Synthesis of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazole-3-thiol/yl-thioglycolic Acids as Possible Anti-inflammatory Agents

P. J. Kothari, V. Kishore, V. I. Stenberg and S. S. Parmar

Departments of Chemistry and Physiology, University of North Dakota, Grand Forks, North Dakota 58202

Received January 3, 1978

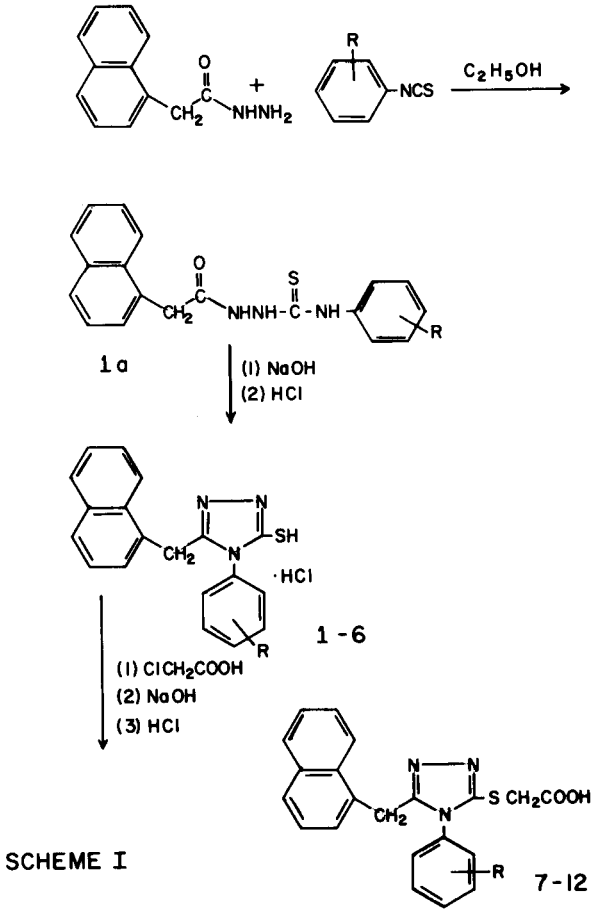
Several 5-(1-naphthylmethyl)-4-aryl-*s*-triazole-3-thiol/yl-thioglycolic acids were prepared as possible anti-inflammatory agents. The infrared, nuclear magnetic resonance and mass spectra of these compounds are reported.

J. Heterocyclic Chem., 15, 1101 (1978)

Diverse pharmacological properties which have been shown to be associated with substituted-*s*-triazoles include sedative, nicotine antagonistic, anticonvulsant (1-3) and anti-inflammatory activities (4). Earlier studies have reported anti-inflammatory properties of several derivatives of naphthylacetic acid (5,6). Amongst these derivatives naproxen and naphthypramide have found therapeutic usage against rheumatoid and osteo-arthritis, respectively. Some naphthylthiosemicarbazides and their corresponding oxadiazoles have recently been reported to exhibit anti-inflammatory properties (7,8). These observations prompted the synthesis of some naphthyl derivatives having the *s*-triazole-3-thiol/yl-thioglycolic acid moiety. The various 5-(1-naphthylmethyl)-4-aryl-*s*-triazole-3-thiol/yl-thioglycolic acids were synthesized according to the steps outlined in Scheme I.

The various 1-(1-naphthylacetyl)-4-aryl thiosemicarbazides (**1a**) were synthesized by condensing 1-naphthylacethydrazide with suitable aryl isothiocyanates. These substituted thiosemicarbazides were cyclized into their corresponding 5-(1-naphthylmethyl)-4-aryl-*s*-triazole-3-thiols (**1-6**) in the presence of aqueous 2*N* sodium hydroxide solution. The various 5-(1-naphthylmethyl)-4-aryl-*s*-triazole-3-yl-thioglycolic acids (**7-12**) were obtained by the reaction of **1-6** with monochloroacetic acid in the presence of aqueous sodium hydroxide solution.

The infrared spectra of **1-12** showed characteristic C=C/C=N absorptions in the region of 1400-1690 cm^{-1}. The substituted-*s*-triazole-3-thiols **1-6** showed a peak in the region between 1310-1335 cm^{-1} due to C=S group which indicates that these thiols (**1-6**) exist in a tautomeric form in acidic and alkaline medium. The characteristic



SCHEME I

Table I

Physical Constants of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazole-3-thiols

Compound No.	R	M.p. °C	Yield %	Solvent of crystallization	Molecular formula	Analysis Calculated C	H	N	Found C	H	N
1	H	248.7	75	Ethanol	$C_{19}H_{15}N_3S$	71.92	4.73	13.24	72.12	4.71	13.27
2	4-Cl	203.8	78	Methanol	$C_{19}H_{14}ClN_3S$	64.77	3.97	11.93	64.71	3.88	11.79
3	4-Br	219.2	95	Ethanol-water	$C_{19}H_{14}BrN_3S$	57.57	3.53	10.60	57.50	3.58	10.31
4	4-I	233.3	100	Acetic acid	$C_{19}H_{14}IN_3S$	51.46	3.16	9.48	51.59	3.23	9.50
5	2-CH_3	232.3	92	Benzene	$C_{20}H_{17}N_3S$	72.50	5.13	12.68	72.50	5.12	12.71
6	2-OCH_3	244.9	96	Xylene	$C_{20}H_{17}N_3OS$	69.16	4.89	12.10	69.14	4.95	12.16

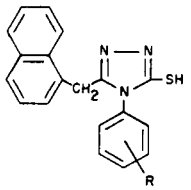
Table II

Physical Constants of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazol-3-yl-thioglycolic Acids

Compound No.	R	M.p. °C	Yield %	Solvent of crystallization	Molecular formula	Analysis Calculated C	H	N	Found C	H	N
7	H	138.1	69	Carbon tetrachloride	$C_{21}H_{17}N_3O_2S$	67.20	4.53	11.19	67.48	4.46	11.23
8	4-Cl	183.6	98	Ethanol	$C_{21}H_{16}ClN_3O_2S$	61.55	3.90	10.24	61.68	3.98	10.25
9	4-Br	191.8	96	Benzene	$C_{21}H_{16}BrN_3O_2S$	55.51	3.52	9.25	55.56	3.56	9.28
10	4-I	196.6	78	Methanol	$C_{21}H_{16}IN_3O_2S$	50.29	3.19	8.38	50.25	3.32	8.46
11	2-CH_3	164.2	95	Toluene	$C_{22}H_{19}N_3O_2S$	67.87	4.88	10.79	67.75	4.91	10.81
12	2-OCH_3	225.5	95	Acetic Acid	$C_{22}H_{19}N_3O_3S$	65.18	4.69	10.37	65.21	4.73	10.41

Table III

Spectral Analyses of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazole-3-thiols



Compound No.	Infrared spectra (a) C=C/C=N	C=S	Nmr spectra (b) R(CH_3)	-CH_2-	aromatic	Mass spectra m/e (Relative intensity)
1	1400, 1500, 1570	1300	--	4.31 (s)	6.84-8.16 (m)	318 (77), 317 (100), 258 (10), 244 (21), 167 (80), 141 (100), 128 (43), 127 (36), 59 (8)
2	1490, 1505, 1580, 1590	1310	--	4.35 (s)	6.84-8.16 (m)	351 (6), 292 (11), 184 (5), 170 (6), 167 (100), 141 (100), 128 (60), 127 (63), 59 (13)
3	1415, 1540, 1560 1580	1325	--	4.34 (s)	6.84-8.16 (m)	337 (15), 229 (13), 215 (54), 167 (100), 156 (16), 141 (100), 128 (100), 127 (78), 59 (53)
4	1545, 1560, 1580	1330	--	4.30 (s)	6.84-8.16 (m)	443 (72), 385 (12), 204 (19), 167 (100), 141 (75), 128 (88), 127 (20), 59 (18)
5	1400, 1460, 1500 1570	1330	1.48 (s)	4.16 (d, J_1 = 5 Hz) 4.35 (d, J_1 = 5 Hz)	6.65-8.16 (m)	332 (16), 331 (61), 167 (37), 127 (100), 59 (6)
6	1410, 1440, 1460 1570, 1575	1335	3.51 (s)	4.19 (s)	6.84-8.16 (m)	----------

(a) The assignments for absorption are expressed in wave numbers (cm^{-1}). (b) Nmr signals are reported in ppm (δ).

absorption for C=O in **7-12** appeared in the region of 1730-1745 cm^{-1}. In the nmr spectra of **1-12**, the protons of the methylene bridge between the naphthyl moiety and the triazole nucleus gave signals between 4.1-4.5 δ while the methylene protons of the thioglycolic acid group in **7-12** exhibited a signal in the region of 3.9-4.0 δ. The mass spectra of all the compounds except **6** and **7** were studied. The molecular ion peak was found to be present in all the compounds although their relative intensities varied from 6-100%. There were no major differences in the fragmentation pattern between thiols and their corresponding thioglycolic acids. One of the major fragmentation patterns was found to be similar to the one described earlier by Potts, *et al* (9), and is shown in Figure 1.

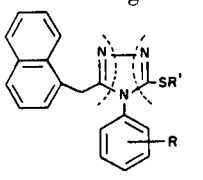
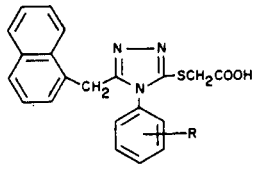


Figure 1. Fragmentation pattern of the *s*-triazoles

Table IV

Spectral Analyses of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazol-3-yl-thioglycolic Acids



Compound No.	Infrared spectra (a) C=O	C=C/C=N	-C-O-H	R(CH_3)	Nmr spectra (b) -S-CH_2-	-CH_2-	Aromatic	Mass spectra m/e (Relative intensity)
7	1740	1265, 1600	--	--	3.90 (s)	4.47 (s)	6.68-8.16 (m)	-- --
8	1745	1520, 1585 1610	1400	--	3.95 (s)	4.48 (s)	6.76-8.16 (m)	409 (30), 319 (100), 292 (34), 241 (28), 167 (100), 153 (87), 141 (84), 128 (57), 127 (37), 116 (100), 91 (34), 44 (100)
9	1745	1500, 1520 1600	1400	--	4.02 (s)	4.49 (s)	6.84-8.32 (m)	453 (13), 410 (49), 363 (59), 286 (7), 167 (100), 153 (68), 141 (100), 128 (87), 127 (54), 116 (36), 91 (24), 44 (49)
10	1745	1520, 1610	1400	--	4.00 (s)	4.38 (s)	6.84-8.16 (m)	442 (24), 410 (31), 334 (100), 297 (17), 204 (20), 167 (100), 153 (28), 141 (81), 128 (89), 127 (43), 116 (32), 91 (38), 44 (80)
11	1735	1500, 1600	1400	1.40 (s)	3.95 (s)	4.25 (d, J_1 = 5 Hz) 4.48 (d, J_1 = 5 Hz)	6.50-8.32 (m)	389 (31), 344 (28), 298 (78), 167 (44), 153 (11), 141 (72), 141 (72), 128 (22), 127 (16), 116 (12), 91 (38), 44 (62)
12	1730	1510, 1600	--	3.46 (s)	3.97 (s)	4.38 (s)	6.76-8.27 (m)	405 (19), 404 (67), 361 (33), 315 (100), 238 (11), 167 (100), 153 (21), 141 (100), 128 (31), 127 (22), 115 (82), 91 (22), 44 (60)

(a and b) As indicated in Table III.

Thus, the cleavage of bonds between N_1-N_2 and N_4-C_5 resulted in the (naphthyl-CH_2CN)$^+$ ion which was observed in all the compounds at m/e 167. This ion lost CN to give (naphthyl-CH_2)$^+$ at m/e 141 which then lost CH_2 to give (naphthyl)$^+$ or $C_{10}H_7^+$ at m/e 127. The cleavage of N_1-N_2 and C_3-N_4 bonds was also observed in all the compounds. Thus in the thiol series, the (CNSH)$^+$ was seen at m/e 59 while thioglycolic acids produced (CNSCH_2COO)$^+$ ion at m/e 116. In all the thioglycolic acids, decarboxylation occurred to a significant extent resulting in a peak at m/e 44. Yet another fragment that was observed in all thioglycolic acids was (SCH_2COOH)$^+$ occurring at m/e 91.

EXPERIMENTAL

The melting points of these compounds were taken on a Fisher John's melting point apparatus and are corrected. The infrared spectra were recorded on a Beckman model-33 double beam spectrophotometer. All compounds were examined as suspensions in nujol in the range of 700-4000 cm^{-1}. The nuclear

magnetic resonance spectra of **1-12** were recorded on a Varian Associates A-60 instrument in DMSO-d_6 using tetramethylsilane as an internal standard. The mass spectra were obtained on a Dupont model 21-490 spectrometer operating at 70 ev.

The arylisothiocyanates used in this study were purchased from Trans World Chemicals, Inc., Washington, D. C., and 1-naphthylacethydrazide was obtained from Fluka, AG Chemische Fabrik, Switzerland.

1-(1-Naphthylacetyl)-4-aryl-thiosemicarbazides (**1a**).

Equimolar quantities of 1-naphthylacethydrazide (0.1 mole) and appropriate aryl isothiocyanates (0.1 mole) in 100 ml. of ethanol were refluxed for 1 hour. The excess of ethanol was removed under reduced pressure. The solid mass thus obtained was washed with ice-cold ethanol, dried and recrystallized from ethanol. The melting points of these 1-(1-naphthylacetyl)-4-aryl-thiosemicarbazides were found to correspond with those reported earlier (8).

5-(1-Naphthylmethyl)-4-aryl-*s*-triazole-3-thiols (**1-6**).

Following the earlier procedure (3), 0.02 mole of 1-(1-naphthylacetyl)-4-aryl-thiosemicarbazide in 100 ml. of 2*N* aqueous sodium hydroxide solution was refluxed for 2-3 hours. The reaction mixture was filtered, cooled, and the filtrate was acidified to *p*H 2 with 2*N* hydrochloric acid. The crude product thus precipitated out was filtered, washed several times with water and recrystallized from a suitable solvent. The physical constants and spectral analyses of various 5-(1-naphthylmethyl)-4-aryl-*s*-triazole-3-thiols are recorded in Tables I and III, respectively.

5-(1-Naphthylmethyl)-4-aryl-*s*-triazole-3-yl-thioglycolic Acids (**7-12**).

A mixture of suitable substituted-*s*-triazole-3-thiol (0.01 mole), monochloroacetic acid (0.01 mole) and 50 ml. of aqueous sodium hydroxide solution (0.02 mole) was refluxed for 3 hours. The reaction mixture was filtered while hot and the filtrate was acidified to *p*H 2 with 2*N* hydrochloric acid. The various substituted-*s*-triazol-3-yl-thioglycolic acids thus precipitated out, were filtered, washed with water and recrystallized from the appropriate solvents. These compounds, recorded in Table II, were characterized by spectral analyses (Table IV).

Acknowledgments.

This investigation was supported in part by the United States Public Health Service NIDA Grant 7-R01-DA 01893-01. The authors wish to express their thanks to Dr. R. G. Severson and Dr. S. P. Singh for their advice and encouragement. Grateful acknowledgment is made to Northwest Area Foundation, Saint Paul, Minnesota for providing a Hill Professorship to S. S. Parmar.

REFERENCES AND NOTES

(1) G. Martin, German Patent, 2,240,043. (Cl. C 07d) March (1973); *Chem. Abstr.*, 78, 136302t (1973).

(2) S. S. Parmar, A. K. Gupta, T. K. Gupta and H. H. Singh, *J. Med. Chem.*, 15, 999 (1972).

(3) S. S. Parmar, V. K. Rastogi, V. K. Agarwal, J. N. Sinha and A. Chaudhari, *Can. J. Pharm. Soc.*, 9, 107 (1974).

(4) T. George, D. V. Mehta, R. Tahilramani, J. David and P. K. Talwalker, *J. Med. Chem.*, **14**, 335 (1971).

(5) J. S. Kaltenbronn, Belgian Patent 647,400 (1964); *Chem. Abstr.*, **63**, 14787c (1965).

(6) M. W. Whitehouse and R. A. Scherrer, "Anti-inflammatory Agents: Chemistry and Pharmacology", Vol. 1, Academic Press, New York, N. Y., 1974, pp. 101-104 and references therein.

(7) V. Kishore, S. S. Parmar, V. I. Stenberg and S. Kumar, *Res. Commun. Chem. Pathol. Pharmacol.*, 11, 581 (1975).

(8) V. Kishore, S. Kumar, N. K. Narain, S. S. Parmar and V. I. Stenberg, *Pharmacology*, 14, 390 (1976).

(9) K. T. Potts, R. Ambruster and E. Houghton, *J. Heterocyclic Chem.*, 8, 773 (1971).