(I, R_2 = aryl, R_3 = H) were the most toxic and most active hypothermic agents, although they were devoid of paralyzing and anticonvulsant properties. The most effective paralyzing and anticonvulsant compounds were those containing an alkyl group in the 3-position and a chloro- or dichloro-substituted phenyl group in the 2-position of the metathiazanone ring.

A comparison of the 2-aryl-3-alkyl-4-metathiazanones with the corresponding 1-dioxides indicated that both types had similar pharmacological profiles but differed in oral absorption, toxicity and duration.

The 1-dioxides showed the maximal activity but had a somewhat shorter duration than the parent compounds. In general, the pharmacological profile found for those metathiazanone derivatives suggested a mephanesen-like type of action. One of the most active members of the present series, 2 - (4 - chlorophenyl) - 3 - methyl- 4 - metathiazanone-1-dioxide, in clinical testing, has been found to be an effective and promising skeletal muscle relaxant.

Detailed pharmacology of most of the compounds reported in the present work will be published elsewhere.

Acknowledgment.—We are indebted to Mr. M. E. Auerbach and Mr. K. D. Fleischer and staffs for the analytical data and corrected melting points, and to Dr. F. Coulston for pre-clinical studies in monkeys.

Experimental[6]

2-Aryl-3-alkyl-4-metathiazanones.—The preparation of these compounds is illustrated below.

3-Methyl-2-(3-pyridyl)-4-metathiazanone.—A solution of 43.2 g. of 3-pyridinecarboxaldehyde, 42.5 g. of β-mercaptopropionic acid and 14 g. of methylamine in 200 ml. of benzene was refluxed for 48 hours with a continuous separator connected to the reaction vessel for removal of water. After this time the theoretical amount of water was collected. The reaction mixture was cooled and washed with dilute ammonium hydroxide. The solid (53 g.) which separated from the benzene solution was collected, washed with water, dried and recrystallized from absolute ethyl alcohol to give 43.5 g. (52%) of product melting at 165.2–168.8°.

Anal. Calcd. for $C_{10}H_{12}N_2OS$: N, 13.45; C, 57.65; H, 5.81. Found: N, 13.43; C, 57.43; H, 6.35.

If no solid was obtained from the benzene solution after washing with ammonium hydroxide the solvent was removed *in vacuo* and the residue was vacuum distilled. In several instances the viscous distillates solidified on standing.

3-Methyl-2-(2-pyridyl)-4-metathiazanone was prepared in 20% yield after refluxing for 72 hours. The product was recrystallized several times from a mixture of benzene–hexane; m.p. 89.5–92° (uncor.).

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.65; H, 5.81; N, 13.45. Found: C, 58.16; H, 6.46; N, 13.16.

3-Methyl-2-(2-thienyl)-4-metathiazanone was prepared in 59% yield after refluxing for 72 hours. The product was recrystallized from Skellysolve C; m.p. 80.6–83.4°.

Anal. Calcd. for $C_9H_{11}NOS_2$: C, 50.67; H, 5.20. Found: C, 50.46; H, 5.50.

2-Aryl-4-metathiazanone-1-dioxides.—The following example illustrates the general procedure for the preparation of these compounds.

3-Methyl-2-(3-pyridyl)-4-metathiazanone 1-Dioxide.—A solution of 36.7 g. of potassium permanganate in 300 ml. of water was added dropwise to a well-stirred solution of 28.3 g. of 2-(3-pyridyl)-3-methyl-4-metathiazanone in 230 ml. of glacial acetic acid. The temperature was kept below 30° with external cooling. A concentrated aqueous sodium bisulfite solution then was added to remove the manganese dioxide. The reaction mixture was basified to a *p*H of 6 and extracted several times with chloroform. The solvent from the combined extracts was distilled *in vacuo* and the residue was triturated with hexane to give 12.5 g. of solid. After recrystallization from ethyl alcohol, 9 g. of product was obtained melting at 163.2–171.8°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S$: C, 49.98; H, 5.04; N, 11.66. Found: C, 50.30; H, 4.67; N, 11.46.

In many instances a solid product was obtained after addition of the bisulfite solution and was filtered off and purified by recrystallization. Only in the case of the 2-(pyridyl) compounds was it necessary to adjust the *p*H. Most of the sulfones were recrystallized from either ethyl or isopropyl alcohol.

3-Methyl-2-(2-pyridyl)-4-metathiazanone 1-dioxide was prepared in 37% yield. After recrystallization from isopropyl alcohol the product melted at 144.6–152.4°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S$: S, 13.34; N, 11.66. Found: S, 13.11; N, 11.61.

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(6) All melting points are corrected unless otherwise indicated.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Some Thiazolines and Thiazolidinones with Antituberculous Activity

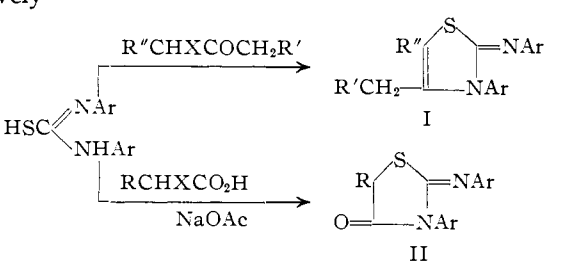
BY R. H. MIZZONI AND P. C. EISMAN

RECEIVED NOVEMBER 25, 1957

A series of 3-aryl-2-arylimino-4-substituted-4-thiazolines and 3-aryl-2-arylimino-4-thiazolidinones were prepared and evaluated as antituberculous agents. Some of the substances are active in this regard.

Appropriately substituted 1,3-bis-thiocarbanilides display a high order of antituberculous activity *in vitro* and in experimental animals.[1] It seemed desirable, therefore, to investigate this property among various cyclic modifications of the parent structure.

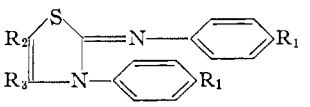
Two such modifications may be found in the 3-aryl-2-arylimino-4-thiazoline and 3-aryl-2-arylimino-4-thiazolidinone structures, I and II respectively



(1) C. F. Huebner, J. L. Marsh, R. H. Mizzoni, R. P. Mull, D. C. Schroeder, H. A. Troxell and C. R. Scholz, THIS JOURNAL, **75**, 2274 (1953); R. L. Mayer, P. C. Eisman and E. A. Konopka, *Proc. Soc. Exptl. Biol. Med.*, **89**, 88 (1955).

TABLE I

3-(R_1-PHENYL)-2-(R_1-PHENYLIMINO)-4-(R_3)-5-(R_2)-4-THIAZOLINES



HX

R_1	R_3 (R_2)	HX	Yield, %	M.p., °C.	Empirical formula	Analyses, % Found	Calculated
$-OCH_2CH_2CH(CH_3)_2$	Me	HCl	61.4[a]	180–181	$C_{26}H_{35}ClN_2O_2S$	S, 6.69	S, 6.74
						Cl, 7.39	Cl, 7.46
$-OCH_2CH_2CH(CH_3)_2$	$4\text{-}BrC_6H_4$	HBr	52.0[a]	234–234.5	$C_{31}H_{36}Br_2N_2O_2S$	N, 4.19	N, 4.26
$-OCH_2CH{=}CH_2$	Me	HCl (+1H_2O)	79.8[a]		$C_{22}H_{25}ClN_2O_3S$	N, 6.60	N, 6.47
						S, 7.29	S, 7.40
$-OCH_2CH_2CH(CH_3)_2$	$-CH_2CH_2NC_5H_{10}$	2HBr	73.5[b]	184 dec.	$C_{32}H_{47}Br_2N_3O_2S$	N, 5.91	N, 6.02
						S, 4.78	S, 4.59
$OC_3H_7(n)$	$-CH_2CH_2NC_5H_{10}$	2HBr	79.8[b]	175–176	$C_{28}H_{39}Br_2N_3O_2S$	N, 6.65	N, 6.55
						S, 4.87	S, 4.99
$OCH_2CH{=}CH_2$	$-CH_2CH_2NC_5H_{10}$	2HBr	44.1[b]	210–212 d.	$C_{28}H_{35}Br_2N_3O_2S$	N, 6.47	N, 6.59
						S, 4.87	S, 5.02
						Br, 24.81	Br, 25.07
$n\text{-}C_4H_9$	$-CH_2CH_2NC_5H_{10}$	2HBr (+1H_2O)	66.5[b]	213	$C_{30}H_{45}Br_2N_3OS$	C, 55.22	C, 54.95
						H, 6.91	H, 6.91
						N, 6.35	N, 6.41
$-OC_2H_5$	Me	HCl	75.4[a]	173	$C_{20}H_{23}ClN_2O_2S$	N, 7.08	N, 7.16
						S, 8.06	S, 8.20
$n\text{-}C_4H_9$	C_6H_5	HCl	67.5[a]	155	$C_{29}H_{33}ClN_2S$	N, 6.00	N, 5.87
						Cl, 7.63	Cl, 7.43
OC_2H_5	C_6H_5	HCl	94.2[a]	132	$C_{25}H_{25}ClN_2O_2S$	N, 5.87	N, 6.18
						Cl, 7.70	Cl, 7.82
$OCH_2CH{=}CH_2$	C_6H_5	HCl	82.1[a]	140	$C_{27}H_{25}ClN_2O_2S$	N, 5.97	N, 5.87
						Cl, 7.58	Cl, 7.43
$OCH_2CH{=}CH_2$	$4\text{-}BrC_6H_4$	HBr	77.1[a]	174.5–176	$C_{27}H_{24}Br_2N_2O_2S$	N, 4.88	N, 4.66
						S, 5.34	S, 5.33
$-OC_3H_7$	C_6H_5	HCl	76.7[a]	149.5–150.5	$C_{27}H_{29}ClN_2O_2S$	N, 5.99	N, 5.82
						Cl, 7.67	Cl, 7.37
$n\text{-}C_4H_9$	$4\text{-}BrC_6H_4$	HBr	68.4[c]	193.5–195	$C_{29}H_{32}Br_2N_2S$	N, 4.87	N, 4.66
						S, 5.38	S, 5.33
$-OC_3H_7$	Me	HCl	72.4[a]	169–170	$C_{22}H_{27}ClN_2O_2S$	N, 6.87	N, 6.68
						S, 7.44	S, 7.65
$-OC_2H_5$	$-CH_2CH_2NC_5H_{10}$	2HBr	64.7[b]	140	$C_{26}H_{35}Br_2N_3O_2S$	N, 7.00	N, 6.85
						Br, 25.91	Br, 26.05
$-C_4H_9\text{-}n$	$CH_3(CH_3)$	HBr	63.4[c]	182–182.5	$C_{25}H_{33}BrN_2S$	N, 6.08	N, 5.91
						S, 7.07	S, 6.77
$OCH_2CH{=}CH_2$	$CH_3(CH_3)$	HBr	53.0[c]	154–155.5	$C_{23}H_{25}BrN_2O_2S$	C, 58.52	C, 58.34
						H, 5.46	H, 5.32
						N, 5.94	N, 5.91
$-C_4H_9\text{-}n$	Me	HCl	75.0[a]	179–180	$C_{24}H_{31}ClN_2S$	C, 69.48	C, 69.45
						H, 7.60	H, 7.52
						N, 7.05	N, 6.75
$-OC_3H_7$	$CH_3(CH_3)$	HBr	70.4[c]	181.5–182	$C_{23}H_{29}BrN_2O_2S$	N, 5.77	N, 5.86
						S, 6.44	S, 6.71
$OCH_2CH_2CH(CH_3)_2$	$CH_3(CH_3)$	HBr	58.4[c]	203.5–204.5	$C_{27}H_{37}BrN_2O_2S$	N, 5.27	N, 5.25
						S, 6.23	S, 6.00
OC_2H_5	$Me(CH_2COOC_2H_5)$	HBr	37.6	160.5	$C_{24}H_{29}BrN_2O_4S$	N, 5.24	N, 5.37
						S, 6.24	S, 6.14
$OCH_2CH_2CH(CH_3)_2$	C_6H_5	..	52.7[a]	121–124	$C_{31}H_{36}N_2O_2S$	S, 6.37	S, 6.40
$-O\text{-}n\text{-}C_8H_{17}$	CH_3	HCl	81.1[a]	153–155	$C_{32}H_{47}ClN_2O_2S$	N, 5.10	N, 5.00
						S, 5.49	S, 5.73
$-O\text{-}n\text{-}C_7H_{15}$	CH_3	HCl	73.1[a]	160–161	$C_{30}H_{43}ClN_2O_2S$	S, 6.32	S, 6.03
						Cl, 6.79	Cl, 6.67
$-O\text{-}n\text{-}C_5H_{11}$	CH_3	..	29.7[a]	68–69	$C_{26}H_{34}N_2O_2S$	N, 6.32	N, 6.38
						S 6.96	S, 7.30
$O\text{-}C_6H_{13}\text{-}n$	CH_3	..	16.1[a]	63–64	$C_{28}H_{38}N_2O_2S$	N, 6.13	N, 6.00
						S, 6.88	S, 6.87
$-OCH_2CH_2CH(CH_3)_2$	C_6H_5	MeI	58.8[a]	201–204	$C_{32}H_{39}IN_2O_2S$	N, 4.31	N, 4.36
$-OCH_2CH_2OC_2H_5$	CH_3	HCl	61.7[a]	143	$C_{24}H_{31}ClN_2O_4S$	N, 5.79	N, 5.84
						Cl, 7.80	Cl, 7.40
$-NHCOCH_3$	CH_3	HCl (+2H_2O)	33.7[a]	236 dec.	$C_{20}H_{25}ClN_4O_5S$	N, 12.26	N, 11.95
						Cl, 7.72	Cl, 7.56

TABLE I (*continued*)

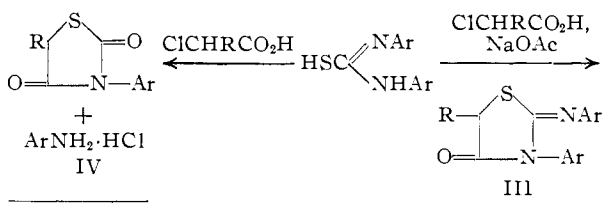
R_1	$R_3(R_2)$	HX	Yield %	M.p., °C	Empirical formula	Analyses, %, Found	Calculated
-COOH	CH_3	HCl	6.4[a,e]	282 dec.	$C_{18}H_{15}ClN_2O_4S$	N, 6.84 Cl, 9.13	N, 7.17 Cl, 9.07
$-OCH_2CH_2CH(CH_3)_2$	$C(CH_3)_3$	HBr	40.0[a]	165–167	$C_{29}H_{31}Br_2N_2O_2S$	N, 5.03 Br, 14.32	N, 4.99 Br, 14.23
$-OCH_2CH(C_2H_5)_2$	CH_3	HCl	74.4[a]	153–155	$C_{28}H_{39}ClN_2O_2S$	N, 5.40 S, 6.26	N, 5.57 S, 6.37
$-OCH_2CH_2CH(Me)(Et)$	CH_3	HCl	62.8[a]	174–176	$C_{28}H_{39}ClN_2O_2S$	N, 5.65	N, 5.57
3-OH-4-COOH	CH_3	..	16.3[a]	246 dec.	$C_{18}H_{14}N_2O_6S$	N, 7.11 S, 8.77	N, 7.25 S, 8.30
$-SCH_2CH_2CH(CH_3)_2$	CH_3	HCl	40.0[a,d]	174	$C_{26}H_{35}ClN_2S_3$	S, 18.73	S, 18.96
$-OCH_2CH_2CH(CH_3)_2$	$-CO_2C_2H_5$	HBr	28.2	166–169	$C_{28}H_{37}BrN_2O_4S$	N, 4.95 Br, 14.03	N, 4.85 Br, 13.84
$-OC_4H_9(n)$	CH_3	HCl	68.4[a]	173	$C_{24}H_{31}ClN_2O_2S$	N, 6.28 Cl, 7.52	N, 6.27 Cl, 7.93
$-OCH_2CH(CH_3)_2$	CH_3	HCl	72.0[a]	210	$C_{24}H_{31}ClN_2O_2S$	N, 6.09 Cl, 7.58	N, 6.27 Cl, 7.93

[a] Adapted from procedure a, Experimental. [b] Adapted from procedure b, Experimental. [c] Reference 3. [d] The thiourea required for this synthesis, 1,3-bis-(*p*-isopentylthiophenyl)-2-thiourea, was prepared according to U.S. Patent 2,664,096. [e] 63% of starting thiourea recovered; a trace of *p*-aminobenzoic acid was also isolated.

The preparation of 4-substituted-4-thiazolines has been described by various workers from 1,3-bis-thiocarbanilides and phenacyl bromide.[2–5] To our knowledge the analogous reaction with α-chloroaliphatic ketones has not been described. Both of these syntheses were found to proceed equally well to furnish the desired 4-substituted-4-thiazolines and 4,5-disubstituted-4-thiazolines.

The preparation of 3-aryl-2-arylimino-4-thiazolidinones has been effected by reaction of symmetrical thiocarbanilides with α-haloacids.[6–16]

In the presence of sodium acetate the reaction leads to the formation of 3-aryl-2-arylimino-4-thiazolidinones(III); in its absence 3-aryl-2,4-thiazolidinediones (IV) arise by acid cleavage of the imino function.



Finzi and Angelini[16] have reported the reaction of S-alkyl ethers of 1,3-bis-thiocarbanilides with thioglycolic acid to give III (R = H).

Certain thiazolines and thiazolidinones were found to possess considerable antituberculous activity. Microbiological findings, which have been published,[17] may be summarized briefly as: (1) 3-(*p*-Alkoxyphenyl-2-(*p*-alkoxyphenylimino)-4-methyl-4-thiazolines, having ether groupings within the range of C_3H_7O to $C_6H_{13}O$ (including $CH_2{=}CHCH_2O$) possess good *in vivo* activity against tuberculous infections of experimental animals. The activity seems to reach a peak where the alkoxy substituent is isopentyloxy. (2) Replacement of the ether groupings by an alkyl substituent (*e.g.*, butyl) results in maintenance of activity. (3) The 4-methyl group may be replaced by a dialkylaminoalkyl substituent without detriment to antituberculous properties. Replacement by an aryl substituent, however, all but abolishes activity. (4) 3-Aryl-2-arylimino-4-thiazolidinones possess antituberculous activity within the limits described under (1). 3-Aryl-2,4-thiazolidinediones, however, are inactive.

The technical assistance of Mrs. Evelyn Wrobel and Miss Judith Ann Siragusa is gratefully acknowledged.

Experimental

Pertinent analytical data have been included in the tables.

Procedure a. 3-(*p*-Isopentyloxyphenyl)-2-(*p*-isopentyloxyphenylimino)-4-methyl-4-thiazoline Hydrochloride.—A solution of 144 g. (0.34 mole) of 1,3-bis-(isopentyloxyphenyl)-2-thiourea and 33.6 g. (0.36 mole) of chloroacetone in 1200 ml. of anhydrous alcohol was refluxed for 10 hours. The solution was concentrated to about 500 ml. and diluted with 6 volumes of ether. The substance obtained on chilling (152 g., m.p. 174–177°) was recrystallized twice from isopropyl alcohol–ether, giving 105 g. of the desired product.

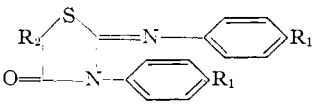
Procedure b. 3-(*p*-Isopentyloxyphenyl)-2-(*p*-isopentyloxyphenylimino)-4-(2-piperidinoethyl)-4-thiazoline Dihydrobromide.—A solution of 20 g. (0.048 mole) of 1,3-bis-(*p*-isopentyloxyphenyl)-2-thiourea and 15.8 g. (0.05 mole) of 1-bromo-4-piperidino-2-butanone hydrobromide in 200 ml. of anhydrous ethanol was refluxed for 3 hours. The solution was filtered hot. Addition of ether and chilling caused the separation of a light yellow crystalline substance;

(2) R. von Walther, *J. prakt. Chem.*, [2] **75**, 187 (1907).
(3) R. M. Hann and E. E. Reid, THIS JOURNAL, **55**, 4998 (1933).
(4) Z. Horii, *J. Pharm. Soc. Japan*, **55**, 21 (1935); *C. A.*, **29**, 3338 (1935).
(5) N. P. Buu-Hoï, N. D. Xuong and N. H. Nam, *J. Chem. Soc.*, 2160 (1956).
(6) F. B. Dains, R. Irvin and C. G. Harrel, THIS JOURNAL, **43**, 613 (1921).
(7) R. M. Hann and K. S. Markley, *J. Wash. Acad. Sci.*, **16**, 169 (1926); *C. A.*, **20**, 1980 (1926).
(8) S. S. Kingsbury and K. S. Markley, *J. Wash. Acad. Sci.*, **18**, 558 (1928); *C. A.*, **23**, 821 (1929).
(9) K. S. Markley and E. E. Reid, THIS JOURNAL, **52**, 2137 (1930).
(10) M. O. Farooq and R. F. Hunter, *J. Indian Chem. Soc.*, **9**, 545 (1932); *C. A.*, **27**, 1870 (1933).
(11) M. R. Chowdhury, R. D. Desai, R. F. Hunter and F. M. K. Solangi, *Rec. trav. chim.*, **52**, 853 (1953).
(12) D. P. Ahuja and S. Dutt, *J. Indian Chem. Soc.*, **28**, 12 (1951).
(13) P. N. Bhargava, *Bull. Chem. Soc. Japan*, **24**, 51 (1951); *C. A.*, **46**, 11182 (1952).
(14) P. N. Bhargava and C. L. Kaul, *J. Indian Chem. Soc.*, **32**, 49 1953); *C. A.*, **49**, 13974 (1955).
(15) P. N. Bhargava, THIS JOURNAL, **73**, 2353 (1951).
(16) C. Finzi and C. Angelini, *Ann. chim. Roma*, **43**, 832 (1953); *C. A.*, **49**, 6230 (1955).

(17) P. C. Eisman, E. A. Konopka, T. Gisi, R. H. Mizzoni and R. L. Mayer, *Am. Rev. Tuberc.*, **77**, 703 (1958).

TABLE II

3-(R_1-PHENYL)-2-(R_1-PHENYLIMINO)-5-(R_2)-4-THIAZOLIDINONES[a]

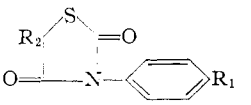


R_1	Yield, %	M.p., °C.	Empirical formula	Analyses, % Found	Calculated
$-OCH_2CH(CH_3)_2$	38.6	142–145	$C_{23}H_{28}N_2O_3S$	C, 66.94	C, 66.95
				H, 6.95	H, 6.84
OC_4H_9-n	41.7	106	$C_{23}H_{28}N_2O_3S$	N, 6.83	N, 6.79
				S, 8.02	S, 7.77
$-OC_7H_{15}$-n	20.4	97.5–98.5	$C_{29}H_{40}N_2O_3S$	N, 6.05	N, 5.64
				S, 6.90	S, 6.45
$-OC_6H_{13}$-n	62.0	104–106.5	$C_{27}H_{36}N_2O_3S$	N, 6.23	N, 6.39
				S, 7.42	S, 7.31
$-OCH_2CH_2CH(Me)(Et)$	73.0	109–111	$C_{27}H_{36}N_2O_3S$	N, 6.30	N, 6.39
				S, 6.86	S, 7.31
$-OCH_2CH(C_2H_5)_2$	63.2	82–83	$C_{27}H_{36}N_2O_3S$	N, 6.29	N, 6.39
				S, 7.24	S, 7.31
$OCH_2CH_2CH(CH_3)_2$[b] (HCl)	17.7	164–166 d.	$C_{26}H_{35}ClN_2O_3S$	S, 6.74	S, 6.53
				Cl, 6.86	Cl, 7.22
$-OC_2H_5$	66.5	111–113	$C_{19}H_{20}N_2O_3S$	N, 7.94	N, 7.86
				S, 8.93	S, 8.99
$N(CH_3)_2$	72.9	215–216	$C_{19}H_{22}N_4OS$	N, 15.68	N, 15.81
				S, 9.13	S, 9.04
$OCH_2CH_2CH(CH_3)_2$	55.6	130–132	$C_{25}H_{32}N_2O_3S$	N, 6.48	N, 6.36
				S, 6.94	S, 7.28
$-OC_3H_7$	40.7	97–98	$C_{21}H_{24}N_2O_3S$	N, 7.25	N, 7.29
				S, 8.54	S, 8.34
$-OCH_2CH{=}CH_2$	27.6	76–77	$C_{21}H_{20}N_2O_3S$	N, 7.48	N, 7.34
				S, 8.85	S, 8.40
$OCH_2CH_2CH(CH_3)_2$[c]	64.5	172–174	$C_{31}H_{35}N_3O_3S$	N, 7.98	N, 7.93
				S, 6.24	S, 6.05

[a] HX as noted; R_2 = H except as noted. [b] R_2 = CH_3. [c] R_2 = 3-pyridylmethynyl-.

TABLE III

3-(p-R_1-PHENYL)-5-(R_2)-2,4-THIAZOLIDINEDIONES



R_1	R_2	Yield, %	M.p. °C.	Empirical formula	Analyses, % Found	Calculated
$-OCH_2CH{=}CH_2$	H	28.8	145–146	$C_{12}H_{11}NO_3S$	N, 5.93	N, 5.62
$-OC_3H_7$	H	29.8	134–136	$C_{12}H_{13}NO_3S$	N, 5.65	N, 5.57
					S, 12.90	S, 12.76
$-OCH_3$	H	22.6	160–161	$C_{10}H_9NO_3S$	N, 6.35	N, 6.27
					S, 14.58	S, 14.36
$-OCH_2CH_2CH(CH_3)_2$	H	69.2	142–146	$C_{14}H_{17}NO_3S$	C, 60.19	C, 60.18
					H, 6.03	H, 6.13
					S, 11.43	S, 11.48
$-OCH_2CH_2CH(CH_3)_2$	C_6H_5N[a]	64.0	166–168	$C_{20}H_{20}N_2O_3S$	N, 7.51	N, 7.60
					S, 8.74	S, 8.70
$-OCH_2CH{=}CH_2$	$C_{11}H_{10}O_4$[b]	44.0	144–145	$C_{23}H_{19}NO_7S$	N, 3.01	N, 3.09
					S, 7.22	S, 7.07
$-OCH_2CH{=}CH_2$	C_6H_5N[c]	54.4	194	$C_{18}H_{14}N_2O_3S$	N, 8.16	N, 8.28
					S, 9.49	S, 9.47
$-OC_3H_7$	$C_{11}H_{10}O_4$[b]	65.8	156.5–157	$C_{23}H_{21}NO_7S$	N, 3.06	N, 3.08
					S, 7.24	S, 7.04
$OCH_2CH_2CH(CH_3)_2$	C_6H_5N[c]	64.5	172–174	$C_{31}H_{35}N_3O_3S$[d]	N, 7.98	N, 7.93
					S, 6.24	S, 6.05

[a] 4-Pyridylmethynyl-. [b] 2,4-Diacetoxybenzylidene-. [c] 3-Pyridylmethynyl-. [d]

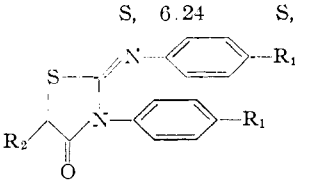
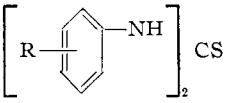


TABLE IV

1,3-BIS-(R-PHENYL)-2-THIOUREAS 

R	Yield, %	M.p., °C.	Empirical formula	Analyses, % Found	Calculated
4-CH_3CONH	77.0	241–243	$C_{17}H_{18}N_4O_2S$	[a]	
4-$(C_2H_5)_2CHCH_2O$	76.0	100–102	$C_{25}H_{36}N_2O_2S$	N, 6.49	N, 6.53
4-$C_2H_5CH(CH_3)CH_2CH_2O$	96.0	174–176.5	$C_{25}H_{36}N_2O_2S$	N, 6.53	N, 6.53
				S, 7.82	S, 7.48
4-$C_6H_{13}O$	53.6	156–157.5	$C_{25}H_{36}N_2O_2S$	N, 6.38	N, 6.53
				S, 7.46	S, 7.48
4-$C_7H_{15}O$	54.3	152–153.5	$C_{27}H_{40}N_2O_2S$	N, 6.17	N, 6.13
				S, 6.77	S, 7.02

[a] Converted directly to the thiazoline without analysis.

this was recrystallized from a mixture of isopropyl alcohol and ether giving 25.6 g. of product.

Procedure c. 3-(*p*-Isopentyloxyphenyl)-2-(*p*-isopentyloxyphenylimino)-4,5-dimethyl-4-thiazoline Hydrobromide.—A solution of 20 g. (0.048 mole) of 1,3-bis-(*p*-isopentyloxyphenyl)-2-thiourea and 7.4 g. (0.049 mole) of 3-bromo-2-butanone in 200 ml. of anhydrous ethanol was refluxed for 3 hours. The solution was filtered hot and the filtrate concentrated to a small volume. Addition of ether effected separation of the product, which was then recrystallized four times from ethanol–ether (15 g.).

Procedure d. 3-(*p*-Ethoxyphenyl)-2-(*p*-ethoxyphenylimino)-5-carboxymethyl-4-methyl-4-thiazoline Hydrobromide.—A solution of 18.8 g. (0.059 mole) of 1,3-bis-(*p*-ethoxyphenyl)-2-thiourea and 13.3 g. (0.059 mole) of ethyl β-bromolevulinate in 200 ml. of anhydrous ethanol was refluxed for three hours. Distillation of the solvent *in vacuo* left an oily residue, which yielded 6.2 g. of crystalline substance, m.p. 141.5–143°, upon recrystallization from isopropyl alcohol–ether. This proved to be 3-(*p*-ethoxyphenyl)-2-(*p*-ethoxyphenyl)-imino-5-carboxymethyl-4-methyl-4-thiazoline.

Anal. Calcd. for $C_{22}H_{24}N_2O_4S$: N, 6.79; S, 7.77. Found: N, 6.96; S, 8.05.

The filtrate remaining upon separation of the free acid was concentrated. The oil thus obtained was recrystallized from isopropyl alcohol–ether, yielding a crystalline solid of m.p. 159–162°. Three recrystallizations from the same medium gave 7.8 g. of the desired ester, m.p. 158–160°.

3-(*p*-Alkoxyphenyl)-2,4-thiazolidinedione. General Method—A solution of the thiocarbanilide (0.2 mole) and chloroacetic acid (0.21 mole) in 80–100 ml. of acetic acid was refluxed for 5–20 hours and then chilled. The crystalline solid which separated was filtered, partially air-dried, and then washed with *ca.* 1 liter of water. In some cases it was necessary to remove part of the acetic acid by distillation *in vacuo*. The product was recrystallized twice from isopropyl alcohol.

3-(*p*-Allyloxyphenyl)-5-(2,4-diacetoxybenzylidene)-2,4-thiazolidinedione.—A solution of 5 g. of 3-(*p*-allyloxyphenyl)-2,4-thiazolidinedione, 3 g. of 2,4-dihydroxybenzaldehyde and 4 g. of anhydrous sodium acetate in 20 ml. of acetic anhydride was refluxed for two hours. The mixture was chilled and diluted with isopropyl alcohol. The resulting precipitate was filtered off; it was then suspended in water, filtered, washed thoroughly with water, and air-dried. Recrystallization was effected from isopropyl alcohol.

3-(*p*-Isopentyloxyphenyl)-2-(*p*-isopentyloxyphenylimino)-5-(3-pyridomethylene)-4-thiazolidinone.—A solution of 15 g. (0.034 mole) of 3-(*p*-isopentyloxyphenyl)-2-(*p*-isopentyloxyphenylimino)-4-thiazolidinone, 4.4 g. (0.04 mole) of pyridine-3-aldehyde and 13.6 g. of anhydrous sodium acetate in 35 ml. of acetic acid was refluxed for 3.5 hours. The mixture was chilled overnight, then filtered, air-dried, and washed with a large quantity of water. The product was recrystallized once from isopropyl alcohol, m.p. 172–174° (13.0 g.).

SUMMIT, N. J.

[CONTRIBUTION OF THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

Schiff Bases and Related Substances. III. Acetylation of a Schiff Base–Thiol Adduct[1]

BY GARDNER W. STACY, RICHARD I. DAY[2] AND RICHARD J. MORATH

RECEIVED DECEMBER 16, 1957

The acetylation of a Schiff base–thiol adduct, N-[α-(*p*-tolylthio)-benzyl]-aniline (I), proceeds with difficulty. Reaction of I with any of several common acetylating agents gives only small amounts of the desired acetyl derivative, N-[α-(*p*-tolylthio)-benzyl]-acetanilide (VI). Evidence that at least one other reaction occurs extensively is found in the isolation of acetanilide, the mercaptal, α,α-bis-(*p*-tolylthio)-toluene (IV) and *p*-tolyl disulfide. An explanation for the formation of these products is presented. Attempted benzoylation of I results in the formation of *p*-tolyl thiolbenzoate and benzanilide and none of the anticipated benzoyl derivative. The acetyl derivative VI can be synthesized in excellent yield by an indirect method from N-(α-acetoxybenzyl)-acetanilide (V). Its structure has been established by Raney nickel desulfurization to N-benzylacetanilide and by hydrolysis to benzaldehyde, aniline and *p*-toluenethiol.

In the hope of gaining further information on the structure and characterization of Schiff base–thiol adducts, we have studied the acetylation of N-[α-(*p*-tolylthio)-benzyl]-aniline (I) under a variety of conditions. Acylation of such acyclic substances has not been reported, although cyclic systems containing the S–C–NH grouping undergo acylation without difficulty. Thus Ratner and Clarke[3] were

(1) Presented in part before the Oregon Section of the American Chemial Society, Salem, Ore., May 21, 1955, and in part at the 1956 and 1957 Northwest Regional Meetings of the American Chemical Society, Seattle, Wash., June 11 and Spokane, Wash., June 13, respectively. Paper II, G. W. Stacy, R. I. Day and R. J. Morath, THIS JOURNAL, **77**, 3869 (1955).

(2) In part abstracted from a thesis submitted by Richard I. Day in partial fulfillment of the requirements for the degree of Doctor of Philosophy, the State College of Washington, June, 1957.

(3) (a) S. Ratner and H. T. Clarke, THIS JOURNAL, **59**, 200 (1937); (b) subsequently, acylation of various substituted thiazolidines has been reported. A. H. Cook and I. M. Heilbron in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson and R. Robinson, eds., Princeton University Press, Princeton, N. J., 1949, p. 926.