic Agents

BY KENYON HAYES, GABRIEL GEVER AND JAMES ORCUTT

Viaud[1] reported the high antihistaminic activity of N,N-dimethyl-N′-(2-furyl)-methyl-N′-(2-pyridyl)-ethylenediamine. This was of much interest to us because of our continuing study of the pharmaceutical applications of furan derivatives. We have prepared and tested a limited series of compounds of general structure I.



I

After this work was completed a number of the compounds presented were described by other workers in the field.[2,2a,2b]

Since the synthetic route employed differs from that of the previous workers and some of the intermediates and furylalkylethylenediamines are new, we wish to describe the work.

The general method of preparation involved the condensation of furfural or 5-halo-2-furaldehydes, with 2-aminopyridine or 2-aminothiazole to yield the azomethines. Of these, N-furfurylidene-2-aminopyridine has been reported by Ridi[3] and Ziering and Buck.[3a] In all instances investigated this condensation proceeded *via* an intermediate N,N′-furfurylidenebisamino compound, as observed by Kirpal and Reiter[4] in the case of benzaldehyde and 2-aminopyridine.

The azomethines were catalytically hydrogenated by a modification of the method of Adkins and Winans[5] to yield the N-furylmethyl-2-aminopyridines. One member of this group, N-(2-furyl)-methyl-2-aminopyridine, has been reported by Ziering and Buck[3a] without experimental directions.

In some cases the Schiff bases were reductively alkylated with a Grignard reagent by the procedure of Moffett and Hoehn.[6] The physical properties of the furylalkylamines are shown in Table I.

Some of the secondary furylalkylamines thus obtained were lithiated with lithium amide in benzene and treated with 2-dimethylaminoethyl

(1) Viaud, *Produits Pharmaceutiques*, **2**, 53 (1947).

(2) Vaughan and Anderson, THIS JOURNAL, **70**, 2607 (1948).

(2a) Kyrides and Zienty, *ibid.*, **71**, 1122 (1949).

(2b) Biel, *ibid.*, **71**, 1306 (1949).

(3) Ridi, *Gazz. chim. ital.*, **71**, 462 (1941).

(3a) Ziering and Buck, "Jubilee Vol. Emil Barell," 378 (1946). We are indebted to the Referee for pointing out Ridi's prior work on this substance. The melting point of this azomethine, as reported by these authors, is not in agreement with our findings. See Experimental.

(4) Kirpal and Reiter, *Ber.*, **60**, 664 (1927).

(5) Adkins and Winans, U. S. Patent 2,175,585 (1939).

(6) Moffett and Hoehn, THIS JOURNAL, **69**, 1792 (1947).

TABLE I

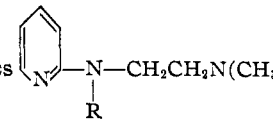
SECONDARY AMINES, R'—CH(R'')—NH—R'''

R'	R''	R'''	Method	B. p., °C.	Mm.	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-C_4H_3O	H	2-C_5H_4N	I	118–119	1.5	75	164.8–165.8[a,b]	$C_{16}H_{13}O_8N_4$[a]	47.55	47.80	3.25	3.48
2-(5-ClC_4H_2O)	H	2-C_5H_4N	I	159–161	5.0	62[c]	61	$C_{10}H_9ON_2Cl$	57.56	57.23	4.35	4.30
2-(5-BrC_4H_2O)	H	2-C_5H_4N	I	134–137	0.6	38[c]	72	$C_{10}H_9ON_2Br$	47.45	47.07	3.58	3.35
2-C_4H_3O	CH_3	2-C_5H_4N	II	110–112	1.6	81	158.5–159.5[a]	$C_{17}H_{15}O_8N_3$[a]	48.93	49.21	3.62	3.71
2-C_4H_3O	CH_3	2-C_7H_5SN	II	125–127	0.5	56	180–181[a,d]	$C_{18}H_{15}O_8SN_3$[a]	42.55	42.54	3.10	3.29
2-(5-BrC_4H_2O)	CH_3	2-C_5H_4N	II	154–156	1.6	51	159.5–160[a,e]	$C_{17}H_{14}O_8N_3Br$[a]	41.14	41.08	2.84	3.07

[a] Picrate from ethanol. [b] Hydrochloride m. p. 165–166°, ref. 6 reports 163–165°. [c] Yield based on starting aldehyde. [d] Free base m. p. 84.5–86.5°. [e] Free base m. p. 46–48°.

TABLE II

TERTIARY AMINES AND THEIR FUMARATES



Code	R	Yield, %	B. p. of bases °C.	Mm.	M. p., °C.	Formula	Fumarate salts Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Other, % Calcd.	Other, % Found	Rel. act.[a]	LD_{50},[b] mg./kg.
PBZ[c]	$C_6H_5CH_2$–	..	.....	...	...	.....	...	...	..	..	.....	...	100	126
F-150	2-$C_4H_3OCH_2$–	71	108–111[d]	0.2	142	$C_{14}H_{19}ON_3 \cdot 1^1/_2C_4H_4O_4$	57.25	57.27	6.01	6.06	N, 10.02	10.30	106	221
F-172	(2-C_4H_3O)(CH_3)CH–	82	121–126	1.0	136	$C_{15}H_{21}ON_3 \cdot C_4H_4O_4$	60.79	61.15	6.67	6.70	N, 11.42	11.37	2	...
F-176	5-Cl-2-$C_4H_2OCH_2$–	62	149–152	2.0	109	$C_{14}H_{18}ON_3Cl \cdot 1^1/_2C_4H_4O_4$	52.92	53.15	5.33	5.50	Cl, 7.82	8.06	134	232
F-180	5-Br-2-$C_4H_2OCH_2$–	85	135–140[e]	0.4	136	$C_{14}H_{18}ON_3Br \cdot C_4H_4O_4$	49.10	49.18	5.04	5.41	Br, 18.15	18.12	203	206

[a] Relative activity; PBZ taken as standard = 100. Based on amount of drug, on a free-base basis, that on the average produced a 50% relaxation of a maximal histaminic spasm of the isolated guinea pig ileum strip. [b] Acute toxicity, on a free-base basis, for 50% mortality in twenty-four hours after oral dosing in CF1 strain, male, white mice. One hundred and twenty or more mice used for each drug, calcd. by method of Bliss, *Ann. Appl. Biol.*, **22**, 134 (1935). [c] Kindly supplied by Ciba Pharmaceutical Co., Summit, N. J. [d] Literature values b. p. 117.5–118° (0.2 mm.),[2a] 136–137 (0.7 mm.),[2] 106–108° (0.02 mm.).[2b] [e] Literature value b. p. 156–158° (0.5 mm.).[2]

chloride[7] to yield the desired tetrasubstituted ethylenediamines in good yield.[8,8a]

The physical constants and summarized pharmacological data for these potential antihistaminic agents are shown in Table II. The free amines are stable, high boiling oils and form fumarate salts which are non-hygroscopic, crystalline solids.

N,N-Dimethyl-N'-(5-chloro-2-furyl)-methyl-N'-(2-pyridyl)-ethylenediamine, F-176, was also prepared by the interaction of N,N-dimethyl-N'-(2-pyridyl)-ethylenediamine[9] and 5-chloro-2-furylmethyl chloride. The latter reagent was readily prepared, although only in a crude state, from ethyl 5-chloro-2-furoate[10] by reduction with lithium aluminum hydride, using the method of Nystrom and Brown,[11] to yield 5-chloro-2-furylmethanol.[12] This in turn was converted to the chloride with thionyl chloride and pyridine by the procedure of Kirner and Jackson.[13]

(7) Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

(8) Method of Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946); (a) Djerassi, Huttrer and Scholz, U. S. Patent 2,406,594 (1946).

(9) Prepared by the method of Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

(10) Hill and Jackson, *Am. Chem. J.*, **12**, 26 (1890).

(11) Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

(12) This alcohol has recently been prepared by a Cannizzaro reaction on 5-chloro-2-furaldehyde, and carefully characterized by Hochstein and Wright, *ibid.*, **71**, 2257 (1949).

(13) Kirner and Jackson, *ibid.*, **50**, 1958 (1928).

Pharmacological Action.[14]—The compounds in Table II were tested for antihistaminic activity on strips of isolated guinea pig ileum by the method of Lee, Dinwiddie and Chen.[15] As a standard for comparison, N-benzyl-N-(2-pyridyl)-N',N'-dimethylethylenediamine hydrochloride (Pyribenzamine, PBZ)[8,8a] was used throughout (see Table II).

The three furylmethyl derivatives, F-150, F-176 and F-180, showed activities equal to, or greater than, PBZ. The 1-(2-furyl)-ethyl compound, F-172, had an activity very much less than the furylmethyl derivative.

In contrast to the report of Vaughan and Anderson[2] the acute toxicity for mice of F-150, as the fumarate salt, by intraperitoneal administration, was observed to be approximately two-thirds the toxicity of PBZ. Oral toxicities showed a similar relationship between the two compounds, as may be seen in Table II.

As the compound of greatest practical interest, F-150 was tested for protection of guinea pigs against a lethal histamine aerosol by the method of Loew, Kaiser and Moore.[16] In agreement with Viaud[1] and Vaughan and Anderson,[2] this compound was found to have an efficacy equal to PBZ.

(14) The pharmacology of some of these compounds will be reported elsewhere, in detail.

(15) Lee, Dinwiddie and Chen, *J. Pharmacol. Exptl. Ther.*, **90**, 83 (1947).

(16) Loew, Kaiser and Moore, *ibid.*, **83**, 120 (1945).

Experimental[17]

A. Azomethines Derived from Various 2-Furaldehydes and Some Heterocyclic Amines

N-(2-Furfurylidene)-2-aminopyridine.[3,3a]—One gram mole each of furfural and 2-aminopyridine in 300 ml. of dry, thiophene-free benzene was azeotropically dehydrated by vigorous refluxing under a Dean-Stark water-trap. One-half mole of water was eliminated rapidly, while ten or more hours were required to complete the reaction. The benzene was distilled off and the residual brown oil vacuum distilled; yield 83%, b. p. 114–116° (1.3 mm.). This bright yellow oil crystallized on standing. A thrice-distilled sample, the middle-half taken each time, showed a constant freezing point of 54.4°. A sample of this recrystallized from ligroin (90–120°) had an m. p. 54.5–55.0°.[18] This material is a sternutator.

Anal. Calcd. for $C_{10}H_8ON_2$: C, 69.75; H, 4.69; N, 16.27. Found: C, 69.31; H, 5.06; N, 16.32.

N,N'-(2-Furfurylidene)-bis-2-aminopyridine.—This substance was observed to be an intermediate in the preparation of the azomethine. Evaporation of an alcoholic solution of two moles of 2-aminopyridine and one mole of furfural gave a 75% yield of a white solid. In the crude state this showed a m. p. of 83–86°, washing with alcohol and ether raised the m. p. to 94–97°, as observed on the Fisher-Johns apparatus. These melting points are highly dependent on the rate of heating. Samples introduced at intervals in a cooling copper block indicate a melting point of 115–117°. The material is almost insoluble in ether and dissolves in hot alcohol and benzene probably by disproportionation into 2-aminopyridine and the azomethine.

Anal. Calcd. for $C_{15}H_{14}ON_4$: C, 67.65; H, 5.29. Found: C, 67.25; H, 5.12.

Vacuum distillation of this material causes quantitative disproportionation into 2-aminopyridine and N-(2-furfurylidene)-2-aminopyridine.

N-(2-Furfurylidene)-2-aminothiazole.—This was prepared in the same manner as the 2-aminopyridine derivative; b. p. 113–118° (1.2 mm.), m. p. 61.5–63°, when crystallized from absolute ether. The m. p. was unchanged after one month[18]; yield 50%.

Anal. Calcd. for $C_8H_6OSN_2$: C, 53.92; H, 3.39. Found: C, 54.29; H, 3.03.

N,N'-(2-Furfurylidene)-bis-2-aminothiazole.—This is an intermediate in the formation of the azomethine and was prepared in the same manner as the 2-aminopyridine isostere. This could not be recrystallized due to thermal instability but was washed with ethanol and ether; m. p. 112–114° (dependent on rate of heating).

Anal. Calcd. for $C_{11}H_{10}OS_2N_4$: C, 47.49; H, 3.67; N, 20.13. Found: C, 47.87; H, 4.03; N, 20.24.

N-(5-Chloro-2-furfurylidene)-2-aminopyridine.—This was prepared in the same manner as the furfurylidene analog. The 5-chloro-2-furaldehyde was prepared by the method of Chute and Wright.[19] This azomethine could not be distilled at a pressure of 0.5 mm. due to vigorous decomposition. It was used as prepared in benzene solution for subsequent reactions.

N-(5-Bromo-2-furfurylidene)-2-aminopyridine.—This azomethine was prepared in the same manner from 5-bromo-2-furaldehyde[20] and 2-aminopyridine. It was used without isolation because of the demonstrated thermal instability of the chloro analog.

B. Secondary Furylalkylamines Derived from Some Furfurylidene Azomethines

Two general methods were employed, of which two examples will be presented. The physical constants are presented in Table I.

N-(5-Bromo-2-furyl)-methyl-2-aminopyridine (Method I).—The solution of azomethine derived from 13.0 g. (0.074 mole) of 5-bromo-2-furaldehyde and 7.0 g. (0.075 mole) of 2-aminopyridine in 50 ml. of dry, thiophene-free benzene, as described above, was treated with 7 g. of Raney nickel[21] and hydrogenated at 70° and 3–4 atmospheres pressure. In twenty minutes the hydrogen uptake was 81% of theoretical and absorption had ceased. The catalyst was removed by filtration with the aid of Filter-Cel. The benzene was distillled off and the residual oil vacuum distilled to give 7.0 g. (38%) of product, b. p. 134–137° (0.6 mm.). This amine solidified and after recrystallization from ligroin (90–120°) gave white needles of m. p. 72°. It formed a picrate of m. p. 158–159°.

N-1-(2-Furyl)-ethyl-2-aminopyridine (Method II).—A Grignard reagent was prepared from 9.8 g. (0.4 atom) of magnesium turnings and 56 g. of methyl iodide in 150 ml. of absolute ether. A solution of 17.2 g. (0.10 mole) of N-(2-furfurylidene)-2-aminopyridine in 100 ml. of dry ether was added to the Grignard solution at reflux during thirty minutes. A white, solid complex formed rapidly. The mixture was left overnight, refluxed one hour, then cooled and cautiously poured over 400 g. of cracked ice. The magnesium complex was decomposed with 225 ml. of 4 *N* hydrochloric acid. The ether layer was discarded, the aqueous portion again washed with ether, and then brought to *p*H 8 with 20% sodium hydroxide. An oil separated, which was extracted with ether. The ether solution was dried with Drierite, the ether removed and the residual oil distilled *in vacuo*. There was obtained 15.2 g. (81%) of yellow oil of b. p. 110–112° (1.6 mm.). It gave a picrate in the form of felted needles of m. p. 158.5–159.5°.

C. Some Furylalkyl Tetrasubstituted Ethylenediamines

The physical constants of the bases and their fumarate salts are presented in Table II. All were prepared by one of the methods of Huttrer, *et al.*,[8,8a] and one example will be described as representative. F-176 was also prepared by a second method, involving a new reagent, and so will be presented.

N,N-Dimethyl-N'-(2-furyl)-methyl-N'-(2-pyridyl)-ethylenediamine (F-150).[1,2,2a,2b]—One-tenth mole (17.4 g.) of N-(2-furyl)-methyl-2-aminopyridine and 2.70 g. of lithium amide (17% excess) in 120 ml. of dry benzene were

(17) All melting points were determined on the Fisher-Johns apparatus unless otherwise indicated.

(18) References (3) and (3a) report a m. p. of 85° and 84–86°, respectively, for this substance when recrystallized from absolute ether. It appeared possible that this was a case of dimorphism since dimorphic forms of isosteric N-(2-thiophenal)-2-aminothiazole have been reported by Hantzsch and Witz, *Ber.*, **34**, 841 (1901). The lower melting form of this latter substance changed spontaneously on standing to the higher melting form, while the reverse transformation occurred on holding the material at its melting point or by crystallization from ethanol at moderate temperature. Our furfurylidene-2-aminopyridine, of freezing point 54.4°, was recrystallized from absolute ether yielding stout rods of m. p. 54.5–55.0°. The melting point of this material remained unchanged for six months in a desiccator over sulfuric acid. Attempts to recrystallize it from ethanol at 40° gave only N,N'-(2-furfurylidene)-bis-2-aminopyridine of m. p. 83–84.5° (dependent on rate of heating). *Anal.* Calcd. for $C_{15}H_{14}ON_4$: N, 21.04. Found: N, 21.18. Attempts to repeat Ridi's preparation gave only the bis-amino compound when the benzene was removed at a low enough temperature to preserve the light yellow color of the product, removal at atmospheric pressure gave a dark product which could be purified only by vacuum distillation yielding material of m. p. 54.5–55°. Thus we have been unable to obtain this azomethine in the reported high melting form.

(19) Chute and Wright, *J. Org. Chem.*, **10**, 541 (1945).

(20) Prepared by the third method of Gilman and Wright, THIS JOURNAL, **52**, 1170 (1930).

(21) Two hundred grams of Raney nickel alloy (Gilman Paint and Varnish Co., Chattanooga, Tenn.) was added rapidly to a solution of 200 g. of sodium hydroxide in one liter of water. After digesting three hours on the steam-bath the suspension was evaporated on a hot-plate until the temperature reached 150°. The slurry was diluted to one liter, 150 ml. of 20% sodium hydroxide added and boiled one hour. The aqueous portion was decanted and the nickel sludge was washed with three liters of water by decantation, allowing twenty minutes for elution, seven to ten times; neutral to litmus; washed five times with absolute alcohol and stored under absolute alcohol.

stirred at gentle reflux for two hours, at which time 95% of the theoretical amount of ammonia had been evolved. A solution of 11.7 g. (8% excess) of freshly prepared 2-dimethylaminoethyl chloride[7] in 25 ml. of dry benzene was added at reflux. Refluxing was continued eight and one-half hours. After cooling, the precipitate of lithium chloride was removed by filtration and washed with benzene. The benzene was removed from the combined filtrates by distillation and the residue vacuum distilled. The product was a viscous yellow oil of b. p. 108–111° (0.02 mm.). The yield after redistillation at 146–149° (2.0 mm.) was 17.4 g. (71%). The F-150 did not crystallize on long standing at 0°, but did yield a solid picrate of m. p. 126–126.5° (from ethanol).

Anal. Calcd. for $C_{14}H_{19}ON_3 \cdot C_6H_3O_7N_3$: C, 50.63; H, 4.68; N, 17.71. Found: C, 50.59; H, 4.48; N, 17.80.

When F-150 was treated with an excess of dry hydrogen chloride in absolute ether a white salt precipitated. When filtered with suction it appeared to be hygroscopic and rapidly changed to a green tar.[22] The salts with maleic, tartaric, oxalic and *d,l*-malic acids are hygroscopic. The salt with fumaric acid, prepared in ethyl Cellosolve (yield 91%), was stable.

N,N-Dimethyl-N′-(5-chloro-2-furyl)-methyl-N′-(2-pyridyl)-ethylenediamine, (F-176).—Twenty-five grams (0.143 mole) of ethyl 5-chloro-2-furoate, prepared by the method of Hill and Jackson[10] (The 5-chloro-2-furoic acid intermediate was analyzed. Calcd. for $C_5H_3O_3Cl$: Cl, 24.21. Found: Cl, 24.22.), was reduced with 4.0 g. of lithium aluminum hydride[11] in absolute ether at reflux during two hours. The alcoholate suspension was poured on ice and acidified with cold 20% sulfuric acid to *p*H 2. The ether extracts of the 5-chloro-2-furylmethanol[12] were washed with 2% sodium hydroxide and dried with Drierite. The ether was distilled off at atmospheric pressure giving 18.4 g. (97% yield) of water-white, crude product. This could not be vacuum distilled at 5 mm. because of vigorous decomposition. Warm, aqueous alcoholic silver nitrate gave no precipitate of silver chloride but the material gave a strong Beilstein halogen test.

A solution of 12.3 g. (0.093 mole) of the crude chlorofurfuryl alcohol in 25 ml. of absolute ether was treated with 10 ml. of dry pyridine at 0°. A solution of 12.5 g. (0.105 mole) of pure thionyl chloride in 15 ml. of dry ether was added with cooling at such a rate as to maintain the temperature below 5°. The suspension was stirred at 0° for five hours, when the ether solution was decanted from the precipitate of pyridine hydrochloride. The solid was well washed with dry ether and the ether removed from the combined extracts by distillation at 100 mm. and a bath temperature of 20°. The residual light yellow liquid was pumped thus to constant weight; 10.8 g. (77% yield). This also, was too unstable to distil *in vacuo*. The material gave a voluminous precipitate with silver nitrate.

Five-hundreths of a mole (8.25 g.) of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine[9] in 50 ml. of dry benzene was lithiated with 1.5 g. of lithium amide by refluxing four hours. After cooling to 40°, 10.8 g. (0.07 mole) of crude 5-chloro-2-furylmethyl chloride in 25 ml. of benzene was added. The suspension was stirred at 40–50° for one-half hour, then refluxed two and one-half hours. The mixture was worked up as in the previous example to yield 6.15 g. of viscous, yellow oil (44% yield based on secondary amine). This gave a fumarate from ethyl Cellosolve. The mixed melting point with F-176 fumarate prepared *via* N-(5-chloro-2-furyl)-methyl-2-aminopyridine was not depressed.

(22) During the preparation of this manuscript Kyrides and Zienty[2a] reported the successful preparation of a monohydrochloride of F-150 by the reaction of equivalent amounts of the base and hydrogen chloride in methanol–ethyl acetate. We have now prepared the stable monohydrochloride of m. p. 118–119° by their method. Biel[2b] reported a dihydrochloride of m. p. 163–164°. We have been unable to prepare a stable trihydrochloride. Excess dry hydrogen chloride in a dry benzene solution of the base gives an oil which was crystallized by cooling. Filtration in the open air caused it to become gummy, without color formation as when ether was employed as solvent.

Summary

1. Two new, and two previously reported, N,N - dimethyl - N′ - (2 - furyl) - alkyl - N′ - (2-pyridyl)-ethylenediamines have been prepared for investigation of their antihistaminic activity. An improved synthetic route has been employed to prepare these substances.

2. A number of azomethines derived from 2-furaldehyde (and 5-halo-2-furaldehydes) and 2-aminopyridine (and 2-aminothiazole) are described. These have been catalytically hydrogenated and/or subjected to reductive alkylation to give some new secondary furfurylamines.

3. A synthesis of 5-chloro-2-furylmethyl chloride is described.

4. The antihistaminic activities and acute toxicities of these furylalkylethylenediamine derivatives are briefly presented. The three 2-furylmethyl compounds of this class show an interesting combination of high activity and low toxicity.

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