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New 1,2,4(H)-Triazole Derivatives as Diuretic Agents

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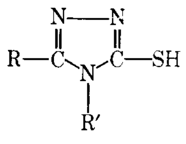
Abstract ☐ Sixty-three new 1,2,4(H)-triazole derivatives have been prepared and their diuretic activity studied in rats. Sequential screening showed 14 compounds possessing significant diuretic activity. 3-Phenyl-4-allyl-5-mercapto-1,2,4(H)-triazole and 3-*o*-chlorophenyl-4-allyl-5-mercapto-1,2,4(H)-triazole were the most potent compounds in the present series.

Keyphrases ☐ Diuretic activity—1,2,4(H)-triazole derivatives ☐ Mercapto-triazoles—synthesis ☐ Structure-activity relationship—triazole rings

In a previous communication (1), the authors reported the diuretic activity of some 1,2,4(H)-triazoles (I). Recently, Yale and Piala (2) have also reported the diuretic properties of some *s*-triazole derivatives amongst which 3-(*p*-aminophenyl)-*s*-triazole-5-thiol (I, R = *p*-NH_2-C_6H_4 and R′ = H) has been claimed to possess good diuretic activity. In view of these interesting results the work has now been extended to some more 3,4-disubstituted-5-mercapto-1,2,4(H)-triazoles.



I

The mercapto-triazoles were synthesized from the corresponding thiosemicarbazides by cyclization with sodium hydroxide or sodium carbonate. Some triazole derivatives were obtained directly in one step from acid hydrazides and the isothiocyanates by heating in excess alkali. When this reaction was carried out at room temperature, it proceeded only as far as the formation of the 1,4-disubstituted thiosemicarbazides.

The list of triazoles prepared, their melting points, yields, analytical data, and diuretic activity are given in Table I.

The requisite thiosemicarbazides were obtained by the reaction of acid hydrazides and isothiocyanates by literature methods. The new thiosemicarbazides are listed in Table II along with their melting points and analytical data.

Since many sulfamoyl compounds are being used clinically as potent diuretics, the conversion of some of the 5-mercapto-1,2,4(H)-triazoles into the corresponding 5-sulfamoyl derivatives was attempted by the usual oxidative chlorination followed by the action of ammonia (3, 4). The 5-sulfamoyl derivatives were obtained in two cases while in some other instances the desired compounds could not be isolated due to extensive decomposition. Moreover, the two sulfamoyl derivatives thus obtained showed activity of lower order than the parent mercapto compounds, *cf.* Yale and Piala (2), hence the preparation of other sulfamoyl derivatives was not pursued.

PHARMACOLOGY

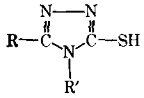
All the 3,4-disubstituted-5-mercapto-1,2,4-triazoles were screened for the diuretic properties in rats at their optimal responsive dose levels by the sequential method of Modi *et al.* (5).

Method—Albino rats (male) weighing about 180–200 g. were taken in groups of four in each cage per test dose. Prior to the experiment the rats were allowed food and water *ad libitum*. During the experiment each group of four animals was housed in an improved metabolism cage described by Modi *et al* (6). One group was used as untreated control and received orally the vehicle only, consisting of 0.5 ml. of 2% starch solution. Another group received hydrochlorothiazide (2.5 mg./kg.) as reference compound, suspended in the vehicle. The other groups received the various test compounds in the same vehicle. The urine was collected for 24 hr. If the total volume of urine in Cage I exceeded 19.3 ml., the compound was considered active and if below 3.7 ml., inactive. However, if the volume was in between these two values, a further evaluation with another cage of four rats was made. If the total volume of urine in Cages I plus II exceeded 30.8 ml. the compound was considered active but if less than 15.2 ml. it was considered inactive. In case the volume was again between the two limits a third cage was taken and similarly a fourth one if necessary as per criteria in Table III.

The compounds that did not meet activity criteria in the fourth cage experiment were given up as not sufficiently active.

Among the compounds with acceptable activity, those which produced urinary volumes more than 125% of controls were selected

Table I—3,4-Disubstituted-5-mercapto-1,2,4(H)-triazoles



Compd. No.	R	R′	Yield, %	M.p., °C.	Molecular Formula	—Nitrogen, %— Found	Calcd.	Diuretic Activity Opt. Res. Dose	Status
1	C_6H_5	C_2H_5	90	141–142	$C_{10}H_{11}N_3S$	20.99	20.48	3	Active
2	C_6H_5	$CH_2CH{=}CH_2$	85	120–121	$C_{11}H_{11}N_3S$	19.27	19.35	5	Active
3	C_6H_5	n-C_3H_7	85	127–128	$C_{11}H_{13}N_3S$	18.82	19.18	3	Active
4	C_6H_5	iso-C_3H_7	95	193–194	$C_{11}H_{13}N_3S$	19.64	19.18	13	Active
5	C_6H_5	n-C_4H_9	50	130–131	$C_{12}H_{15}N_3S$	18.13	18.02	20	Active
6	C_6H_5	iso-C_4H_9	83	178–179	$C_{12}H_{15}N_3S$	18.19	18.02	0.6	Active
7	C_6H_5	C_6H_{11}	84	193	$C_{14}H_{17}N_3S$	16.01	16.21	11	Active
8	C_6H_5	C_6H_5	87	277–278	$C_{14}H_{11}N_3S$	16.77	16.60	5	Active
9	2-ClC_6H_4	C_2H_5	87	194–195	$C_{10}H_{10}ClN_3S$	17.31	17.54	3	Inactive
10	2-ClC_6H_4	$CH_2CH{=}CH_2$	85	147–148	$C_{11}H_{10}ClN_3S$	16.50	16.70	10	Active
11	2-ClC_6H_4	n-C_3H_7	86	166–167	$C_{11}H_{12}ClN_3S$	16.35	16.57	10	Inactive
12	2-ClC_6H_4	iso-C_3H_7	89	206–208	$C_{11}H_{12}ClN_3S$	16.66	16.57	6	Inactive
13	2-ClC_6H_4	n-C_4H_9	91	154–155	$C_{12}H_{14}ClN_3S$	15.49	15.70	6	Inactive
14	2-ClC_6H_4	iso-C_4H_9	82	157–158	$C_{12}H_{14}ClN_3S$	15.45	15.70	3	Inactive
15	2-ClC_6H_4	C_6H_{11}	93	219–220	$C_{14}H_{16}ClN_3S$	14.42	14.31	3	Inactive
16	2-ClC_6H_4	C_6H_5	88	219–221	$C_{14}H_{10}ClN_3S$	14.50	14.61	10	Inactive
17	3-ClC_6H_4	C_2H_5	77	159–160	$C_{10}H_{10}ClN_3S$	18.25	17.54	6	Inactive
18	3-ClC_6H_4	iso-C_4H_9	71	138–139	$C_{12}H_{14}ClN_3S$	15.56	15.70	3	Inactive
19	4-ClC_6H_4	H	66	286	$C_8H_6ClN_3S$	19.62	19.86	12	Inactive
20	4-ClC_6H_4	C_2H_5	93	203–204	$C_{10}H_{10}ClN_3S$	17.42	17.54	6	Inactive
21	4-ClC_6H_4	iso-C_4H_9	84	193–195	$C_{12}H_{14}ClN_3S$	15.78	15.70	7	Inactive
22	4-ClC_6H_4	C_6H_{11}	92	192–194	$C_{14}H_{16}ClN_3S$	14.40	14.31	12	Inactive
23	2,4-$Cl_2C_6H_3$	H	76	273 dec.	$C_8H_5Cl_2N_3S$	17.33	17.07	7	Active
24	2-OHC_6H_4	H	79	290	$C_8H_7N_3OS$	21.08	21.76	20	Inactive
25	2-OHC_6H_4	C_2H_5	85	247–248	$C_{10}H_{11}N_3OS$	19.29	19.00	3	Inactive
26	2-OHC_6H_4	iso-C_4H_9	76	195–196	$C_{12}H_{15}N_3OS$	16.84	16.87	20	Inactive
27	2-OHC_6H_4	C_6H_{11}	89	171–172	$C_{14}H_{17}N_3OS$	15.33	15.27	7	Inactive
28	2-OHC_6H_4	4′-ClC_6H_4	78	286–287	$C_{14}H_{10}ClN_3OS$	13.97	13.83	—	—
29	3-OHC_6H_4	C_2H_5	67	179–181	$C_{10}H_{11}N_3OS$	18.88	19.00	6	Inactive
30	3-OHC_6H_4	$CH_2CH{=}CH_2$	65	152–153	$C_{11}H_{11}N_3OS$	18.30	18.02	3	Inactive
31	3-OHC_6H_4	n-C_3H_7	73	187	$C_{11}H_{13}N_3OS$	17.67	17.86	5	Inactive
32	3-OHC_6H_4	iso-C_3H_7	76	212–213	$C_{11}H_{13}N_3OS$	17.84	17.86	13	Inactive
33	3-OHC_6H_4	n-C_4H_9	82	186–188	$C_{12}H_{15}N_3OS$	16.62	16.87	5	Active
34	3-OHC_6H_4	iso-C_4H_9	55	201–202	$C_{12}H_{15}N_3OS$	16.64	16.87	—	—
35	3-OHC_6H_4	C_6H_{11}	85	263–266	$C_{11}H_{13}N_3OS$	15.04	15.27	3	Active
36	3-OHC_6H_4	C_6H_5	83	247–248	$C_{14}H_{11}N_3OS$	15.70	15.61	13	Inactive
37	4-OHC_6H_4	C_2H_5	62	212–214	$C_{10}H_{11}N_3OS$	19.25	19.00	20	Inactive
38	4-OHC_6H_4	$CH_2CH{=}CH_2$	59	168–169	$C_{11}H_{11}N_3OS$	17.63	18.02	7	Inactive
39	4-OHC_6H_4	n-C_3H_7	77	178–181	$C_{11}H_{13}N_3OS$	17.70	17.86	6	Inactive
40	4-OHC_6H_4	iso-C_3H_7	81	285–286	$C_{11}H_{13}N_3OS$	17.64	17.86	20	Inactive
41	4-OHC_6H_4	n-C_4H_9	82	185–186	$C_{12}H_{15}N_3OS$	16.96	16.87	14	Inactive
42	4-OHC_6H_4	iso-C_4H_9	60	217–219	$C_{12}H_{15}N_3OS$	17.13	16.87	13	Inactive
43	4-OHC_6H_4	C_6H_{11}	85	247–249	$C_{14}H_{17}N_3OS$	15.34	15.27	10	Inactive
44	4-OHC_6H_4	C_6H_5	87	267–268	$C_{14}H_{11}N_3OS$	15.35	15.61	10	Inactive
45	2-OH-5-ClC_6H_3	C_6H_5	72	239–240	$C_{14}H_{10}ClN_3OS$	14.08	13.84	—	—
46	2-OH-5-BrC_6H_3	C_2H_5	61	205–206	$C_{10}H_{10}BrN_3OS$	13.84	14.00	6	Inactive
47	2-OH-5-BrC_6H_3	$CH_2CH{=}CH_2$	67	163–165	$C_{11}H_{10}BrN_3OS$	13.41	13.46	3	Inactive
48	2-OH-5-BrC_6H_3	iso-C_3H_7	57	200–204	$C_{11}H_{12}BrN_3OS$	13.22	13.38	5	Inactive
49	2-OH-5-BrC_6H_3	iso-C_4H_9	58	192–193	$C_{12}H_{14}BrN_3OS$	12.48	12.80	7	Inactive
50	2-OH-5-BrC_6H_3	C_6H_{11}	73	221–225	$C_{14}H_{16}BrN_3OS$	11.98	11.87	12	Inactive
51	2-OH-5-BrC_6H_3	C_6H_5	76	160–163	$C_{14}H_{10}BrN_3OS$	11.98	12.07	6	Inactive
52	3,4,5-$(CH_3O)_3C_6H_2$	H	65	285	$C_{11}H_{13}N_3O_3S$	15.45	15.73	4	Inactive
53	3,4,5-$(CH_3O)_3C_6H_2$	C_2H_5	80	199–200	$C_{13}H_{17}N_3O_3S$	14.04	14.23	7	Active
54	3,4,5-$(CH_3O)_3C_6H_2$	iso-C_4H_9	77	204–206	$C_{15}H_{21}N_3O_3S$	12.83	13.00	6	Inactive
55	3,4,5-$(CH_3O)_3C_6H_2$	C_6H_{11}	89	228–230	$C_{17}H_{23}N_3O_3S$	11.86	12.03	7	Inactive
56	3-Pyridyl	H	57	295 dec.	$C_7H_6N_4S$	31.76	31.46	0.7	Inactive
57	3-Pyridyl	C_2H_5	84	177–178	$C_9H_{10}N_4S$	26.76	27.18	6	Active
58	3-Pyridyl	iso-C_4H_9	92	202–203	$C_{11}H_{14}N_4S$	24.34	23.93	6	Inactive
59	3-Pyridyl	C_6H_{11}	95	224–226	$C_{13}H_{16}N_4S$	21.22	21.54	6	Inactive
60	4-Pyridyl	H	80	290	$C_7H_6N_4S$	30.93	31.46	7	Inactive
61	4-Pyridyl	C_2H_5	89	231–233	$C_9H_{10}N_4S$	26.70	27.18	12	Inactive
62	4-Pyridyl	iso-C_4H_9	83	238–239	$C_{11}H_{14}N_4S$	23.66	23.93	6	Inactive
63	4-Pyridyl	C_6H_{11}	90	298 dec.	$C_{13}H_{16}N_4S$	21.12	21.54	8	Inactive

for further studies on electrolyte excretion. The results are presented in Table IV.

Results and Structure-Activity Relationship—Among the 63 compounds screened 14 were found to possess diuretic activity.

The introduction of a phenyl group in Position 3 of the triazole ring gave the most active compounds in the present series. The introduction of substituents in this phenyl (except chlorine in ortho position) or the replacement of the phenyl with pyridyl group reduced the activity considerably. Substitution in Position 4 did not significantly alter the activity.

3-Phenyl-4-allyl-5-mercapto-1,2,4(H)-triazole (2) and 3-*o*-chlorophenyl-4-allyl-5-mercapto-1,2,4(H)-triazole (10) were the most active compounds in the present series.

EXPERIMENTAL

3-(3′,4′,5′-Trimethoxyphenyl)-4-ethyl-5-mercapto-1,2,4(H)-triazole (53)—1-(3′,4′,5′-Trimethoxybenzoyl)-4-ethylthiosemicarbazide (4.7 g., 0.015 mole) was dissolved in 1 *N* sodium hydroxide

Table II—1,4 Disubstituted Thiosemicarbazides

R—CO—NH—NH—CS—NH—R′

Compd. No.	R	R′	Yield, %	M.p., °C.	Molecular formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	C_6H_5	C_2H_5	94	192–193	$C_{10}H_{13}N_3OS$	18.83	18.91
2	C_6H_5	$CH_2—CH=CH_2$	89	172–173	$C_{11}H_{13}N_3OS$	17.87	17.62
3	C_6H_5	n-C_3H_7	76	163–164	$C_{11}H_{15}N_3OS$	17.72	17.65
4	C_6H_5	n-C_4H_9	83	154–155	$C_{12}H_{17}N_3OS$	16.73	16.48
5	C_6H_5	iso-C_4H_9	80	177–178	$C_{12}H_{17}N_3OS$	16.73	16.68
6	C_6H_5	C_6H_{11}	80	170–172	$C_{14}H_{19}N_3OS$	15.16	14.80
7	2-ClC_6H_4	C_2H_5	91	163–164	$C_{10}H_{12}ClN_3OS$	16.31	15.90
8	2-ClC_6H_4	$CH_2—CH=CH_2$	87	165	$C_{11}H_{12}ClN_3OS$	15.58	15.38
9	2-ClC_6H_4	n-C_3H_7	79	161–162	$C_{11}H_{14}ClN_3OS$	15.47	15.65
10	2-ClC_6H_4	iso-C_3H_7	80	157–158	$C_{11}H_{14}ClN_3OS$	15.47	15.21
11	2-ClC_6H_4	n-C_4H_9	86	131–132	$C_{12}H_{16}ClN_3OS$	14.71	14.53
12	2-ClC_6H_4	iso-C_4H_9	73	161–162	$C_{12}H_{16}ClN_3OS$	14.71	14.66
13	2-ClC_6H_4	C_6H_{11}	82	161–162	$C_{14}H_{18}ClN_3OS$	13.48	13.35
14	2-ClC_6H_4	C_6H_5	64	139–141	$C_{14}H_{12}ClN_3OS$	13.74	14.04
15	3-ClC_6H_4	C_2H_5	87	185–186	$C_{10}H_{12}ClN_3OS$	16.31	16.42
16	3-ClC_6H_4	iso-C_4H_9	61	195–196	$C_{12}H_{16}ClN_3OS$	14.71	14.18
17	4-ClC_6H_4	C_2H_5	89	203–204	$C_{10}H_{12}ClN_3OS$	16.31	16.50
18	4-ClC_6H_4	iso-C_4H_9	72	193–194	$C_{12}H_{16}ClN_3OS$	14.71	14.43
19	4-ClC_6H_4	C_6H_{11}	85	215–216	$C_{14}H_{18}ClN_3OS$	13.48	13.85
20	2,4-$Cl_2C_6H_3$	H	87	213–214	$C_8H_7Cl_2N_3OS$	15.91	16.08
21	2-OHC_6H_4	C_2H_5	86	242–244	$C_{10}H_{13}N_3O_2S$	17.57	17.77
22	2-OHC_6H_4	iso-C_4H_9	66	164–166	$C_{12}H_{17}N_3O_2S$	15.73	15.51
23	2-OHC_6H_4	C_6H_{11}	72	192–194	$C_{14}H_{19}N_3O_2S$	14.33	14.14
24	2-OHC_4H_4	4-ClC_6H_4	78	199–201	$C_{14}H_{12}ClN_3O_2S$	13.06	13.52
25	3-OHC_6H_4	C_2H_5	73	209–210	$C_{10}H_{13}N_3O_2S$	17.57	17.48
26	3-OHC_6H_4	$CH_2CH=CH_2$	75	208	$C_{11}H_{13}N_3O_2S$	16.73	16.87
27	3-OHC_6H_4	n-C_3H_7	69	204–205	$C_{11}H_{15}N_3O_2S$	16.60	16.32
28	3-OHC_6H_4	iso-C_3H_7	69	211–212	$C_{11}H_{15}N_3O_2S$	16.60	16.46
29	3-OHC_6H_4	n-C_4H_9	71	193–194	$C_{12}H_{17}N_3O_2S$	15.73	15.21
30	3-OHC_6H_4	iso-C_4H_9	68	201–202	$C_{12}H_{17}N_3O_2S$	15.73	15.91
31	3-OHC_6H_4	C_6H_{11}	75	214–215	$C_{14}H_{19}N_3O_2S$	14.33	13.96
32	3-OHC_6H_4	C_6H_5	65	202–203	$C_{14}H_{13}N_3O_2S$	14.63	14.67
33	4-OHC_6H_4	C_2H_5	82	204–205	$C_{10}H_{13}N_3O_2S$	17.57	17.20
34	4-OHC_6H_4	n-C_3H_7	85	188–189	$C_{11}H_{15}N_3O_2S$	16.60	16.33
35	4-OHC_6H_4	iso-C_4H_9	80	190–191	$C_{12}H_{17}N_3O_2S$	15.73	15.80
36	4-OHC_6H_4	C_6H_{11}	84	203–204	$C_{14}H_{19}N_3O_2S$	14.33	14.42
37	4-OHC_6H_4	C_6H_5	73	185–186	$C_{14}H_{13}N_3O_2S$	14.63	15.05
38	2-OH-5-ClC_6H_3	C_6H_5	83	175–176	$C_{14}H_{12}ClN_3O_2S$	13.06	13.32
39	2-OH-5-BrC_6H_3	C_2H_5	78	209–210	$C_{10}H_{12}BrN_3O_2S$	13.20	13.24
40	2-OH-5-BrC_6H_3	iso-C_4H_9	68	212–214	$C_{12}H_{16}BrN_3O_2S$	12.13	12.26
41	2-OH-5-BrC_6H_3	C_6H_{11}	78	200–202	$C_{14}H_{18}BrN_3O_2S$	11.29	11.11
42	2-OH-5-BrC_6H_3	C_6H_5	88	189–190	$C_{14}H_{12}BrN_3O_2S$	11.47	11.74
43	3,4,5-$(CH_3O)_3C_6H_2$	C_2H_5	74	197–199	$C_{13}H_{19}N_3O_4S$	13.41	13.02
44	3,4,5-$(CH_3O)_3C_6H_2$	iso-C_4H_9	67	186–187	$C_{15}H_{23}N_3O_4S$	12.31	12.03
45	3,4,5-$(CH_3O)_3C_6H_2$	C_6H_{11}	83	167–168	$C_{17}H_{25}N_3O_4S$	11.44	11.25
46	3-Pyridyl	C_2H_5	58	163–165	$C_9H_{12}N_4OS$	25.00	25.25
47	3-Pyridyl	iso-C_4H_9	68	173–175	$C_{11}H_{16}N_4OS$	22.22	22.07
48	3-Pyridyl	C_6H_{11}	87	190–192	$C_{13}H_{18}N_4OS$	20.15	20.17
49	4-Pyridyl	C_2H_5	74	230–231	$C_9H_{12}N_4OS$	25.00	24.51
50	4-Pyridyl	iso-C_4H_9	71	207–208	$C_{11}H_{16}N_4OS$	22.22	23.34
51	4-Pyridyl	C_6H_{11}	86	218–219	$C_{13}H_{18}N_4OS$	20.15	20.51

(25 ml.) and the solution was heated under reflux for 1 hr. At the end of this period, the reaction mixture was filtered, the filtrate was cooled and acidified with hydrochloric acid. The white solid that separated was filtered after 30 min., washed with water, and dried to give 3-(3′,4′,5′-trimethoxyphenyl)-4-ethyl-5-mercapto-1,2,4(H)-triazole; (3.56 g., 80%), m.p. 199–200°.

3-Phenyl-4-cyclohexyl-5-mercapto-1,2,4(H)-triazole (7)—To 1-benzoyl-4-cyclohexylthiosemicarbazide (1 g., 0.0036 mole) was added 5% aqueous sodium carbonate (25 ml.) and the mixture refluxed for 4 hr. It was then worked up as described above to give 3-phenyl-4-cyclohexyl-5-mercapto-1,2,4(H)-triazole (0.792 g., 84%) and crystallized from ethanol–water (1:1), m.p. 193°.

Table III—Criteria for Judging Diuretic Activity

Cages	Cumulative Urine Volume Required for Acceptable Activity in ml.	Cumulative Urine Volume Required for Rejection in ml.
I	19.3 or more	3.7 or less
I + II	30.8 or more	15.2 or less
I + II + III	42.3 or more	26.7 or less
I + II + III + IV	53.7 or more	38.1 or less

1-Salicyloyl-6-cyclohexylthiosemicarbazide (23)—To a solution of 2-hydroxybenzhydrazide (3.04 g., 0.02 mole) in ethanol (20 ml.) was added cyclohexylisothiocyanate (2.85 ml., 0.02 mole), followed by aqueous sodium hydroxide (10 ml. of 2 N, 0.02 mole). This reaction mixture was stirred for 3 hr. at room temperature and was left for 36 hr. It was then filtered and the filtrate acidified with hydrochloric acid. The white solid that precipitated was collected, washed with water, and dried to get 1-salicyloyl-4-phenylthiosemicarbazide (4.22 g., 72%) which on crystallization from 70% ethanol melted at 192–194°.

3-Phenyl-4-n-butyl-5-mercapto-1,2,4-(H)-triazole (5)—Benzhydrazide (2.72 g., 0.02 mole) was dissolved in ethanol (25 ml.) and to this soltuion was added n-butylisothiocyanate (2.3 g., 0.02 mole) followed by sodium hydroxide solution (25 ml. of 2 N). The mixture was heated to reflux on a water bath for 5 hr. and then poured into cold water. On acidification with hydrochloric acid 3-phenyl-4-n-butyl-5-mercapto-1,2,4(H)-triazole separated (2.31 g., 50%). On crystallization from ethanol the product melted at 130–131°. The mixed melting point with the product obtained on cyclization of

Table IV—Diuretic Effect after Administration of the Compounds Orally to Rats; Values in Urine as % of Control

Compound No.	Volume	Na^+	K^+	Cl^-
1	125	121	219	277
2	163.5	772.5	118	378.5
4	125.5	182	141.5	296
5	152.5	138	280	287
6	141.5	520.0	162.5	323.0
7	133.5	90	158	266
8	154.5	276.0	164	255
10	155.8	1000	139.3	410
Hydrochloro-thiazide	166	1000	250	538.5

1-phenyl-4-*n*-butylthiosemicarbazide was not depressed.

3-p-Chlorophenyl-6-isopropyl-1,2,4(H)-triazole-5-sulfonamide—A stirred mixture of 3-*p*-chlorophenyl-4-isopropyl-5-mercapto-1,2,4-(H)-triazole (5.0 g.), water (135 ml.), and ferric chloride solution (0.7 ml. of 60%) was stirred and cooled to 0°. Chlorine gas was then passed into the mixture for 1 hr. maintaining the temperature between 0–5°. The reaction mixture was allowed to stand at this temperature for 15 min. more and then filtered. The solid was pressed on filter paper and immediately added to aqueous ammonia (150 ml. of 20%). This solution was left at room temperature for 6 hr. and then filtered. The filtrate was acidified with hydrochloric acid to pH 6. The white solid that separated, on purification by redissolving in alkali and precipitating with acid followed by crystallization from ethanol, gave 3-*p*-chlorophenyl-4-isopropyl-1,2-4(H)-triazole-5-sulfonamide (2.8 g.), m.p. 214–215°.

Anal.—Calcd. for $C_{11}H_{13}ClN_4O_2S$: N, 18.64. Found: 18.69.

Similarly, 3-*o*-chlorophenyl-4-phenyl-1,2,4(H)-triazole-5-sulfonamide was obtained in 32% yield, m.p. 240°.

Anal.—Calcd. for $C_{14}H_{11}ClN_4O_2S$: N, 16.74. Found: N, 16.53.

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DRUG STANDARDS

Analysis of Metronidazole

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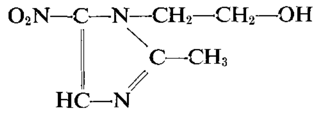
Abstract □ The literature on the identification, assay, and use of metronidazole has been surveyed. Based on published information, private communications, and laboratory experimentation, qualitative tests and quantitative assays have been developed for metronidazole, metronidazole suppositories (vaginal tablets), and metronidazole tablets. Extraction of metronidazole from suppositories and tablets is with hot acetone. Assays are based on titration of metronidazole in acetic anhydride with 0.1 *N* perchloric acid in glacial acetic acid, using malachite green indicator. The visual endpoint coincides with that determined potentiometrically. Supporting data is presented, including UV and IR spectra.

Keyphrases □ Metronidazole dosage forms—analysis □ Colorimetric method—identity □ UV spectrophotometry—identity □ IR spectrophotometry—identity

Metronidazole,[1] $C_6H_9N_3O_3$; mol. wt. 171.15, is 2-methyl - 5 - nitroimidazole - 1 - ethanol or 1 - (2 - hydroxyethyl)-2-methyl-5 nitroimidazole. It was recognized in "Addendum 1964" of the BP 1963 (1) as the drug and in the form of tablets. These two forms and the suppository have been admitted to USP XVIII. The structural formula may be represented as



[1] Flagyl, G. D. Searle & Co., Chicago, Ill.

EXPERIMENTAL

Physical Properties—Metronidazole occurs as white to pale yellow crystals or crystalline powder, stable in air, but darkening on exposure to light. It is sparingly soluble in water, in alcohol, and in chloroform, and is slightly soluble in ether. The melting range is 159–163°.

Identity Tests—*A.*—Heat about 10 mg. in a water bath for 5 min. with 1 ml. of water, 0.25 ml. of hydrochloric acid, and 10 mg. of zinc powder, filter, cool, add 1 ml. of freshly prepared sodium nitrite solution (1 in 100), then remove excess nitrite by addition of 1 ml. of freshly prepared sulfamic acid solution (1 in 100). To 1 ml. of this solution add 1 ml. of betanaphthol T.S.: an intense red color is produced. (This differs from the BP test in that the reaction takes place in an acid medium.)