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

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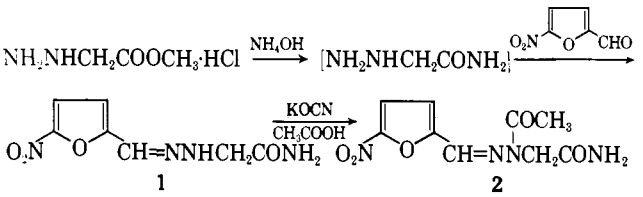
A series of 2-[1-acyl-2-(5-nitrofurfurylidene)hydrazino]acetamides has been synthesized and tested for antibacterial activity in mice. Structure–activity relationships are developed.

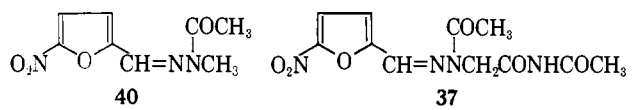
In a continuing program on the synthesis of potential chemotherapeutic nitrofurans, it was of interest to prepare 2-(5-nitrofurfurylidenehydrazino)acetamide (**1**) and some derivatives of this compound.

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**.



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 $C_9H_{10}N_4O_5$. 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-



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.

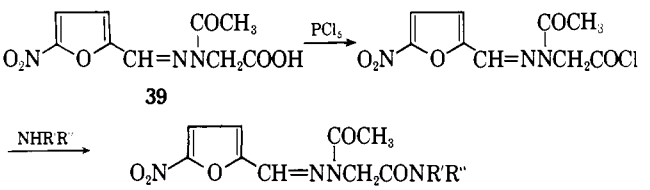
Because of these results a synthetic program devoted to the synthesis of analogs of **2** was initiated and the compounds listed in Table I were prepared.

(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-



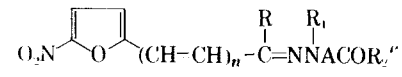
tion, chlorination, and reaction with amines. (4) Monoacetylation of **2** or diacetylation of **1** with acetic anhydride and sulfuric acid.

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

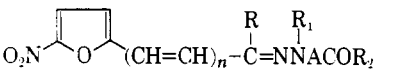


No.	R_1	R	Method	Yield, %	Solvent[a]	M.p., °C.[b]	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
1	H	NH_2	A	75	A	205–208	$C_5H_5N_3O_4$	39.62	39.30	3.80	3.52	26.41	26.58
2	$COCH_3$	NH_2	C	86	B	238–239, 254	$C_9H_{10}N_4O_5$	42.52	42.33	3.97	4.13	22.04	22.32
3[c]	H	NH_2	A	42	B	194–198	$C_5H_{10}N_4O_7$	45.38	45.15	1.23	4.34	23.52	23.83
4[d]	$COCH_3$	NH_2	C	80	A	222–230	$C_{11}H_{12}N_4O_8$	47.14	46.97	4.32	4.52	19.99	19.90
5[e]	H	NH_2	A	47	D	183.5–186.5	$C_8H_{10}N_4O_5$	42.48	42.48	4.46	4.46	24.77	25.01
6[e]	$COCH_3$	NH_2	F	68	A	187–188	$C_{10}H_{12}N_4O_6$	44.78	44.60	4.51	4.57	20.89	20.51
7[h]	H	NH_2	A	48	A	167–170	$C_8H_{10}N_4O_5$	42.48	42.21	4.46	4.38	24.77	24.78
8[h]	$COCH_3$	NH_2	D	27	E	154–157	$C_{10}H_{12}N_4O_6$	44.78	44.86	4.51	4.72	20.89	20.89
9	CHO	NH_2	E	66	A	211–213	$C_5H_6N_4O_4$	40.00	39.98	3.36	3.51	23.33	23.12
10	COC_2H_5	NH_2	C	30	B	227–228	$C_{10}H_{12}N_4O_6$	44.78	44.70	4.51	4.61	20.89	20.78
11	COC_3H_7	NH_2	C	30	A	190–195.5	$C_{11}H_{14}N_4O_6$	46.81	46.78	5.00	4.96	19.85	20.10
12	$COCH_2CH_2(CH_3)_2$	NH_2	F	60	A	163–165	$C_{12}H_{16}N_4O_6$	48.64	48.69	5.44	5.41	18.91	18.91
13	$COCH(CH_3)_2$	NH_2	F	49	A	218–220	$C_{11}H_{14}N_4O_6$	46.81	46.73	5.00	5.28	19.85	19.81
14	$COCH(CH_2)_4CH_2$	NH_2	F	37	E	170–171	$C_{14}H_{18}N_4O_6$	52.17	51.91	5.63	5.68	17.38	17.43
15	$COCHCl_2$	NH_2	F	48	E	195–205	$C_8H_8Cl_2N_4O_6$	33.45	33.72	2.48	2.56	21.98[g]	21.92[g]
16	$COCH_2C_6H_5$	NH_2	F	49	A	170–172	$C_{15}H_{14}N_4O_6$	54.54	54.47	4.27	4.35	16.96	16.96
17	$COCH{=}CHCH_3$	NH_2	F	38	D	210–213	$C_{11}H_{12}N_4O_6$	47.14	47.17	4.32	4.36	19.99	19.92
18	COC_6H_5	NH_2	F	14	A	170–171	$C_{14}H_{12}N_4O_6$	53.16	53.16	3.82	3.98	17.72	17.54
19	$COC_6H_4NO_2$-*p*	NH_2	F	39	B	278–281	$C_{14}H_{11}N_5O_8$	46.54	46.53	3.07	3.08	19.39	19.25
20	$SO_2C_6H_5$	NH_2	G	19	A	158–163	$C_{13}H_{12}N_4O_8S$	44.32	44.34	3.43	3.55	9.08	9.26
21	$COOCH_3$	NH_2	H	28	B	240–243	$C_9H_{10}N_4O_6$	40.00	40.17	3.75	3.78	20.74	21.12
22	$COOC_2H_5$	NH_2	H	45	A	190–192	$C_{10}H_{12}N_4O_6$	42.25	42.58	4.26	4.47	19.71	19.69
23	$COOC_3H_7$	NH_2	H	34	A	183–185	$C_{11}H_{14}N_4O_6$	44.30	44.22	4.73	4.82	18.79	18.97
24	$COOC_4H_9$	NH_2	H	44	A	185–187	$C_{12}H_{16}N_4O_6$	46.15	46.43	5.16	5.25	17.94	17.96
25	$COOCH_2CH(CH_3)_2$	NH_2	H	39	D	163–167	$C_{12}H_{16}N_4O_6$	46.15	46.13	5.16	5.14	17.94	18.06
26	$COOCH_2CH_2CH_2Cl$	NH_2	H	32	A	149–150.5	$C_{11}H_{13}ClN_4O_6$	39.72	39.61	3.94	4.09	10.67[g]	10.85[g]
27	H	$NHCH_3$	A	80	A	163–165	$C_8H_{10}N_4O_5$	42.48	42.42	4.46	4.37	24.77	24.81
28	$COCH_3$	$NHCH_3$	D	91	E	203–206.5	$C_{10}H_{12}N_4O_6$	44.78	44.59	4.51	4.51	20.89	20.74
29	H	NHC_2H_5	A	58	E	145–148	$C_9H_{12}N_4O_5$	45.00	45.19	5.04	5.18	23.33	23.47
30	$COCH_3$	NHC_2H_5	D	88	A	204–206.5	$C_{11}H_{14}N_4O_6$	46.81	47.14	5.00	5.00	19.85	19.70
31	$COCH_3$	$NHCH_2OH$	J	63	F	176–176.5	$C_{10}H_{12}N_4O_7$	42.25	42.33	4.26	4.34	19.71	19.68
32	$COCH_3$	$N(C_2H_5)_2$	K	40	A	168–171	$C_{13}H_{18}N_4O_6$	50.31	50.32	5.85	6.01	18.06	18.02
33	$COCH_3$	$NCH_2CH_2CH_2CH_2$	K	42	A	206–208	$C_{13}H_{16}N_4O_6$	50.64	50.84	5.23	5.33	18.18	18.21
34	$COCH_3$	$NCH_2CH_2OCH_2CH_2$	K	45	A	158–160	$C_{12}H_{16}N_4O_7$	48.15	48.10	4.97	5.04	17.28	17.17
35	$COCH_3$	$NCH_2(CH_2)_3CH_2$	K	41	E	150–158	$C_{14}H_{18}N_4O_6$	52.17	52.18	5.63	5.67	17.38	17.41
36	$COCH_3$	NHC_6H_5	K	28	D	213–218	$C_{15}H_{14}N_4O_6$	54.54	54.21	4.27	4.25	16.96	16.82
37	$COCH_3$	$NHCOCH_3$	C	69	D	213.5–214.5	$C_{11}H_{12}N_4O_8$	44.60	45.01	4.08	4.25	18.91	19.13
38	H	OH	B	24	C	135–136	$C_5H_5N_3O_5$	39.44	39.33	3.31	3.45	19.72	19.87
39	$COCH_3$	OH	I	64	E	215–220	$C_8H_9N_3O_6$	42.36	42.37	3.56	3.59	16.47	16.46

[a] Recrystallization solvents. A = ethanol, B = nitromethane, C = ethyl acetate, D = acetonitrile, E = 2-propanol, F = 7% formaldehyde. [b] Caled. and found values for chlorine. [c] Caled. and found values for sulfur. [d] Melting points were taken on a Fisher-Johns melting point apparatus. [e] $n = 0$, R = H, A = CH_2 unless otherwise noted. [f] $n = 1$. [g] A = $CHCH_3$. [h] R = CH_3.

TABLE II

BIOLOGICAL ACTIVITY



No.	n	A	R	R_1	R_2	ED_{50} (mg./kg.)/MIC (mg./100) *S. aureus*	ED_{50} (mg./kg.)/MIC (mg./100) *S. typhosa*
				I. Variations of R_1			
				a. Hydrogen or alkanoyl			
1	0	CH_2	H	H	NH_2	>1120/>4	>1120/>4
2α	0	CH_2	H	$COCH_3$	NH_2	20/1	22/2
2β	0	CH_2	H	$COCH_3$	NH_2	120/1	120/2
3	1	CH_2	H	H	NH_2	>600/5	>600/3
4	1	CH_2	H	$COCH_3$	NH_2	93/0.2	>780/0.6
5	0	$CHCH_3$	H	H	NH_2	>330/>12	>330/>12
6	0	$CHCH_3$	H	$COCH_3$	NH_2	43/1	>840/5
7	0	CH_2	CH_3	H	NH_2	>160/>20	>160/>20
8	0	CH_2	CH_3	$COCH_3$	NH_2	>240/10	>240/10
9	0	CH_2	H	CHO	NH_2	55/1	28/0.3
10	0	CH_2	H	COC_2H_5	NH_2	33/1	>360/10
11	0	CH_2	H	COC_3H_7	NH_2	48/0.6	>132/20
12	0	CH_2	H	$COCH_2CH(CH_3)_2$	NH_2	195/0.5	>420/>15
13	0	CH_2	H	$COCH(CH_3)_2$	NH_2	45/0.4	>420/>20
14	0	CH_2	H	$COCH(CH_2)_4CH_2$	NH_2	>840/1	>840/>8
				b. Chloroalkanoyl			
15	0	CH_2	H	$COCHCl_2$	NH_2	>1680/—	>1680/—
				c. Arylalkanoyl			
16	0	CH_2	H	$COCH_2C_6H_5$	NH_2	280/0.2	>1320/>13
				d. Alkenoyl			
17	0	CH_2	H	$COCH{=}CHCH_3$	NH_2	>840/0.6	>840/5
				e. Aroyl			
18	0	CH_2	H	COC_6H_5	NH_2	28/0.6	>480/10
19	0	CH_2	H	$COC_6H_4NO_2$-*p*	NH_2	>840/—	840/—
				f. Sulfonyl			
20	0	CH_2	H	$SO_2C_6H_5$	NH_2	840/0.4	>840/4
				g. Alkoxycarbonyl			
21	0	CH_2	H	$COOCH_3$	NH_2	>210/0.8	94/0.4
22	0	CH_2	H	$COOC_2H_5$	NH_2	75/1	118/1
23	0	CH_2	H	$COOC_3H_7$	NH_2	780/1	>840/1
24	0	CH_2	H	$COOC_4H_9$	NH_2	>1680/—	840/—
25	0	CH_2	H	$COOCH_2CH(CH_3)_2$	NH_2	>420/1	420/10
26	0	CH_2	H	$COOCH_2CH_2CH_2Cl$	NH_2	590/1	>1680/4
				II. Variations of R_2			
				a. Monoalkylamino			
27	0	CH_2	H	H	$NHCH_3$	168/>20	168/20
28	0	CH_2	H	$COCH_3$	$NHCH_3$	92/1	>280/20
29	0	CH_2	H	H	NHC_2H_5	>280/>20	>280/>20
30	0	CH_2	H	$COCH_3$	NHC_2H_5	82/3	>1020/10
31	0	CH_2	H	$COCH_3$	$NHCH_2OH$	210/1	>210/6
				b. Dialkylamino			
32	0	CH_2	H	$COCH_3$	$N(C_2H_5)_2$	136/5	>840/>20
33	0	CH_2	H	$COCH_3$	$NCH_2CH_2CH_2CH_2$	367/3	>840/>20
34	0	CH_2	H	$COCH_3$	$NCH_2CH_2OCH_2CH_2$	87/3	>840/>20
35	0	CH_2	H	$COCH_3$	$NCH_2(CH_2)_3CH_2$	168/3	>600/>10
				c. Arylamino			
36	0	CH_2	H	$COCH_3$	NHC_6H_5	>840/—	>840/—
				d. Acylamino			
37	0	CH_2	H	$COCH_3$	$NHCOCH_3$	113/0.6	>1320/5
				e. Hydroxyl			
38	0	CH_2	H	H	OH	>120/>20	>120/>20
39	0	CH_2	H	$COCH_3$	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% carboxymethylcellulose 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 continued 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 100 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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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

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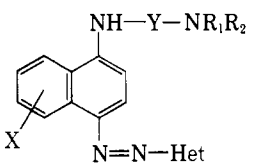
A series of N-mono- and N,N-dialkyl-N′-1-naphthylalkylenediamines were prepared by: (1) alkylation of 1-naphthylamine with an alkylaminoalkyl halide; (2) reductive alkylation of 1-naphthylamine with an amino aldehyde or ketone; (3) treatment of a N-(ω-haloalkyl)-1-naphthylamine with an amine; (4) reaction 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-



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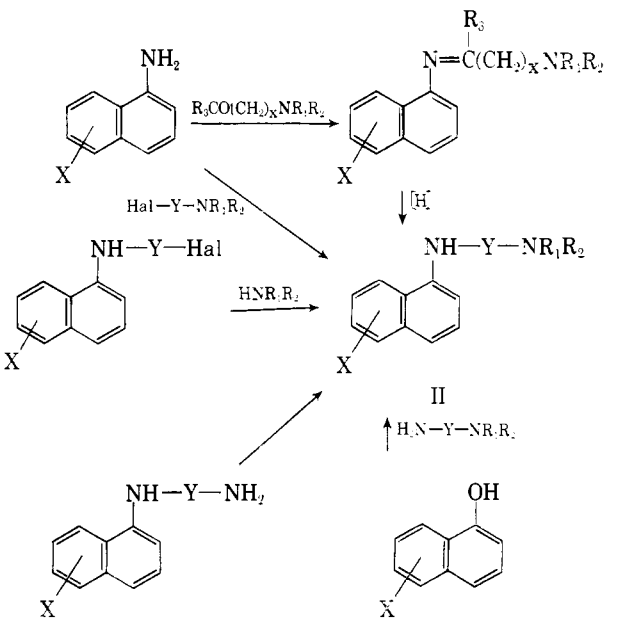
alkyl-N′-1-naphthylalkylenediamines (II), where R_1 and R_2 represent hydrogen, alkyl, or aralkyl groups, Y an alkylene radical, and X a hydrogen or halogen atom or alkoxy group. This paper describes in detail the methods used for the synthesis of these intermediates.

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 procedure 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

Chart A



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