Substituted s-Triazoles and Related Compounds

HARRY L. YALE AND JOSEPH J. PIALA

The Squibb Institute for Medical Research, New Brunswick, New Jersey

Received September 7, 1965

5-(*p*-Aminophenyl)-*s*-triazole-3-thiol, administered intraperitoneally into the rat, produced diuresis and natriuresis. The synthesis and subsequent screening of a number of related derivatives made possible a correlation of structure with activity.

The diuretic and natriuretic activity seen in the rat following the intraperitoneal administration of 5-(*p*-aminophenyl)-*s*-triazole-3-thiol (**9**) indicated that a new class of diuretic compounds had been found, and a number of related compounds were synthesized to exploit this lead. Examples of the preparative methods employed are shown in Charts I–V.

Structure–Activity Relationships.—The most potent compound was **9**; elimination of the 3-SH group (**2**) or the *p*-amino group (**8**) resulted in complete loss of diuretic and natriuretic activity; conversion of the 3-SH group in **9** to $-SCH_2CO_2H$ or $-SCH_3$ also resulted in complete loss of activity; and, finally, replacement of the 3-SH group in **9** by $-NH_2$ and acetylation of the 5-(p-$H_2NC_6H_5$) group (**32**) gave an inactive compound. Weakly active compounds were obtained from **9** by (a) conversion of the 3-SH group to $-SO_2NH_2$ (**26**), or (b) replacement of the 5-(p-$H_2NC_6H_5$) group by 4-pyridyl

CHART I

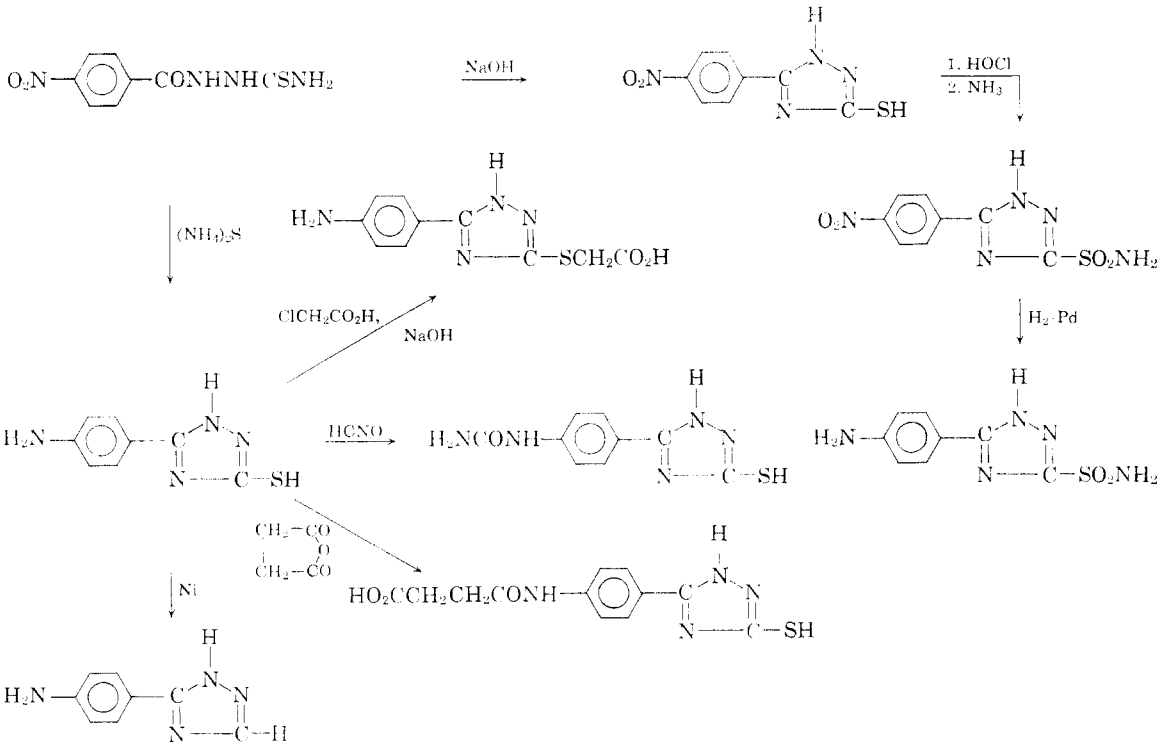
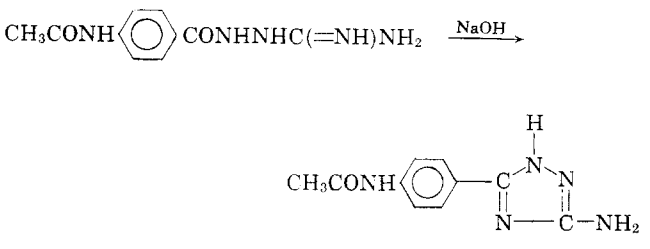


CHART II



The triazoles prepared are listed in Table I, along with their physical constants, analyses, and diuretic and natriuretic activities[1]; a number of intermediate 1-aroyl-3-thiosemicarbazides are listed in Table II, along with their physical constants and analyses.

(1) Diuretic and natriuretic activities of this series of compounds were determined in male albino rats weighing 140 to 240 g. The animals, fasted for 18 hr. before each test, were deprived of both food and water through the experiment. At zero time they received intraperitoneally the test compound dissolved in 0.9% saline solution or suspended in 0.25% agar solution, depending upon the solubility of the compound, along with an oral hydrating dose of 0.9% saline for a total fluid intake of 25 ml./kg. Each compound was administered at the LD_5 level, roughly approximated in several rats. The four rats receiving the compound were placed in metabolism cages, from which the spontaneously voided urine of all was collected 5 and 24 hr. later. Aliquots of each specimen were analyzed for Na^+ by means of a Process and Instruments flame photometer. Control outputs were obtained concomitantly in rats that received the hydrating solution only. Urine and sodium outputs in Table I are expressed as percentages of water and sodium input, respectively.

CHART III

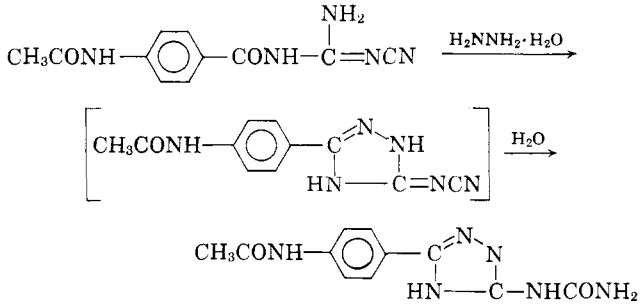


CHART IV

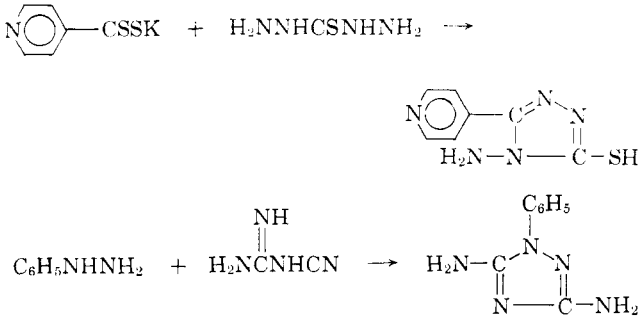
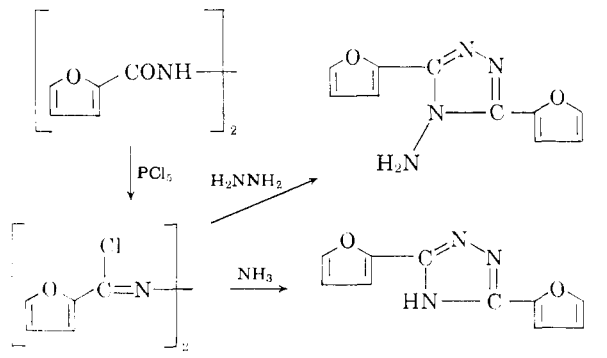


CHART V



(**19**) (the 2-pyridyl, 3-pyridyl, and 4-quinolyl compounds **17**, **18**, and **21**, respectively, were inactive). The substitution in **9** of the 5-(*p*-$H_2NC_6H_4$) group by 2-pyrazinyl (**22**) gave a weakly active diuretic but an ineffective natriuretic agent. Substitution of the 5-(*p*-$H_2NC_6H_4$) group of **9** by *p*-HOC_6H_4 (**10**), *p*-H_2NSO_2-C_6H_4 (**11**), or *p*-$H_2NCONHC_6H_4$ (**12**) resulted in a decrease or complete loss of activity. Introduction of an *o*-hydroxy group into **9** gave **16**, possessing good diuretic but no natriuretic properties. The dose of **29** required to achieve good diuretic and natriuretic activity was impractical. All other structural modifications of **9** gave, in general, inactive compounds.

Experimental Section

3-Phenyl-*s*-triazole (1). Method A.—A mixture of 9.0 g. (0.11 mole) of **8**, 100 ml. of absolute ethanol, and 15 g. of Davison sponge nickel (filtered with suction but still damp) was refluxed for 3 hr. and filtered hot. The filtrate, concentrated from the steam bath, gave an oil which crystallized spontaneously; recrystallization from equal parts of toluene–Skellysolve E gave 5.0 g. of **1**.

***p*-(*s*-Triazol-5-yl)phenylurea (6). Method B.**—To 6.0 g. (0.031 mole) of **2** in 40 ml. of 1 *N* aqueous HCl was added 3.4 g. (0.042 mole) of potassium cyanate. Reaction was prompt and a solid separated. This was filtered and recrystallized from propanol to give **6**.

4-(*s*-Triazol-5-yl)succinanilic Acid (7). Method C.—A mixture of 8.0 g. (0.042 mole) of **2**, 5.0 g. (0.05 mole) of succinic anhydride, and 600 ml. of anhydrous acetonitrile was stirred and refluxed for 18 hr. and cooled; the solid was filtered and dried to give 11.0 g. of material, m.p. 248–250°. Recrystallization from 95% ethanol gave 4.0 g. of **7**.

5-Phenyl-*s*-triazole-3-thiol (8). Method D.—A solution of 70.0 g. (0.36 mole) of 1-benzoyl-3-thiosemicarbazide in 360 ml. of 5% aqueous NaOH was heated for 4 hr. on the steam bath, cooled, and acidified with glacial acetic acid. The solid which separated was filtered and recrystallized from water to give 47.8 g. of **8**.

5-(*p*-Aminophenyl)-*s*-thiazole-3-thiol (9). Method E.—A mixture of 26.0 g. (0.19 mole) of 1-(*p*-nitrobenzoyl)-3-thiosemicarbazide and 175 ml. of commercial 20% aqueous ammonium sulfide solution was heated on the steam bath for 1.5 hr. in an open flask maintaining a constant volume by the addition of water. The hot solution was filtered rapidly from the precipitated sulfur and the filtrate was cooled. The solid which separated was filtered and recrystallized from water to give 14.7 g. of **9**.[2]

***p*-(3-Mercapto-*s*-triazol-5-yl)phenylurea (12). Method F.**—To a solution of 6.7 g. (0.035 mole) of **2** in 3500 ml. of water at 70° was added 4.34 g. (0.043 mole) of nitrourea; the mixture was kept 10 min. at 80°, heated to boiling, allowed to cool, and filtered. The filtrate, when concentrated *in vacuo* to about 100 ml. and cooled, gave 5.0 g. of solid. Recrystallization from water gave 4.0 g. of **12**.

3-Ethyl-1-[*p*-(3-mercapto-*s*-triazol-5-yl)phenyl]urea (13). Method G.—A mixture of 5.8 g. (0.03 mole) of **2**, 1000 ml. of anhydrous acetonitrile, and 4.4 g. (0.06 mole) of ethyl isocyanate was refluxed for 16 hr. and cooled, and the solid was filtered to give 7.5 g. of crude **13**, m.p. >310°. Recrystallization from 95% ethanol gave 6.3 g. of **13**.

3-(Methylthio)-5-(4-pyridyl)-*s*-triazole (24). Method H.—To 53.4 g. (0.3 mole) of **19** and 20.0 g. (0.3 mole) of 85% KOH in 500 ml. of methanol was added 43.0 g. (0.3 mole) of methyl iodide, dropwise. Subsequently, the mixture was refluxed gently for 3 hr. and concentrated to dryness on the steam bath, and 150 ml. of water was added. A clear solution formed momentarily and then a solid separated; this was filtered and recrystallized from water to give 27.6 g. of **24**.

5-(*p*-Aminophenyl)-*s*-triazol-3-ylmercaptoacetic Acid (25). Method I.—A mixture of 10.0 g. (0.056 mole) of **9**, 5.3 g. (0.056 mole) of chloroacetic acid, and 4.5 g. (0.12 mole) of NaOH was refluxed for 2 hr., cooled, and acidified with acetic acid. The solid which crystallized slowly from the acid solution was filtered and recrystallized from water to give 11.5 g. of **25**.

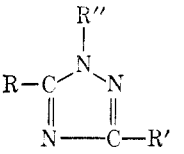
5-(*p*-Aminophenyl)-*s*-triazole-3-sulfonamide (26). Method J.—5-(*p*-Nitrophenyl)-*s*-triazole-3-thiol was prepared by method D in 73% yield, m.p. 253–255° dec., after recrystallization from water (*Anal.* Calcd. for $C_8H_6N_4O_2S$: C, 43.24; H, 2.72; N, 25.21. Found: C, 43.08; H, 2.73; N, 24.87.). A stirred suspension of 25.0 g. (0.113 mole) of the ***p*-nitrophenyl derivative,** in 400 ml. of 2 *N* aqueous HCl was maintained at 5–8° while diffused with chlorine gas for 2 hr. The sulfonyl chloride was filtered and added gradually with stirring to 400 ml. of concentrated aqueous NH_3, and the mixture was kept for 18 hr. at room temperature. The trace of solid was filtered and the filtrate was acidified with glacial acetic acid. After filtration and air drying, the solid weighed 21.0 g., m.p. 216–218° dec. Recrystallization from 50% ethanol gave 12.0 g. (40% yield) of 5-(*p*-nitrophenyl)-*s*-triazole-3-sulfonamide, m.p. 244–246° dec. (*Anal.* Calcd. for $C_8H_7N_5O_4S$: C, 35.68; H, 2.62; N, 26.01. Found: C, 35.43; H, 2.55; N, 25.35.). The product from the previous step (12.0 g.) was dissolved in 200 ml. of warm 95% ethanol, 2 g. of 5% palladium on charcoal in 50 ml. of 95% ethanol was added, and the mixture was hydrogenated under 3.5 kg./cm.^{2} for 0.25 hr. The catalyst was filtered, the filtrate was concentrated to dryness, and the residue was recrystallized from water to give 7.0 g. of **26**.

5-(4-Acetamidophenyl)-3-amino-*s*-triazole Hydrate (32).

(2) These reactants were reported by J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martin, and W. A. Lott [*J. Am. Chem. Soc.*, **73**, 906 (1951)] to yield 1-(*p*-aminobenzoyl)-3-thiosemicarbazide. The compound was, in fact, an unusually stable monohydrate of **9**, since drying at 137° *in vacuo* was required to obtain anhydrous **9**. The authors are grateful to Dr. E. Hoggarth of Imperial Chemicals Industries for first calling their attention to the correct structure.

TABLE I

SUBSTITUTED s-TRIAZOLES AND RELATED COMPOUNDS



No.	R	R′	R″	Method of prepn. (see Exptl. Section)	Recrystn. solvent	Yield, %	M.p., °C.
1	C_6H_5	H	H	A	*a*	58	116–117[b]
2	*p*-$H_2NC_6H_4$	H	H	A	*c*, *d*	42	187–189
3	3-Pyridyl	H	H	A	*e*	58	160–162
4	4-Pyridyl	H	H	A	*f*	63	214–216
5	*p*-(H_2NSO_2)C_6H_4	H	H	A	*f*	50	263–266
6	*p*-(H_2NCONH)C_6H_4	H	H	B	*i*	48	237–238 dec.
7	*p*-($HO_2CCH_2CH_2CONH$)C_6H_4	H	H	C	*j*	40	250–251
8	C_6H_5	SH	H	D	*f*	54	253–255[k]
9	*p*-$H_2NC_6H_4$	SH	H	E	*f*	62	300–301
10	*p*-HOC_6H_4	SH	H	D	*f*	40	289–291
11	*p*-(H_2NSO_2)C_6H_4	SH	H	D	*m*	76	299–300 dec.
12	*p*-(H_2NCONH)C_6H_4	SH	H	F	*f*	42	280–282 dec.
13	*p*-($C_2H_5NHCONH$)C_6H_4	SH	H	G	*j*	80	>310
14	*p*-($HO_2CCH_2CH_2CONH$)C_6H_4	SH	H	C	*m*	65	>310
15	*p*-($C_2H_5SO_2$)C_6H_4	SH	H	D	*f*	64	267–269
16	4,2-$H_2N(HO)C_6H_3$	SH	H	D	*m*	58	309–310 dec.
17	2-Pyridyl	SH	H	D	*f*	66	270–272 dec.
18	3-Pyridyl	SH	H	D	*o*	80	285–286
19	4-Pyridyl	SH	H	D	*j*	60	>310
20	4-Pyridyl	SH	H	D	*o*	50	305–306
21	4-Quinolyl	SH	H	D	*f*	76	184–186 dec.
22	2-Pyrazinyl	SH	H	D	*o*	62	290–291
23	CH_3	SH	H	D	*i*	62	264–265[r]
24	4-Pyridyl	SCH_3	H	H	*f*	48	165–167
25	*p*-$H_2NC_6H_4$	SCH_2CO_2H	H	I	*f*	81	103–105
26	*p*-$H_2NC_6H_4$	SO_2NH_2	H	J	*f*	66	278–279 dec.
27	*p*-($C_2H_5NHCONH$)C_6H_4	SO_2NH_2	H	G	*m*	68	>310
28	*p*-($HO_2CCH_2CH_2CONH$)C_6H_4	SO_2NH_2	H	C	*m*	56	260–261 dec.
29	4-Pyridyl	SO_2NH_2	H	J	*m*	53	315–317 dec.
30	C_6H_5	NH_2	H	*t*	*f*	43	186–187[u]
31	2-Thenyl	NH_2	H	*t*	*f*	55	207–209
32	*p*-$CH_3CONHC_6H_4$	NH_2	H	K	*f*	37	188–190 dec.
33	*p*-$CH_3CONHC_6H_4$	$NHCONH_2$	H	L	*m*	46	>310
34	CH_3	NH_2	H	*v*	*w*	43	149–151[v]
35	4-Pyridyl	SH	NH_2	*x*	*f*	44	226–227 dec. solidifying, remelting 248–249 dec.
36	NH_2	C_6H_5	NH_2	*y*	*z*	46	177–178
37	2-Furyl	2-Furyl	H	*aa*	*f*	37	185–186
38	2-Furyl	2-Furyl	NH_2	M	*j*	18	255–256
39	4-Pyridyl	4-Pyridyl	NH_2	M	Not recrystd.	30	>310
40	4-Pyridyl	4-Pyridyl	4-Pyridyl·NH	N	*bb*	22	290–292 dec.

[a] Toluene–Skellysolve. [b] E. Hoggarth [*J. Chem. Soc.*, 1160 (1949)] reported m.p. 121°. [c] Water. [d] Recrystallization from xylene gave the anhydrous compound, m.p. 196–197°. *Anal.* Calcd. for $C_8H_8N_4$: C, 59.88; H, 5.04; N, 34.98. Found: C, 60.04; H, 5.03; N, 34.53. The anhydrous compound in absolute ethanol with ethereal HCl gave a **dihydrochloride**, m.p. 258–260°, after recrystallization from absolute ethanol–ether. *Anal.* Calcd. for $C_8H_8N_4 \cdot 2HCl$: Cl, 30.41; N, 24.02. Found: Cl, 30.37; N, 24.25. [e] Xylene. [f] Water. [g] *Anal.* Calcd.: neut. equiv., 146. Found: neut. equiv. ($HClO_4$), 139. [h] *Anal.* Calcd.: S, 14.30. Found: S, 13.99. [i] 1-Propanol. [j] 95% ethanol. [k] E. Hoggarth[b] prepared this compound by a different procedure and reported m.p. 256°. [l] *Anal.* Calcd.: S, 15.25. Found: S, 15.66. [m] Water–N,N-dimethylformamide. [n] *Anal.* Calcd.: S, 12.18. Found: S, 12.02. [o] 5% aqueous HCl. [p] The base melted at 278–279° dec. after recrystallization from water. *Anal.* Calcd. C, 47.18; H, 3.39; N, 31.44. Found: C, 47.21; H, 3.62; N, 31.30. [q] Recrystallization from 5% aqueous HCl gave the hydrochloride hemihydrate, m.p.

Method K.—To a stirred suspension of 12.6 g. (0.11 mole) of aminoguanidine hydrochloride in 100 ml. of pyridine, at 0°, was added gradually 22.5 g. (0.011 mole) of *p*-acetamidobenzoyl chloride. The solution was stirred for 1.5 hr. at 0° when a solid separated; cooling and stirring was discontinued, the mixture was kept for 18 hr. at room temperature and diluted with 300 ml. of water, and the solution was neutralized with powdered $NaHCO_3$. Concentration of the neutral mixture to about 100 ml. *in vacuo* gave 24.0 g. of solid, m.p. 262–265° dec. An analytical sample of ***p*-acetamidobenzamidoguanidine** was obtained by recrystallization from water and melted at 270–271° dec. (*Anal.* Calcd. for $C_{10}H_{13}N_5O_2$: N, 29.77. Found: N, 29.44). The

Formula	Calcd., % C	H	N	Found, % C	H	N	LD_5, mg./kg.	Renal activity of LD_5 dose in rats i.p. 5 hr. Urine, %	Na, %	24 hr. Urine, %	Na, %
$C_8H_7N_3$	...	...	28.95	...	...	28.93	252	0	0	15	23
$C_8H_8N_4 \cdot 0.5H_2O$	56.80	5.36	33.11	56.96	5.15	32.98	725	0	0	35	75
$C_7H_6N_4$	57.51	4.14	38.34	57.50	3.88	38.38	340	8	37	4	24
$C_7H_6N_4$	57.51	4.14	38.34[g]	57.51	4.04	38.29	295	0	0	0	52
$C_8H_3N_4O_2S$	...	...	24.99[h]	...	...	24.93	130	...	...	...	...
$C_9H_9N_5O$	53.20	4.47	34.47	53.03	4.39	34.67	88	...	...	...	...
$C_{12}H_{12}N_4O_3$	55.38	4.65	21.63	55.62	4.83	21.94	1200	...	...	...	...
$C_8H_7N_3S$	54.21	3.98	23.72	54.39	3.86	23.83	790	0	0	0	0
$C_8H_{10}N_4OS \cdot H_2O$	...	...	26.65[l]	...	...	26.36	15	116	...	295	81
$C_8H_9N_3O_2S \cdot H_2O$	45.47	4.30	15.18	45.77	4.54	15.06	38	0	...	0	...
$C_8H_8N_4O_2S_2$	37.49	3.16	21.86	37.10	3.08	22.02	430	56	119	30	71
$C_9H_9N_5OS$	45.94	3.86	29.77	46.11	4.12	30.05	198	0	0	88	138
$C_{11}H_{13}N_5OS$	50.17	4.95	...[n]	50.24	5.08	...	480	0	0	6	15
$C_{12}H_{12}N_4O_3S$	49.31	4.14	19.17	49.21	4.15	18.91	2150	0	0	0	0
$C_{10}H_{11}N_3O_2S_2$	44.60	4.12	15.16	44.88	4.16	15.27	1260	0	0	0	0
$C_8H_8N_4OS$	46.17	3.88	26.90	46.41	4.07	27.04	790	0	0	223	0
$C_7H_6N_4S$	47.18	3.39	31.44	47.39	3.58	31.39	304	0	0	0	0
$C_7H_6N_4S \cdot HCl$[p]	39.15	3.29	...	38.82	3.77	...	120	0	0	0	0
$C_7H_6N_4S$[q]	47.18	3.39	31.44	47.18	3.36	31.18	156	17	62	66	138
$C_7H_6N_4S \cdot HCl$	39.15	3.29	...	39.11	3.06	...	184	0	0	0	0
$C_{11}H_8N_4S$[q]	57.88	3.53	24.55	58.05	3.29	24.31	560	0	0	0	0
$C_6H_5N_5S$	40.21	2.81	39.08	39.96	2.96	38.81	780	53	0	154	0
$C_3H_5N_3S$	31.20	4.36	27.76	31.49	4.46	27.50	>1200	0	0	0	0
$C_8H_8N_4S$	49.98	4.20	29.15	49.58	3.95	29.49	156	0	0	0	0
$C_{10}H_{10}N_4O_2S$	48.00	4.03	22.40	47.91	4.13	22.34	>3000	0	0	0	0
$C_8H_9N_5O_2S$	40.19	3.80	29.30	40.01	3.67	29.04	1200	68	41	67	0
$C_{11}H_{14}N_6O_3S$	42.57	4.54	27.08	42.78	4.35	26.79	238	0	0	11	0
$C_{12}H_{13}N_5O_5S$	42.47	3.86	20.64	42.22	3.91	20.73	>2400	0	0	0	0
$C_7H_7N_5O_2S$	...	...	31.10[s]	...	...	31.15	1200	0	0	115	282
$C_8H_8N_4$	60.00	5.04	...	60.37	4.78	...	150	...	...	...	...
$C_6H_6N_4S$	43.36	3.64	33.72	43.19	3.54	33.64	408	0	0	0	0
$C_{10}H_{11}N_5O \cdot H_2O$	51.03	5.57	29.77	50.88	5.61	29.45	1260	0	0	0	0
$C_{11}H_{12}N_6O_2 \cdot 0.5H_2O$	49.06	4.68	31.21	48.85	4.50	30.80	256	0	0	0	0
$C_3H_6N_4$	36.73	6.16	...	36.33	6.24	...	>2400	0	0	0	52
$C_7H_7N_5S$	43.50	3.65	36.24	43.57	3.45	36.75	370	6	0	0	0
$C_8H_9N_5$	54.84	5.18	...	54.99	5.05	...	1000	0	0	38	61
$C_{10}H_7N_3O_2$	...	...	20.88	...	...	21.06	235	25	44	57	36
$C_{10}H_8N_4O_2$	55.55	3.72	25.91	55.78	3.52	25.44	1750	0	0	0	0
$C_{12}H_{10}N_6$	60.49	4.19	35.27	60.29	4.08	34.91	1200	0	0	0	0
$C_{18}H_{13}N_7O \cdot 2HCl$	...	...	23.55[cc]	...	...	23.82	2400	...	...	...	...

269–270°. *Anal.* Calcd.: C, 48.26; H, 3.68; N, 20.46; H_2O, 3.29. Found: C, 48.57; H, 3.34; N, 20.03; H_2O, 4.04. [r] X. Girard [*Compt. rend.*, **225,** 458 (1947)] reported m.p. 260–261°. [s] *Anal.* Calcd.: S, 14.24. Found: S, 14.50. [t] The procedure of E. Hoggarth [*J. Chem. Soc.* 612 (1950)] was used. [u] E. Hoggarth[t] reported m.p. 186–187°. [v] The procedure of J. Thiele and K. Heidenreich [*Ber.*, **26,** 2599 (1893)] was used; they reported m.p. 148°. [w] Ethyl acetate. [z] The procedure of H. Bode-König, W. Siefken, and H. A. Offe [*ibid.*, **87,** 825 (1954)] was used; they report m.p. 210 dec., solidifying and remelting at 248–252° dec. [y] The procedure of J. P. Turner and J. Walker [*J. Chem. Soc.*, 4542 (1952)] was used; they report m.p. 174–175°. [z] Ethylene dichloride. [aa] The procedure of A. Pinner and N. Caro [*Ber.*, **28,** 465 (1895)] was used; they report m.p. 185°. [bb] 90% methanol. [cc] *Anal.* Calcd.: Cl, 17.03. Found: Cl, 16.81.

crude product from the previous step, 23.0 g., and 250 ml. of 5% aqueous NaOH was treated as in the preparation of **8** above. The yield of **32**, after recrystallization from water, was 8.5 g.

5-(4-Acetamidophenyl)-3-ureido-s-triazole (33). Method L.— To a stirred solution of 14.0 g. (0.2 mole) of 85% KOH in 45 ml. of water, 11.0 g. (0.13 mole) of dicyandiamide, and 55 ml. of acetone, at 0 to 5°, was added gradually 20 g. of *p*-acetamidobenzoyl chloride. The mixture was kept for 18 hr. at room temperature, diluted with 300 ml. of water, filtered, and the filtrate was acidified with acetic acid. The solid was filtered and air dried to give 9.1 g. of material, m.p. 235–239° dec. An analytical sample, recrystallized from 50% aqueous N,N-dimethylformamide, melted

TABLE II

1-AROYL-3-THIOSEMICARBAZIDES

RCONHNHCSNH$_2$

R	Method of prepn.	Recrystn. solvent	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
p-$CH_3CO_2C_6H_4$	O	*a*	23	210–211	$C_{10}H_{11}N_3O_3S$	45.47	4.30	15.18	45.77	4.54	15.06
p-$H_2NSO_2C_6H_4$	P	*b*	95	231–233 dec.	$C_8H_8O_2S_2$	...	...	20.43	...	...	20.34
p-$C_2H_5SO_2C_6H_4$	O	*b*	80	219–220	$C_{10}H_{13}N_3O_3S_2$	41.79	4.57	...	41.98	4.60	...
4,2-$H_2N(HO)C_6H_3$	P	*b*	24	210–212	$C_8H_{10}N_4O_2S$	...	...	24.76	...	...	24.90
2-Pyridyl	P	*b*	86	197–199 dec.	$C_7H_8N_4OS$	...	...	28.55	...	...	28.21
4-Quinolyl	P	*b*	80	184–186 dec.	$C_{11}H_{10}N_4OS$	53.64	4.10	...	53.34	4.48	...
2-Pyrazinyl	P	*b*	95	222–223 dec.	$C_6H_7N_5OS$	36.54	3.58	35.53	36.74	3.70	35.45

[a] 95% ethanol. [b] Water.

at 250–252° dec. (*Anal.* Calcd. for $C_{11}H_{11}N_5O_2$: N, 28.57. Found: N, 28.19.). The crude product from the previous step (9.0 g.), 200 ml. of 95% ethanol, and 2.5 ml. of 85% hydrazine hydrate were refluxed for 4 hr. and cooled, and the solid was filtered. The air-dried material, 5.6 g., was recrystallized from aqueous N,N-dimethylformamide to give 4.5 g. of **33**.[3]

4-Amino-3,5-bis(2-furyl)-*s*-triazole (38). Method M.—The reaction between 33.0 g. (0.15 mole) of 1,2-bis(2-furoyl)hydrazine and 15.0 g. (0.40 mole) of 85% hydrazine hydrate by the literature procedure[4] gave 5.7 g. of **38**.

N-(3,5-Di-4-pyridyl-*s*-triazol-4-yl)isonicotinamide Dihydrochloride (40). Method N.—To 20.0 g. (0.084 mole) of **39** in 100 ml. of pyridine, at 0–5°, was added in portions 17.8 g. (0.1 mole) of sublimed isonicotinyl chloride hydrochloride. The reaction mixture was stirred for 18 hr. at room temperature, heated for 3 hr. on the steam bath, cooled, and treated with 250 ml. of ice water. The precipitated solid was filtered and dried to give 8.0 g. of **39**. To the filtrate was added 20 ml. of concentrated aqueous NH_3 and the solution was concentrated to dryness *in vacuo*. The residue was dissolved in 600 ml. of boiling absolute ethanol and allowed to cool to room temperature, the NH_4Cl was filtered, the filtrate was concentrated to 200 ml. and again filtered, and the filtrate was diluted with 400 ml. of hexane. The solid which separated was filtered and dried to give 9.3 g. (32% yield) of crude base, m.p. 267–268° dec., but this compound could not be purified by recrystallization.

To the base, 6.9 g. (0.02 mole) in 150 ml. of absolute ethanol, was added 0.062 mole of HCl in ether solution. The crystalline product was filtered and recrystallized from 90% methanol to give 6.2 g. of **40**.

1-(*p*-Acetoxybenzoyl)-3-thiosemicarbazide. Method O.—To 2.30 g. (0.25 mole) of powdered semicarbazide and 40 ml. of pyridine, with ice-water cooling, was added dropwise 49.6 g. (0.25 mole) of *p*-acetoxybenzoyl chloride in 50 ml. of dry benzene. The mixture was stirred for 4 hr. at room temperature and diluted with 200 ml. of water, and the oily solid was filtered. Recrystallization from 95% ethanol gave 14.5 g. of product.

1-(*p*-Sulfamoylbenzoyl)-3-thiosemicarbazide. Method P.—A mixture of 21.5 g. (0.1 mole) of *p*-sulfamoylbenzoyl hydrazide, 7.1 g. (0.1 mole) of dry ammonium thiocyanate, and 8.6 g. of concentrated HCl in 90 ml. of water was heated on the steam bath for 16 hr. and then cooled; the solid was filtered and air dried to give 26 g. of product.

(3) D. W. Kaiser and G. A. Peters [*J. Org. Chem.*, **18**, 196 (1953)] have described the formation of 3-ureido-5-aryl-*s*-triazoles by this reaction; they did not prepare **33**.

(4) R. M. Herbst and J. A. Garrison, *ibid.*, **18**, 872 (1953). It is of interest that A. Pinner [*Ann.*, **298**, 32 (1897)] obtained **38**, m.p. 245°, by heating 3,6-bis(2-furyl)-1,2-dihydro-1,2,4,5-tetrazine in 25% HCl but reported the product to be 3,6-bis(2-furyl)-1,4-dihydro-1,2,4,5-tetrazine. R. Stolle [*J. prakt. Chem.*, [2] **75**, 416 (1907)] showed that 3,6-disubstituted dihydrotetrazines, but not including Pinner's compound, when so treated gave triazoles. Hence, F. K. Beilstein ("Handbuch der organischen Chemie," Vol. 27, 4th ed., 1919, p. 790) lists **38** by the above corrected structure.

Iodinated 5- and 8-Hydroxyisoquinolines as Potential Amebicides

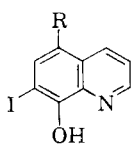
F. SCHENKER, R. A. SCHMIDT, W. LEIMGRUBER, AND A. BROSSI

Department of Chemical Research, Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey

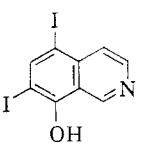
Received July 30, 1965

Some iodinated 5- and 8-hydroxyisoquinolines have been synthesized and evaluated for antiamebic activity *in vitro* and *in vivo* in comparison with Vioform. With the exception of 5,7-diiodo-8-isoquinolinol (III) and 5-iodo-8-isoquinolinol (VII), which were weakly active when tested *in vitro* against *Endamoeba histolytica*, none of the substances showed antiamebic activity at the doses employed.

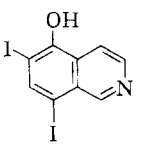
Various iodinated 8-hydroxyquinolines such as Diiodoquin (I) and Vioform (II) are frequently used in the prophylactic and therapeutic treatment of intestinal amebiasis. We wish to report the synthesis of the isomeric isoquinoline analogs III and IV of Diiodoquin and the results of the evaluation of their antiamebic properties.



I, R = I
II, R = Cl



III



IV

8-Isoquinolinol (VIII) is of potential interest as a starting material for the synthesis of 5,7-diiodo-8-isoquinolinol (III). This compound has been described by Robinson,[1] who prepared it in an overall yield of 15% by sulfonation of isoquinoline at 300° followed by alkali fusion of the resulting sulfonic acid mixture. Since the structure of VIII had been assigned solely on the basis of nonidentity with 5-, 6-, and 7-hydroxyisoquinoline, we decided to refrain from the use of Robinson's method for the preparation of this compound and, instead, utilized the *p*-aminophenol V in the synthesis of III (Scheme I). The diazonium

(1) R. A. Robinson, *J. Am. Chem. Soc.*, **69**, 1944 (1947).