Chemotherapeutic Nitrofurans. IX.[1]
2-[1-Acyl-2-(5-nitrofurfurylidene)hydrazino]acetamides

FRANK F. EBETINO, WARREN F. CAREY, AND BENJAMIN F. STEVENSON
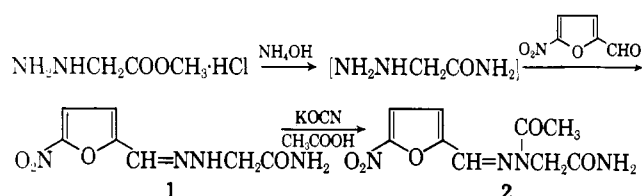
Eaton Laboratories Division, The Norwich Pharmacal Company, Norwich, New York

A series of 2-[1-acyl-2-(5-nitrofurfurylidene)hydrazino]acetamides has been synthesized and tested for antibacterial activity in mice. Structure–activity relationships are developed.

In a continuing program on the synthesis of potential chemotherapeutic nitrofurans, it was of interest to prepare 2-(5-nitrofurfurylidenehydrazino)acetamide (**1**) and some derivatives of this compound.

Methyl hydrazinoacetate hydrochloride was readily converted to the corresponding amide in concentrated ammonium hydroxide solution, and the amide was reacted without isolation with 5-nitro-2-furaldehyde to give a 75% yield of the hydrazone **1**.

NH$_2$NHCH$_2$COOCH$_3$·HCl $\xrightarrow{\text{NH}_4\text{OH}}$ [NH$_2$NHCH$_2$CONH$_2$] $\xrightarrow{\text{O}_2\text{N}\text{-furan-CHO}}$

O$_2$N—furan—CH=NNHCH$_2$CONH$_2$ **1** $\xrightarrow[\text{CH}_3\text{COOH}]{\text{KOCN}}$ O$_2$N—furan—CH=NNCH$_2$CONH$_2$ (COCH$_3$) **2**

Treatment of **1** with potassium cyanate in glacial acetic acid did not produce the expected semicarbazone, but gave a compound with an empirical formula of C$_9$H$_{10}$N$_4$O$_5$. This substance showed NH absorption bands at 2.9 and 3.1 μ and C=O bands at 5.90 and 5.97 μ in the infrared, and an absorption maximum at 368 mμ in the ultraviolet, indicating that **1** had been acetylated. The same compound was also obtained by acetylating **1** with acetic anhydride.

To determine the position of the acetyl group, the ultraviolet absorption maxima of several nitrofurans were compared. Thus, the monoalkylated hydrazone **1** absorbs at 404 mμ, whereas the acetylated mono-
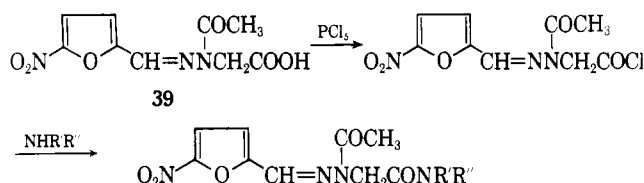
O$_2$N—furan—CH=NNCH$_3$ (COCH$_3$) **40**   O$_2$N—furan—CH=NNCH$_2$CONHCOCH$_3$ (COCH$_3$) **37**
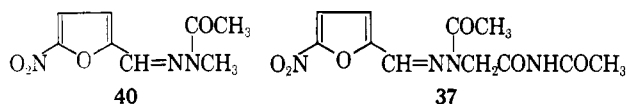
alkylated hydrazone **40** absorbs at 375 mμ.[2] Further evidence for the acetylhydrazone structure **2** is derived from the fact that the diacetylated derivative **37**, prepared from **1** or **2**, shows typical –CONHCO– absorption[3] in the infrared at 5.76 and 6.0 μ which is not exhibited by **2**. Compound **37** also absorbs at 368 mμ which is in agreement with the acetylhydrazone structure.

The antibacterial screening of **1** and **2** indicated that **2** was highly active *in vivo* against *Staphylococcus aureus* and *Salmonella typhosa*, whereas **1** was inactive.

Because of these results a synthetic program devoted to the synthesis of analogs of **2** was initiated and the compounds listed in Table I were prepared.

(1) For the preceding paper in this series, see J. G. Michels, G. Gever, and P. H. L. Wei, *J. Med. Pharm. Chem.*, **5**, 1042 (1962).

(2) F. F. Ebetino, J. J. Carroll, and G. Gever, *ibid.*, **5**, 513 (1962).

(3) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958, p. 221.

The general methods for the preparation of these compounds are as follows and examples of these methods are given in the Experimental section. (1) Acylation of **1** and other carbonyl derivatives of 2-hydrazinoacetamide with anhydrides or with acid chlorides in dimethylformamide or in pyridine. (2) Reaction of methyl hydrazinoacetate hydrochloride with amines, followed by reaction with a nitrofuran carbonyl reagent and acylation. (3) Condensation of 5-nitro-2-furaldehyde with hydrazinoacetic acid followed by acyla-

O$_2$N—furan—CH=NNCH$_2$COOH (COCH$_3$) **39** $\xrightarrow{\text{PCl}_5}$ O$_2$N—furan—CH=NNCH$_2$COCl (COCH$_3$)

$\xrightarrow{\text{NHRR''}}$ O$_2$N—furan—CH=NNCH$_2$CONR'R'' (COCH$_3$)

tion, chlorination, and reaction with amines. (4) Monoacetylation of **2** or diacetylation of **1** with acetic anhydride and sulfuric acid.

Compound **2** has been isolated in two crystal forms. The α form melts at 254° and is obtained as voluminous pale yellow needles, while the β form melts at 238–239° and exists usually as much more dense, granular, yellow rhomboids. The polymorphs were identical by elemental analysis and solution spectra in the infrared and ultraviolet. However, they differed when examined in the solid state in the infrared. The α form, which is the less stable modification, was converted to β by grinding in a mortar, shaking in water, or recrystallizing from various solvents with rapid cooling. The β form was converted to α by pouring a hot dimethylformamide, acetic acid, or dimethyl sulfoxide solution of the compound into cold water. Conversion of β to α also takes place at the melting point of β or recrystallizing from nitromethane with slow cooling to room temperature and then rapid cooling in an ice bath. The α form is more soluble in water than the β form.

Other members of this series (**12**, **16**, **18**, **34**) also exhibit polymorphism but they have not been studied as extensively.

Structure–Activity Relationships.—A tabulation of the structural variations of the compounds prepared and their *in vitro* and *in vivo* antibacterial activities are shown in Table II. Minimum inhibitory concentrations (MIC) were determined by twofold dilutions in nutrient broth inoculated with 1 × 10^4 viable cells and incubated at 37° for 24 hr. The *in vivo* biological data were obtained in male CFW mice weighing 18–20 g. Groups of 10 or 20 mice were inoculated intraperitoneally with a lethal challenge of *Staphylococcus aureus* or *Salmonella typhosa* in 5% mucin, which produced

TABLE I

$$O_2N\text{—furan—}(CH\text{—}CH)_m\text{—}\overset{R_1}{\underset{}{C}}=NNACOR_2''$$

No.	R_1	R	Method	Yield %	Solvent	M.p., °C	Formula	% Carbon Calcd.	Found	% Hydrogen Calcd.	Found	% Nitrogen Calcd.	Found
1	H	NH₂	A	73	A	205–208	C₇H₅N₃O₄	39.62	39.30	3.80	3.52	26.41	26.58
2	COCH₃	NH₂	C	86	B	238–239, 254	C₉H₁₀N₄O₅	42.52	42.33	3.97	4.13	22.01	22.32
3	H	NH₂	A	42	B	194–198	C₈H₁₀N₄O₃	45.38	45.15	4.23	4.31	23.52	23.83
4	COCH₃	NH₂	C	80	A	222–230	C₁₁H₁₂N₄O₅	47.11	46.97	4.32	4.52	19.99	19.90
5	H	NH₂	A	47	D	183.5–186.5	C₉H₁₀N₄O₃	42.44	42.44	4.46	4.46	24.77	25.01
6	COCH₃	NH₂	F	64	A	187–188	C₁₀H₁₂N₄O₅	42.78	44.60	4.51	4.57	20.89	20.51
7	H	NH₂	A	48	A	167–170	C₉H₁₀N₄O₃	42.44	42.21	4.46	4.38	24.77	24.78
8	COCH₃	NH₂	D	25	E	154–157	C₁₀H₁₂N₄O₅	41.78	44.86	4.46	4.72	20.89	20.89
9	CHO	NH₂	E	66	A	211–213	C₈H₅N₃O₃	40.00	39.98	3.36	3.51	20.89	23.12
10	COC₂H₅	NH₂	C	30	B	227–228	C₁₀H₁₂N₄O₅	44.74	44.70	4.51	4.61	20.89	20.78
11	COC₃H₇	NH₂	C	30	A	190–195.5	C₁₂H₁₄N₄O₅	46.81	46.78	5.00	4.96	19.85	20.10
12	COCH₂CH₂CH(CH₃)₂	NH₂	F	60	A	163–165	C₁₂H₁₄N₄O₅	48.64	48.69	5.44	5.41	18.91	18.91
13	COCH(CH₃)₂	NH₂	F	49	A	218–220	C₁₂H₁₄N₄O₅	46.81	46.73	5.00	5.26	19.85	19.81
14	COCH(CH₂)₄CH₂	NH₂	F	37	E	170–171	C₁₄H₁₈N₄O₅	52.17	51.91	5.63	5.68	17.38	17.43
15	COCHCl₂	NH₂	F	45	E	195–205	C₉H₉Cl₂N₄O₅	33.45	33.72	2.48	2.56	21.98	21.94
16	COCH₂C₆H₅	NH₂	F	19	A	170–172	C₁₅H₁₄N₄O₅	54.51	54.47	4.27	4.36	16.96	16.96
17	COCH=CHCH₃	NH₂	F	36	D	210–213	C₁₁H₁₂N₄O₅	47.11	47.17	4.32	4.36	19.99	19.92
18	COC₆H₅	NH₂	F	14	B	170–171	C₁₄H₁₂N₄O₅	53.16	53.16	3.82	3.94	17.22	17.54
19	COC₆H₄NO₂-p	NH₂	F	39	A	278–281	C₁₄H₁₁N₅O₇	46.54	46.33	3.05	3.08	19.39	19.25
20	SO₂C₆H₅	NH₂	G	19	B	158–163	C₁₃H₁₂N₄O₆S	44.32	44.31	3.43	3.55	19.08	19.26
21	COOCH₃	NH₂	H	28	A	240–243	C₉H₈N₄O₆	40.00	40.17	3.73	3.74	20.71	21.12
22	COOC₂H₅	NH₂	H	15	A	190–192	C₁₀H₁₂N₄O₆	42.25	42.68	4.26	4.17	19.71	19.69
23	COOC₃H₇	NH₂	H	34	A	183–185	C₁₁H₁₃N₄O₆	44.30	44.22	4.73	4.82	18.79	18.95
24	COOC₄H₉	NH₂	H	44	D	185–187	C₁₂H₁₆N₄O₆	46.15	46.43	5.16	5.23	17.94	17.96
25	COOCH₂CH(CH₃)₂	NH₂	H	39	A	163–167	C₁₂H₁₆N₄O₆	46.15	46.13	5.16	5.14	17.94	18.06
26	COOCH₂CH₂CH₂Cl	NH₂	A	80	A	149–150.5	C₈H₃ClN₄O₆	39.72	39.61	3.91	4.09	10.67	10.85
27	H	NHCH₃	D	91	E	163–165	C₁₀H₁₂N₄O₃	42.44	42.42	4.46	4.37	21.77	20.87
28	H	NHCH₃	A	58	E	203–206.5	C₁₀H₁₂N₄O₃	44.78	44.59	4.51	4.51	20.89	20.71
29	COCH₃	NHC₂H₅	A	88	E	146–148	C₉H₁₂N₄O₃	45.00	45.49	5.01	5.18	23.33	23.45
30	COCH₃	NHC₃H₇	D	63	A	204–206.5	C₁₁H₁₄N₄O₅	46.81	47.11	5.00	5.00	19.85	19.70
31	COCH₃	NHCH₂CH₂OH	J	63	F	176–176.5	C₁₀H₁₄N₄O₆	42.25	42.33	4.26	4.31	19.71	19.68
32	COCH₃	N(C₂H₅)₂	K	40	A	168–171	C₁₃H₁₈N₄O₅	50.31	50.32	5.85	6.01	18.06	18.02
33	COCH₃	NCH₂CH₂CH₂CH₂CH₂	K	42	A	206–208	C₁₃H₁₆N₄O₅	50.64	50.84	5.23	5.33	18.18	18.21
34	COCH₃	NCH₂CH₂OCH₂CH₂	K	45	A	158–160	C₁₃H₁₆N₄O₆	48.15	48.10	4.97	5.01	17.28	17.17
35	COCH₃	NCH₂(CH₂)₃CH₂	K	11	E	150–158	C₁₄H₁₈N₄O₅	52.17	52.48	5.63	5.67	17.38	17.41
36	COCH₃	NHC₆H₅	K	28	D	213–218	C₁₅H₁₄N₄O₅	54.51	54.21	4.27	4.25	16.96	16.82
37	COCH₃	NHCOCH₃	C	69	D	213.5–214.5	C₁₀H₁₂N₄O₆	41.60	45.01	4.06	4.27	18.91	19.13
38	H	OH	B	21	C	135–136	C₇H₅N₃O₅	39.44	39.83	3.31	3.45	19.72	19.85
39	COCH₃	OH	I	64	E	215–220	C₉H₅N₃O₆	42.36	42.37	3.56	3.59	16.17	16.16

Recrystallization solvents: A = ethanol, B = nitromethane, C = ethyl acetate, D = acetonitrile, E = 2-propanol, F = ... Melting points were taken on a Fisher-Johns melting point apparatus. Calcd. and found values for chlorine. Calcd. and found values for sulfur. $n = 0$, R = H, A = CH unless otherwise noted. $n = 1$, A = CHCH...

TABLE II

BIOLOGICAL ACTIVITY

$$O_2N\overset{}{\underset{O}{\square}}(CH=CH)_n\text{-}\overset{R}{\underset{}{C}}=N\overset{R_1}{\underset{}{N}}ACOR_2$$

No.	n	A	R	R₁	R₂	S. aureus	S. typhosa
						ED₅₀ (mg./kg.)/MIC (mg./100)	
				I. Variations of R₁			
				a. Hydrogen or alkanoyl			
1	0	CH₂	H	H	NH₂	>1120/>4	>1120/>4
2α	0	CH₂	H	COCH₃	NH₂	20/1	22/2
2β	0	CH₂	H	COCH₃	NH₂	120/1	120/2
3	1	CH₂	H	H	NH₂	>600/5	>600/3
4	1	CH₂	H	COCH₃	NH₂	93/0.2	>780/0.6
5	0	CHCH₃	H	H	NH₂	>330/>12	>330/>12
6	0	CHCH₃	H	COCH₃	NH₂	43/1	>840/5
7	0	CH₂	CH₃	H	NH₂	>160/>20	>160/>20
8	0	CH₂	CH₃	COCH₃	NH₂	>240/10	>240/10
9	0	CH₂	H	CHO	NH₂	55/1	28/0.3
10	0	CH₂	H	COC₂H₅	NH₂	33/1	>360/10
11	0	CH₂	H	COC₃H₇	NH₂	48/0.6	>132/20
12	0	CH₂	H	COCH₂CH(CH₃)₂	NH₂	195/0.5	>420/>15
13	0	CH₂	H	COCH(CH₃)₂	NH₂	45/0.4	>420/>20
14	0	CH₂	H	COCH(CH₂)₄CH₂	NH₂	>840/1	>840/>8
				b. Chloroalkanoyl			
15	0	CH₂	H	COCHCl₂	NH₂	>1680/—	>1680/—
				c. Arylalkanoyl			
16	0	CH₂	H	COCH₂C₆H₅	NH₂	280/0.2	>1320/>13
				d. Alkenoyl			
17	0	CH₂	H	COCH=CHCH₃	NH₂	>840/0.6	>840/5
				e. Aroyl			
18	0	CH₂	H	COC₆H₅	NH₂	28/0.6	>480/10
19	0	CH₂	H	COC₆H₄NO₂-p	NH₂	>840/—	840/—
				f. Sulfonyl			
20	0	CH₂	H	SO₂C₆H₅	NH₂	840/0.4	>840/4
				g. Alkoxycarbonyl			
21	0	CH₂	H	COOCH₃	NH₃	>210/0.8	94/0.4
22	0	CH₂	H	COOC₂H₅	NH₂	75/1	118/1
23	0	CH₂	H	COOC₃H₇	NH₂	780/1	>840/1
24	0	CH₂	H	COOC₄H₉	NH₂	>1680/—	840/—
25	0	CH₂	H	COOCH₂CH(CH₃)₂	NH₂	>420/1	420/10
26	0	CH₂	H	COOCH₂CH₂CH₂Cl	NH₂	590/1	>1680/4
				II. Variations of R₂			
				a. Monoalkylamino			
27	0	CH₂	H	H	NHCH₃	168/>20	168/20
28	0	CH₂	H	COCH₃	NHCH₃	92/1	>280/20
29	0	CH₂	H	H	NHC₂H₅	>280/>20	>280/>20
30	0	CH₂	H	COCH₃	NHC₂H₅	82/3	>1020/10
31	0	CH₂	H	COCH₃	NHCH₂OH	210/1	>210/6
				b. Dialkylamino			
32	0	CH₂	H	COCH₃	N(C₂H₅)₂	136/5	>840/>20
33	0	CH₂	H	COCH₃	NCH₂CH₂CH₂CH₂	367/3	>840/>20
34	0	CH₂	H	COCH₃	NCH₂CH₂OCH₂CH₂	87/3	>840/>20
35	0	CH₂	H	COCH₃	NCH₂(CH₂)₃CH₂	168/3	>600/>10
				c. Arylamino			
36	0	CH₂	H	COCH₃	NHC₆H₅	>840/—	>840/—
				d. Acylamino			
37	0	CH₂	H	COCH₃	NHCOCH₃	113/0.6	>1320/5
				e. Hydroxyl			
38	0	CH₂	H	H	OH	>120/>20	>120/>20
39	0	CH₂	H	COCH₃	OH	>1020/>20	>1020/>20

100% mortality in 2 to 3 days in the control groups. Varying amounts of each compound (limited by toxic considerations) were suspended in 0.75% carboxy- methylcellulose and administered orally 30 min. after infection. The criteria for activity adopted here includes graded dose–survival relationships. The

Miller Tainter method[4] was used to calculate 50% protection values (ED$_{50}$).

Effect of Variations of R$_1$.—Significant antibacterial activity is evident only when R$_1$ is alkanoyl (a), benzoyl (e), or alkoxycarbonyl (g). When R$_1$ is hydrogen, dichloroacetyl, phenylacetyl, crotonoyl, or benzenesulfonyl, activity diminishes.

In the alkanoyl series, as the chain is lengthened or branched, in vivo activity decreases against both S. aureus and S. typhosa. Decreasing the chain length to formyl lessens activity against S. aureus but not against S. typhosa. When A is a branch chain such as —CHCH$_3$ or when n = 1, staphylococcus activity is retained but salmonella activity is reduced. When R is methyl, activity is adversely affected.

When R$_1$ is unsubstituted benzoyl (e), staphylococcus activity comparable to that of the acetyl group results, but salmonella activity suffers.

Alkoxycarbonyl groups (g) show optimum in vivo activity when the alkyl group is ethyl. Increasing or decreasing the length of this alkyl chain reduces activity.

The difference in activity of 2α and 2β may be related to the different solubilities of each of the modifications.

In summary, compounds comparable to 2 against one or both bacterial infections result when R$_1$ is acetyl (6), propionyl (10), formyl (9), butyryl (11), methylpropionyl (13), benzoyl (18), and ethoxycarbonyl (22).

Effect of Variations of R$_2$.—When R$_2$ is arylamino or hydroxyl, the resulting compounds are ineffective. Simple mono and dialkylamino groups reduce salmonella activity and moderate activity against staphylococcus. Some activity against staphylococcus and salmonella occurs when R$_2$ is acetamido. The data on the compounds within this group show that alteration of the R$_2$ group (NH$_2$) of 2 diminishes antibacterial activity.

Several of these compounds produce significant blood and urine levels in laboratory animals and 9, 12, and 13 have been evaluated for these characteristics in humans. These results will be reported elsewhere.

Experimental

The preparation of the 39 substituted hydrazines reported in this paper (Table I) was accomplished by the following general methods.

A. 2-(5-Nitrofurfurylidenehydrazino)acetamide (1).—Methyl hydrazinoacetate hydrochloride[5] (1020 g., 7.25 moles) was added to 10.2 l. of 28% aqueous ammonia and the solution was allowed to stand at room temperature for 35 min. At the end of this time air was bubbled through the solution to remove excess ammonia and then acetic acid was added to pH 5. After the addition of 10 l. of water, a solution of 920 g. (6.25 moles) of 5-nitro-2-furaldehyde in 6 l. of methanol was added over 40 min. The yellow solid was collected on a filter and washed with water, 50% methanol, and then ether.

B. (5-Nitrofurfurylidenehydrazino)acetic Acid (38).—To a solution of 4.02 l. (4120 g., 70 moles) of 85% hydrazine hydrate and 826 g. (20.6 moles) of sodium hydroxide in a 12-l. flask heated to 90° was added a solution of 945 g. (10 moles) of chloroacetic acid in 1.5 l. of water over 2 hr., keeping the temperature at 100–105°. The solution was then refluxed for 1 hr. and distilled in vacuo until 3.5–4 l. of distillate were collected. The residue was treated with 5.7 l. of Polyglycol P400[6] and distillation con-

tinued until no more distillate was collected. The mixture was filtered hot and the solid rinsed several times with methanol and dried in a steam oven. The yield of impure sodium hydrazinoacetate was 1530 g.

A charcoaled solution of 500 g. (4.46 moles) of sodium hydrazinoacetate in 1.8 l. of water was adjusted to pH 6 with acetic acid with cooling, and treated with a solution of 375 g. (2.66 moles) of 5-nitro-2-furaldehyde in 2.8 l. of ethanol. After stirring for several minutes an orange precipitate separated. The mixture was cooled and the solid filtered and washed with 2-propanol. The yield of sodium (5-nitrofurfurylidenehydrazino)acetic acid was 304 g. (29%), m.p. 165–175°.

A charcoaled solution of 87 g. of the sodium salt in 1.6 l. of water was acidified with 10% hydrochloric acid and the yellow solid filtered and rinsed with water.

C. 2-[1-Acetyl-2-(5-nitrofurfurylidene)hydrazino]acetamide (2).—(1) A suspension of 35 g. (0.165 mole) of 1 in 180 ml. of acetic anhydride was heated to the boiling point and maintained at this temperature until the solid dissolved. After cooling, the solid was filtered and washed with ether.

The diacetylated compound was prepared by heating 1 or 2 with acetic anhydride on the steam bath in the presence of concentrated sulfuric acid (1 ml./0.08 mole).

(2) To a suspension of 5 g. (0.0236 mole) of 1 in 50 ml. of glacial acetic acid was added 4 g. (0.0494 mole) of potassium cyanate. After the addition of 25 ml. of acetic acid, the mixture was allowed to stand at room temperature for 18 hr. The insoluble solid (3.2 g. (64%) of 1) was filtered and the filtrate diluted with 100 ml. of water to give 0.65 g. (10.8%) of 2. Concentrating the filtrate and diluting the residual oil with water gave a second crop of 2 (0.45 g., 7.5%).

D.—This method is the same as C–1 except that the mixture was heated at steam bath temperature.

E. 2-[1-Formyl-2-(5-nitrofurfurylidene)hydrazino]acetamide (9).—A mixture of 176 ml. (1.87 moles) of acetic anhydride and 74 ml. (1.95 moles) of 98% formic acid was heated at 50–60° for 2 hr. with stirring. The solution was cooled to 30°, and 50 g. (0.236 mole) of 1 added while maintaining the temperature at 32°. The mixture was stirred at room temperature for 2 hr., cooled, and the solid filtered and rinsed with ether.

F. 2-[1-Isovaleryl-2-(5-nitrofurfurylidene)hydrazino]acetamide (12).—To a suspension of 106 g. (0.5 mole) of 1 in 375 ml. of dimethylformamide was added 70 ml. (0.575 mole) of isovaleryl chloride with cooling to maintain a temperature of 20°. After 30 min. at room temperature, the solution was poured into 2250 ml. of water and the precipitate filtered and washed with water. In some cases it was necessary to add sodium carbonate solution to the water to promote crystallization.

G.—This method is similar to F except that pyridine was used in place of dimethylformamide.

H.—This method is similar to F except that 3–4 moles of acid chloride per mole of 1 were used.

I. [1-Acetyl-2-(5-nitrofurfurylidene)hydrazino]acetic Acid (39).—A suspension of 100 g. (0.425 mole) of sodium (5-nitrofurfurylidenehydrazino)acetate (Method B) in 300 ml. of acetic anhydride was heated on a steam bath for 10 min. with stirring. The mixture was cooled and treated with ether to give a yellow solid (111 g.). The solid was added to 2100 ml. of water and the mixture adjusted to pH 8 with 10% sodium carbonate solution. After adding a filtering aid (Celite) the mixture was filtered and the filtrate acidified with 10% hydrochloric acid to give a yellow solid.

J. 2-[1-Acetyl-2-(5-nitrofurfurylidene)hydrazino]-N-hydroxymethylacetamide (31).—To 4.5 g. (0.018 mole) of 2 in 5 ml. of 37% formaldehyde diluted with 15 ml. of water was added 0.1 g. of sodium carbonate. The mixture was heated at the boiling point for 15 min. and then filtered. The precipitate which separated on cooling was collected and washed with 25 ml. of water, 7 ml. of methanol, and 25 ml. of ether.

K. 2-[1-Acetyl-2-(5-nitrofurfurylidene)hydrazino]-N,N-diethylacetamide (32).—A stirred suspension of 76.5 g. (0.3 mole) of 39 (Method I) in 950 ml. of benzene was treated with 67.5 g. (0.325 mole) of phosphorus pentachloride and heated at 45° until hydrogen chloride evolution subsided. In this manner the temperature was increased to the boiling point 5° at a time and then the mixture was heated at the boiling point for several minutes. The hot mixture was stirred under vacuum (water pump) until the internal temperature dropped to 20° and then filtered. The filtrate was treated with diethylamine with stir-

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ring and cooling until just basic. The solid was filtered and washed with benzene and water.

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Dr. John C. Howard for preparing compound **31**, and to the Microbiology and Physical and Analytical sections for supplying the biological, analytical, and ultraviolet absorption data.

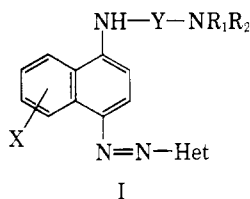# N-Mono- and N,N-Dialkyl-N'-1-naphthylalkylenediamines

Leslie M. Werbel, David B. Capps, Edward F. Elslager, William Pearlman.
Franklin W. Short, Enta A. Weinstein, and Donald F. Worth

*Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan*

A series of N-mono- and N,N-dialkyl-N'-1-naphthylalkylenediamines were prepared by: (1) alkylation of 1-naphthylamine with an alkylaminoalkyl halide; (2) reductive alkylation of 1-naphthylamine with an amino aldehyde or ketone; (3) treatment of a N-(ω-haloalkyl)-1-naphthylamine with an amine; (4) reaction of 1-naphthol with an alkylenediamine; (5) the action of ethylene oxide, aldehydes, or alkyl halides on a N-(1-naphthyl)ethylenediamine. The use of sodium hydrosulfite in the Bucherer reaction with 1-naphthol is described. 1-(1-Naphthyl)aziridine was prepared by the action of strong base on N-(2-bromoethyl)-1-naphthylamine.

During the course of continuing efforts in these Laboratories to develop new schistosomicidal agents, it was discovered that various 4-(aminoalkylamino)-1-naphthylazo heterocyclic compounds of structure I exhibit strong therapeutic activity against *Schistosoma mansoni* infections in experimental animals.[1,2] The synthesis of many of these azo compounds required the preparation of the corresponding N-mono- and N,N-di-

NH—Y—NR₁R₂ structure

I

alkyl-N'-1-naphthylalkylenediamines (II), where R_1 and R_2 represent hydrogen, alkyl, or aralkyl groups, Y an alkylene radical, and X a hydrogen or halogen atom or alkoxy group. This paper describes in detail the methods used for the synthesis of these intermediates.

Chart A outlines the major synthetic routes used in the present work. The classic technique for the attachment of an alkylaminoalkyl side chain to an aromatic amine involves alkylation of the amine with an alkylaminoalkyl halide in ethanol[3] or in a hydrocarbon solvent in the presence of an acid acceptor such as potassium carbonate.[4] Where the alkylaminoalkyl halides are readily available,[5] the latter method affords a convenient route since the salts can be used directly (method I, Tables I and II). When the carbonate pro-

Chart A
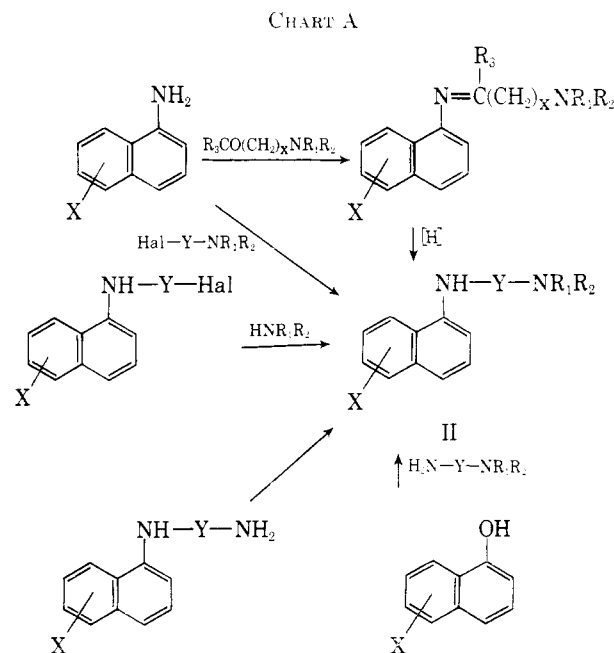
cedure gave poor yields or where it was necessary to prepare the intermediate aminoalkyl halides[6-14] from the corresponding amino alcohols, it was often advantageous to pre-form the more reactive anion of the aromatic amine, utilizing sodium hydride (method II, Tables I and II) or sodamide. Although no extensive comparisons of these methods were made, the sensitivity of the reaction to temperature and base is illustrated by the condensation of 1-naphthylamine with

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(5) The hydrochloride salts of N,N-dimethyl-2-chloroethylamine, 2-chlorotriethylamine, N-(2-chloroethyl)diisopropylamine, N,N-diethyl-3-chloropropylamine, N,N-dimethyl-2-chloropropylamine, and 3-chloro-N,N,2-trimethylpropylamine were purchased from the Michigan Chemical Co., St. Louis, Mich.; 2-bromotriethylamine hydrobromide from Columbia Organic Chemical Co., Columbia, So. Carolina; N-2-chloroethylpyrrolidine hydrochloride from the Aldrich Chemical Co., Milwaukee, Wis.

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