Potential Broad Spectrum Anthelmintics IV: Design, Synthesis, and Antiparasitic Screening of Certain 3,6-Disubstituted-(7*H*)-*s*-triazolo-[3,4-*b*][1,3,4]thiadiazine Derivatives

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Abstract □ A series of 3,6-disubstituted-(7*H*)-*s*-triazolo[3,4-*b*][1,3,4]-thiadiazine derivatives were prepared. The compounds were designed to obtain structural similarities and/or bear isosteric relation with certain fused systems encountered in some well-known antiparasitic drugs. The substituents in all products were selected according to the Topliss scheme. Preliminary screening for antiparasitic activity, using *Ascaris vitulorum*, showed that the 6-substituted derivatives were generally more active than the 3-substituted ones and that the π effect is more pronounced than the σ effect.

Keyphrases □ Anthelmintics—potential broad spectrum, design, synthesis, antiparasitic screening of certain 3,6-disubstituted-(7*H*)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives □ Antiparasitic screening—potential broad spectrum anthelmintics, design, synthesis of certain 3,6-disubstituted-(7*H*)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives □ Thiadiazine, derivatives—potential broad spectrum, design, synthesis, antiparasitic screening of certain 3,6-disubstituted-(7*H*)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine derivatives

In the past few years, studies have been concerned with the design, synthesis, and screening for anthelmintic activity of several fused systems bearing structural and isosteric relationships with (±) 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazone (tetramisole) (1), the well-known broad spectrum anthelmintic. As a result, a variety of compounds derived from imidazo[1,2-*b*]thiazole (2, 3), imidazo[1,2-*b*][1,3,4]thiadiazole, thiazolo[2,3-*b*]thiadiazole (4), thiazolo[2,3-*c*]tetrazole (5) as well as their open-ring counterparts were developed.

In view of the recently reported antiparasitic activity of some derivatives of triazole (6, 7), a novel series of potential anthelmintics were prepared in which the triazole is a part of the fused heterocyclic system. The compounds of interest, namely 3,6-disubstituted-(7*H*)-*s*-triazolo[3,4-*b*]-[1,3,4]thiadiazines (III–XLIV), Scheme I, were designed to contain various substituents selected according to the Topliss scheme (8). The purpose was to study the effect of the different possible variations of π and σ on the biological activity of the parent compound.

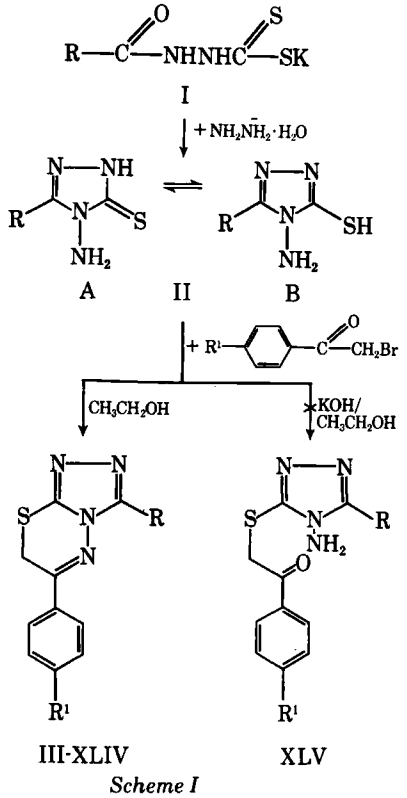
RESULTS AND DISCUSSION

Chemistry—Compounds III–XLIV were prepared in accordance with the sequence of reactions presented in Scheme I. The potassium salts of N^1-acyl-N^2-dithiocarbazates (I), synthesized from the reaction of the corresponding acylhydrazines (9–13) with carbon disulfide and potassium hydroxide, were treated with hydrazine hydrate in refluxing ethanol to give the 3-substituted-4-amino-*s*-triazolo-5-thiones (II) (14). The IR spectra of these triazoles indicated their existence in thione form *A* rather than in thiol form *B*. Condensation of the triazoles (II) with the appropriately substituted phenacylbromides (15, 16) in refluxing ethanol gave the required 3,6-disubstituted-(7*H*)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines (III–XLIV). The yields and physical constants of the products are recorded in Table I.

Unlike earlier claims (18, 19), the trials to synthesize the noncyclic analogs of compounds III–XLIV, namely the 3-(4-substituted aryl)-4-amino -5- [*S*-(4-substituted-phenacyl)mercapto]-(4*H*)-1,3,4-triazoles (XLV), which bear the same spatial arrangement as the triazolothiadiazines (III–XLIV), were fruitless. The reactions, even under the mildest conditions, always yielded the cyclized products.

The IR spectra of the products (III–XLIV) were compatible with the structures assigned. In particular, the thioureido (I, II, III, and IV) bands located for the C=S and —NH mixed vibrational coupling in the triazole (II) were greatly affected. The bands contributing to the —NH moiety of the —CSNH function at 1515 and 1090 cm^{-1} completely disappeared while those at 1315 and 950 cm^{-1}, characteristic for the C=S function (20), became weaker in intensity. The absence of the carbonyl absorbance at 1660–1630 cm^{-1} has also confirmed the cyclic structures. The PMR spectra showed the signals at the expected chemical shifts. The compounds containing the methyl groups in the aryl substituents showed a singlet in the region of 2.37–2.50 ppm, while those containing the methoxy functions showed the singlet at 3.73–3.87 ppm. The C_7-methylinic protons appeared as a singlet in the region of 4.42–4.43 ppm. The chemical shifts of the aromatic protons of the 3- and 6-aryl functions were dependent on the nature of the *p*-substituents in these groups.

For more concerted evidence, the mass spectra of compounds XXVII and XXX, as representative examples, were run, and the structure of the ions formed, under electron impact, was assigned. The spectrum of 3-*p*-methoxyphenyl-6-*p*-bromophenyl-(7*H*)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (XXX) showed the molecular ion peak at *m/z* 400 (402 for M+2). Its



Scheme I

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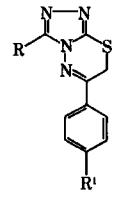

Table I—Yields, Physical Constants, Microanalytical Data, and Antiparasitic Activity of the Synthesized 3,6-Disubstituted-(7*H*)-*s*-triazolo[3,4-b][1,3,4]thiadiazine Derivatives.

Compound No.	*R*	R^1	Melting Point	Yield, %	Molecular Formula	Analysis, % Calc.	Found	π or $\Sigma\pi$	σ or $\Sigma\sigma$	Antiparasitic Activity Time[a]	Observed Effect
III	C_6H_5	H	113–114[b]	70				0.00	0.00	15–25	D[c]
IV	C_6H_5	NO_2	305	72	$C_{16}H_{11}N_5O_2S$	C 56.97 H 3.26 N 20.77 S 9.49	56.50 3.50 21.00 9.30	0.24	0.78	30–35	R[d]
V	C_6H_5	Cl	239–240	92	$C_{16}H_{11}ClN_4S$	C 58.89 H 3.37 Cl 10.73 S 9.81	59.00 3.50 10.80 9.50	0.70	0.23	7–12	D
VI	C_6H_5	Br	244–245	94	$C_{16}H_{11}BrN_4S$	C 51.75 H 2.96 Br 21.56 N 15.09 S 8.62	51.70 3.20 21.30 14.70 8.30	1.19	0.23	7–10	D
VII	C_6H_5	CH_3	192–194	78	$C_{17}H_{14}N_4S$	C 66.67 H 4.57 N 18.30 S 10.45	66.60 4.10 18.60 10.80	0.60	−0.17	20–30	R
VIII	C_6H_5	OCH_3	216–217	50	$C_{17}H_{14}N_4OS$	C 63.35 H 4.34 N 17.39	62.90 4.49 17.50	−0.04	−0.27	20–30	R
IX	$C_6H_4Cl(p)$	H	260–261	94	$C_{16}H_{11}ClN_4S$	C 58.89 H 3.37 Cl 10.73 N 17.17 S 9.81	58.80 3.40 11.10 17.50 9.60	0.70	0.23	20	D
X	$C_6H_4Cl(p)$	NO_2	246–247	63	$C_{15}H_{10}ClN_5O_2S$	C 51.75 H 2.69 Cl 9.43 S 8.60	51.50 3.10 9.10 8.20	0.94	1.01	35	R
XI	$C_6H_4Cl(p)$	Cl	276–278	56	$C_{16}H_{10}Cl_2N_4S$	C 53.33 H 2.77 Cl 19.44 N 15.55 S 8.88	53.00 3.10 18.90 15.90 9.20	1.40	0.46	7	D
XII	$C_6H_4Cl(p)$	Br	275–276	79	$C_{16}H_{10}BrClN_4S$	C 47.40 H 2.46 Br 19.75 N 13.82 S 7.90	47.70 2.40 19.40 14.00 7.70	1.89	0.46	7–10	D
XIII	$C_6H_4Cl(p)$	CH_3	253–254	71	$C_{17}H_{13}ClN_4S$	C 60.00 H 3.82 Cl 10.29	59.90 3.80 10.40	1.30	0.06	35	D
XIV	$C_6H_4Cl(p)$	OCH_3	235–236	62	$C_{17}H_{13}ClN_4OS$	C 57.30 H 3.65 Cl 9.80 N 15.73 S 8.98	57.60 3.80 10.10 15.30 9.40	0.66	−0.04	30	D
XV	$C_6H_4Br(p)$	H	258–259	90	$C_{16}H_{11}BrN_4S$	C 51.75 H 2.96 Br 21.56 N 15.09 S 8.62	51.60 2.95 22.00 15.50 8.80	1.19	0.23	10	D
XVI	$C_6H_4Br(p)$	NO_2	247–249	73	$C_{16}H_{10}BrN_5O_2S$	C 46.15 H 2.40 Br 19.23 N 16.82 S 7.69	46.10 2.50 19.00 17.20 7.30	1.43	1.01	50	R
XVII	$C_6H_4Br(p)$	Cl	271–273	83	$C_{16}H_{10}BrClN_4S$	C 47.40 H 2.46 Br 19.75 Cl 8.64 N 13.82	47.30 2.80 19.00 8.40 14.00	1.89	0.46	12–15	D
XVIII	$C_6H_4Br(p)$	Br	266–267	94	$C_{16}H_{10}Br_2N_4S$	C 42.66 H 2.22 Br 35.55 N 7.11	42.30 2.30 35.10 7.30	2.38	0.46	5–10	D

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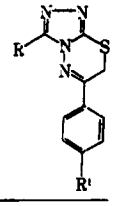

Table I–*Continued*

Compound No.	R	R^1	Melting Point	Yield, %	Molecular Formula	Analysis, %		π or $\Sigma\pi$	σ or $\Sigma\sigma$	Antiparasitic Activity	
						Calc.	Found			Time[a]	Observed Effect
XIX	$C_6H_4Br(p)$	CH_3	262–263	70	$C_{17}H_{13}BrN_4S$	C 52.98 H 3.37 Br 20.77 N 14.54 S 8.31	53.10 3.70 20.50 14.25 8.00	1.79	0.06	25	D
XX	$C_6H_4Br(p)$	OCH_3	258–260	82	$C_{17}H_{13}BrN_4OS$	C 50.87 H 3.27 Br 19.95 S 7.96	50.40 3.25 19.60 8.30	1.15	−0.04	25	D
XXI	$C_6H_4CH_3(p)$	H	200–201	81	$C_{17}H_{14}N_4S$	C 66.67 H 4.57 N 18.30	66.70 4.80 18.00	0.60	−0.71	25–35	R
XXII	$C_6H_4CH_3(p)$	NO_2	300	62	$C_{17}H_{13}N_5O_2S$	C 58.11 H 3.70 N 19.94 S 9.11	58.40 3.80 19.70 9.40	0.84	0.61	85	R
XXIII	$C_6H_4CH_3(p)$	Cl	210–212	76	$C_{17}H_{13}ClN_4S$	C 60.00 H 3.82 Cl 10.29 S 9.41	59.90 3.80 10.70 9.50	1.30	0.06	20	D
XXIV	$C_6H_4CH_3(p)$	Br	185–187	86	$C_{17}H_{13}BrN_4S$	C 52.98 H 3.37 Br 20.77 N 14.54 S 8.31	53.30 3.70 20.50 14.25 8.00	1.79	0.06	25	D
XXV	$C_6H_4CH_3(p)$	CH_3	170–172	76	$C_{18}H_{16}N_4S$	C 67.50 H 5.00 N 17.50 S 10.00	67.20 4.70 17.10 10.40	1.20	−0.34	70	R
XXVI	$C_6H_4CH_3(p)$	OCH_3	181–183	80	$C_{18}H_{16}N_4OS$	C 64.82 H 4.76 S 9.52	63.93 4.90 9.40	0.56	−0.44	40–50	R
XXVII	$C_6H_4OCH_3(p)$	H	200–203	81	$C_{17}H_{14}N_4OS$	C 63.35 H 4.34 N 17.39	63.60 4.50 17.00	−0.04	−0.27	30–35	D
XXVIII	$C_6H_4OCH_3(p)$	NO_2	251–253	39	$C_{17}H_{13}N_5O_3S$	C 55.58 H 3.54 N 19.07 S 8.71	55.60 3.90 19.40 8.30	0.20	−0.51	90	R
XXIX	$C_6H_4OCH_3(p)$	Cl	211–213	59	$C_{17}H_{13}ClN_4OS$	C 57.30 H 3.65 Cl 9.83 N 15.73	57.50 3.70 9.80 15.80	0.66	−0.04	20–25	R
XXX	$C_6H_4OCH_3(p)$	Br	217–218	80	$C_{17}H_{13}BrN_4OS$	Br 19.95 N 13.96 S 7.98	19.60 14.30 8.30	1.15	−0.44	15–25	D
XXXI	$C_6H_4OCH_3(p)$	CH_3	164–166	51	$C_{18}H_{16}N_4OS$	C 64.28 H 4.76 N 16.66 S 9.52	64.40 4.90 17.00 9.10	0.56	−0.44	45	R
XXXII	$C_6H_4OCH_3(p)$	OCH_3	172–173	72	$C_{18}H_{16}N_4O_2S$	C 61.36 H 4.54 N 15.90 S 9.09	61.00 4.70 16.20 9.20	−0.08	−0.54	60–65	R
XXXIII	$C_6H_4NH_2(p)$	H	244–245	59	$C_{16}H_{13}N_5S$	C 62.54 H 4.23 S 10.42	62.10 4.30 10.00	−1.23	−0.66	30	R
XXXIV	$C_6H_4NH_2(p)$	NO_2	251–253	43	$C_{16}H_{12}N_6O_2S$	N 23.86 S 9.09	23.50 9.50	−0.99	0.12	50–60	R
XXXV	$C_6H_4NH_2(p)$	Cl	239–241	44	$C_{16}H_{12}ClN_5S$	C 56.22 H 3.51 Cl 10.39 N 20.49 S 9.37	56.20 3.60 10.40 20.60 8.90	−0.53	−0.43	15–20	R
XXXVI	$C_6H_4NH_2(p)$	Br	237–238	64	$C_{16}H_{12}BrN_5S$	C 49.74 H 3.10 Br 20.72 S 8.29	49.70 3.30 21.00 8.50	−0.04	−0.43	15–20	R

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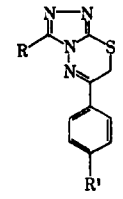


Table I–*Continued*

Compound No.	R	R[1]	Melting Point	Yield, %	Molecular Formula	Analysis, %		π or Σπ	σ or Σσ	Antiparasitic Activity	
						Calc.	Found			Time[a]	Observed Effect
XXXVII	$C_6H_4NH_2$(p)	CH_3	254–255	59	$C_{17}H_{15}N_5S$	C 63.50 H 4.30 S 9.69	63.80 4.80 9.70	−0.63	−0.83	25–35	R
XXXVIII	$C_6H_4NH_2$(p)	OCH_3	182–184	50	$C_{17}H_{15}N_5OS$	C 60.51 H 4.45 N 20.77	60.32 4.90 20.90	−1.27	−0.93	25–30	R
XXXIX	4-pyridyl	H	230–231[e]	81						20–25	R
XXXX	4-pyridyl	NO_2	250–252	59	$C_{15}H_{10}N_6O_2S$	C 53.25 H 2.95 S 9.46	52.98 2.60 9.80			30	R
XLI	4-pyridyl	Cl	254–255	75	$C_{15}H_{10}ClN_5S$	C 55.04 H 3.05 S 9.78	54.90 3.30 9.40			7–10	D
XLII	4-pyridyl	Br	262–264	79	$C_{15}H_{10}BrN_5S$	C 48.38 H 2.68 Br 21.50 S 8.60	48.20 3.10 21.20 8.30			7–10	D
XLIII	4-pyridyl	CH_3	237–239	78	$C_{16}H_{13}N_5S$	C 62.54 H 4.23 S 10.42	62.60 4.10 10.30			25	R
XLIV	4-pyridyl	OCH_3	230–231	62	$C_{16}H_{13}N_5OS$	C 59.07 H 4.16 N 21.53 S 9.84	59.30 4.60 21.20 10.00			25–30	R

[a] Time in minutes for 100% deaths or relaxation. [b] The compound is reported in Ref. 18. [c] D = Death. [d] R = Relaxation. [e] Reference 17.

fragmentation as shown in Scheme II followed four different pathways. In accordance with pathway 1, the molecule eliminated sulfur giving ion *A* at *m/z* 368 (370). In pathway 2, a *p*-bromophenyl ion was removed from compound XXX giving ion *B*, *m/z* 245, which on elimination of a nitrogen molecule and a cyanide group yielded ion *C* at *m/z* 191. This ion in turn eliminated cyanide and methylene fragments to give the phenoxyethylenesulfide ion *D* at *m/z* 151, or underwent successive cleavage of carbon monosulfide, methylene, cyanide, methyl, carbon monoxide moieties, and hydrogen producing ions *E* and *F* at *m/z* 133 and 63, respectively. The *p*-methoxyphenylcyanide ion *E* was shown as the base peak. In alternative fragmentation pathway 3, the product cleaved ion *E* and nitrogen to produce *p*-bromophenylthiazole ion *G* at *m/z* 241 (243). This on further elimination of carbon monosulfide, methylene, and cyanide fragments gave *p*-bromophenylcyanide ion *H* at *m/z* 181 (183) and *p*-bromophenyl ion *I* at *m/z* 155 (157). In pathway 4, however, the molecule eliminated ions *H* and *E* leading to ion *J* at *m/z* 219 and ion *N* at *m/z* 90. Ion *J* either eliminated a hydrogen sulfide and a methyl group giving ion *M* at *m/z* 158 or cleaved a methylene and accepted two hydrogens to produce ion *K* at *m/z* 207. Further cleavage of a *p*-methoxyphenyl ion or ion *E* from ion *K* gave ion *L* at *m/z* 102 and the pseudothiourea ion at *m/z* 75. The mass spectrum of compound XXVII showed the molecular ion peak at *m/z* 322 and the ion at 133, corresponding to *p*-methoxyphenylcyanide, as the base peak. The additional ions shown were indicative that the fragmentation of the compound followed the fragmentation pattern proposed for compound XXX.

Antiparasitic Screening—The effect of the synthesized compounds III–XLIV on *Ascaris vitulorum* worms was evaluated in accordance with a method developed previously (21). As shown in Table I, the products containing substituted phenyl groups in the 3 position were generally less active than those having the same type of substituents at the 6 position. In addition, due to increased π effect, the biological activity was higher for compounds containing 4-chloro and 4-bromophenyl substituents relative to the nonsubstituted ones.

The tolyl derivatives were found to be less potent compared with the phenyl derivatives. This finding, as well as the fact that compounds containing the nitro group ($\sigma = 0.78$) or the methoxyl group ($\sigma = 0.27$) were less active than the substituted derivatives, led to the assumption that the π effect is more predominating in this series of compounds. Moreover, the equipotent activity of the products containing 4-pyridyl and phenyl functions has been attributed to the isostericity of both functional groups.

EXPERIMENTAL[1]

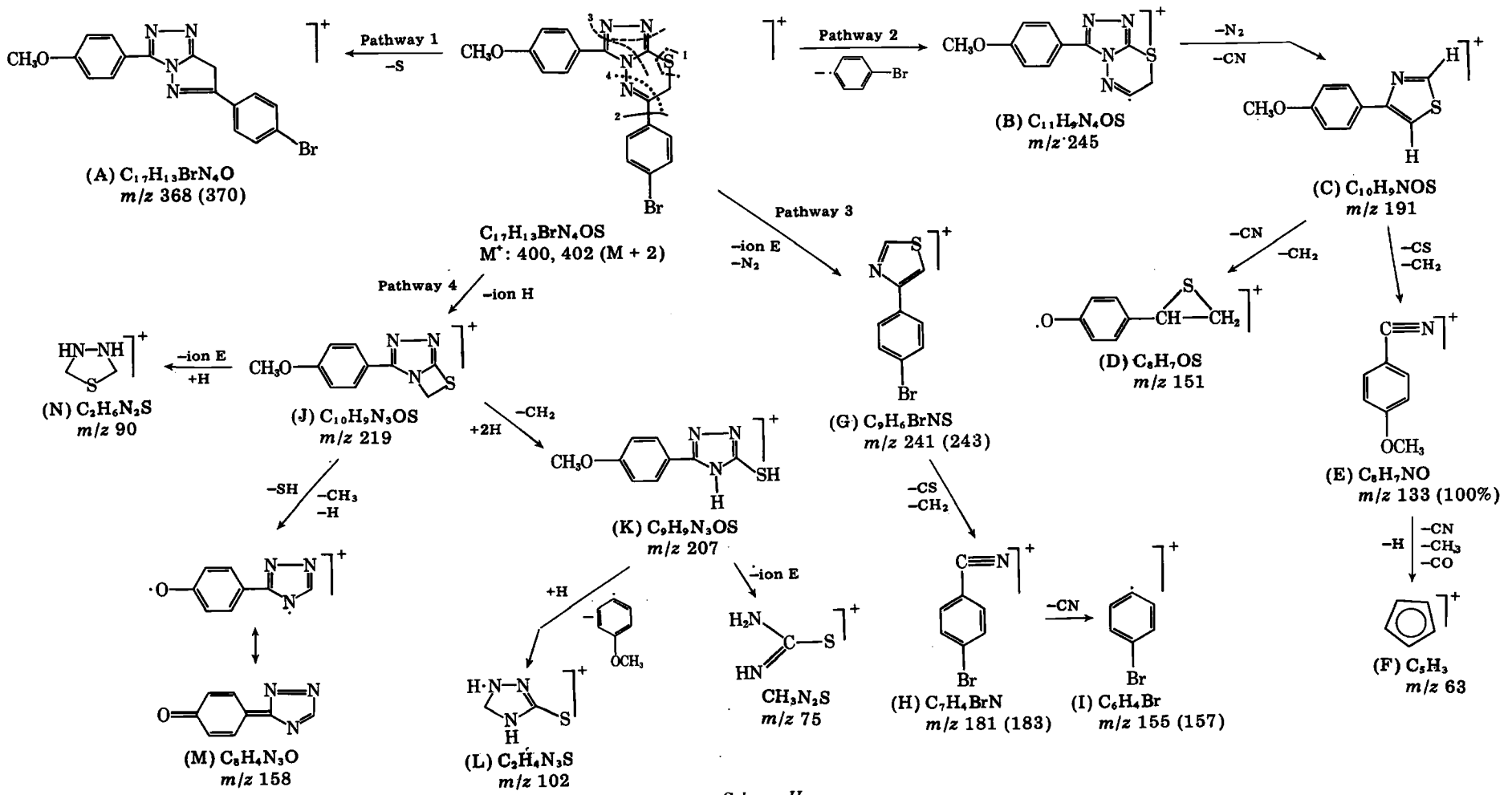
Potassium Salts of 3-Aroyl Dithiocarbazates (I)—Compound I was prepared, as reported (14), starting from the corresponding acid hydrazides. They were obtained in nearly quantitative yield and employed in the following reactions without further purification.

3-Substituted-4-amino-5-mercapto-(4*H*)-1,2,4-triazoles (II)—Compound II was prepared by reaction of potassium salts of 3-aroyl dithiocarbazates with 98% hydrazine hydrate according to the reported method (14).

3,6-Disubstituted - (7*H*)-*s*-triazolo[3,4 - *b*][1,3,4]thiadiazines (III–XLIV)—Equimolar amounts of the triazoles (II) and the appropriate phenacyl bromide derivative in anhydrous ethanol were heated under reflux for 2 hr. After cooling, the mixtures were neutralized with ammonium hydroxide to separate the free base. Filtration, washing with water, and crystallization from boiling ethanol separated the products as white or pale yellow crystals. The physical constants of the products are recorded in Table I. Mass spectra for compound XXVII, *m/z* (relative abundance percent): M^+ at 322 (97), 293 (3), 290 (4), 288 (2), 245 (2), 219 (8), 191 (4), 177 (4), 161 (40), 158 (8), 151 (7), 145 (16), 133 (97), 132 (26), 130 (7), 118 (10), 117 (16), 103 (100), 90 (29), 77 (48), 63 (13), 58 (36), 51 (2); and for compound XXX: 402 (M+2) and 400 (M^+) (63), 370 (13), 368 (13), 245 (3), 241 (5), 239 (5), 219 (10), 207 (10), 197 (8), 195 (6), 191 (4), 183 (31), 181 (36), 161 (39), 158 (8), 157 (8), 155 (8), 151 (5), 145 (13), 133 (100), 118 (8), 116 (8), 103 (26), 102 (49), 90 (27), 76 (3), 75 (21), 63 (13), 58 (36), 51 (17), 50 (17).

3-Substituted-4-amino-5-[*S*-(substituted phenacyl)mercapto]-(4*H*)-1,2,4-triazole (XLV) (Attempted Preparation)—A solution of 3-(4-methoxyphenyl)-4-amino-5-mercapto-*s*-triazole (0.1 mole) in 1 *N* methanolic potassium hydroxide (20 ml) was stirred while cooling in an

[1] All melting points were uncorrected. IR spectra were measured for Nujol Mulls on a Beckmann 4210 IR Spectrophotometer. PMR spectra were measured for dimethyl sulfoxide-d_6 solutions on a high resolution T-60A Varian NMR Spectrometer. The mass spectra were taken to 70 eV on an AEIMS 902 Mass Spectrometer attached to an AEIDS 30 data system.


Pathway 1
–S
Pathway 2
–N₂
–CN
Pathway 3
–ion E
–N₂
Pathway 4
–ion H
–ion E
+H
–CH₂
+2H
–SH
–CH₃
–H
–CN
–CH₂
–CS
–CH₂
–CN
–H
–CN
–CH₃
–CO
+H
–ion E
(A) C₁₇H₁₃BrN₄O
m/z 368 (370)
C₁₇H₁₃BrN₄OS
M⁺: 400, 402 (M + 2)
(B) C₁₁H₉N₄OS
m/z 245
(C) C₁₀H₉NOS
m/z 191
(D) C₈H₇OS
m/z 151
(E) C₈H₇NO
m/z 133 (100%)
(F) C₅H₃
m/z 63
(G) C₉H₆BrNS
m/z 241 (243)
(H) C₇H₄BrN
m/z 181 (183)
(I) C₆H₄Br
m/z 155 (157)
(J) C₁₀H₉N₃OS
m/z 219
(K) C₉H₉N₃OS
m/z 207
(L) C₂H₄N₃S
m/z 102
(M) C₈H₄N₃O
m/z 158
(N) C₂H₆N₂S
m/z 90
CH₃N₂S
m/z 75

Scheme II

ice bath until a precipitate developed. This was dissolved by addition of methanol and the solution was treated by a dropwise addition of a solution of 4-chlorophenacyl bromide (0.2 mole) in methanol (20 ml) while maintaining the pH at 7–7.5 by 1 *N* methanolic potassium hydroxide. The final mixture was stirred for 1 hr while cooling in ice and for an additional hour at room temperature. Dilution with cold water (60 ml) caused complete separation of the product, which was found to be the cyclized product (XXIX) as evidenced by mixed melting point determination and superimposability of IR. Repeating the reaction for a shorter period of time (15 min) in aqueous methanol again gave the cyclized product (XXIX).

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Influence of Environment and Substituents on the Stability of the Radical Cations of Several Phenothiazine Derivatives

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Abstract □ The UV decay spectra of the radical cations of several phenothiazine derivatives in different environments was studied. The influence of the substituents on the reference spectrum could be seen, as well as a relationship between the stability of such radicals and the acidity of the environment. There is also an influence of the substituents on the stability of the radicals in the different environments studied. The instability of the radicals in solution has been studied to relate to the pharmacological activity of neuroleptics.

Keyphrases □ Phenothiazine—derivatives, influence of environment and substituents on the stability of the radical cation □ Neuroleptics—phenothiazine derivatives, influence of environment and substituents on the stability of the radical cations □ Radical cations—influence of environment and substituents on stability, phenothiazine derivatives

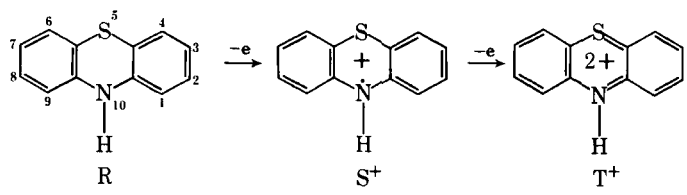
The physicochemical study of phenothiazines has increased in recent years. One of the most common properties of phenothiazine and its derivatives is that they are oxidized easily (1–3). The fact that various oxidized compounds were found (4) among metabolic degradation products suggested that the phenothiazines could act in humans in their oxidized form or produce a redox reaction. Based on this, it was proposed (5) that certain products could act in humans by means of an energy or electron transfer. The phenothiazines, then, can act as electron donors if there are adequate acceptors. Evidence has been presented that the drugs interact with dopamine receptors, and a good correlation has been found between drug potency and the strength of this interaction (6, 7). Several investigators have proposed that the cation radical formed by the oxidation of a phenothiazine derivative (8) such as chlorpromazine, could be an intermediate of the metabolism of the drug and may be the active pharmacological entity (8, 9).

In the present report a study of the kinetics of decay of the first oxidation product of several phenothiazine derivatives in different environments is described, and their instability is related to the substituents and their pharmacological activity.

BACKGROUND

The influence of the R_2 substituents and the structure of the R_{10} side chain on the antipsychotic activity of phenothiazines has been studied (10). However, information about substituent effects on the radical cation behavior is less prevalent due to the difficulty in studying the reactive cation radicals; therefore, it is useful to investigate the behavior of the radicals as a function of structure, given the possible involvement of the radicals in the metabolism of the drugs and in their activity.

The cation radicals of phenothiazine were first obtained in 1913 (11). It was stated that the phenothiazine oxidation proceeds by two steps (12):



Scheme I

0022-3549/83/0100-0050$01.00/0