The Synthesis of Substituted 2-Aminothiazoles

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Received May 11, 1979

The preparation of 4- and 5-acyl- and aroyl-2-substituted aminothiazoles is described. The condensation of thioureas with acyl halides leading to 4,5-disubstituted-2-aminothiazoles and 7-(4*H*)benzothiazolones is discussed. A discussion of the isolation of various intermediates and the mechanistic pathway is also included. A number of 2-anilino or 2-benzyl-4- or 5-aroylthiazoles possessed moderate oral antitubercolosis activity (2).

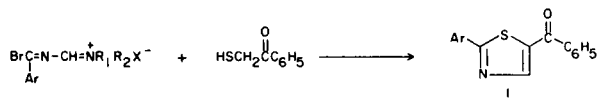
J. Heterocyclic Chem., **16**, 1377 (1979).

A series of 2-aryl-4-[3′-(benzylideneamino)-4′-methoxyphenyl]thiazoles was reported to possess *in vitro* antitubercular activity (3). We prepared a number of 2-substituted amino-5-aroylthiazoles and some exhibited good *in vivo* activity against a lethal *M. tuberculosis* H37Rv infection in mice (2).

2-Unsubstituted-amino-5-thiazolyl phenyl ketones were reported in the literature (4) and were synthesized from 2-bromo-3-phenyl-1,3-propanediones and thiourea. The synthesis of 2-aryl-5-thiazolyl phenyl ketones (I) from *N,N*-dialkyl-*N′*-haloalkylformamidines and α-mercaptoacetophenones (5) is shown in Scheme I. The syntheses of I from *N*-thiobenzoylformamidines (II) and phenacyl halides (6) was also reported (6, Scheme 2a).

The latter procedure appeared the most promising and in a similar fashion 1-(dimethylaminomethylene)-3-aryl-(benzyl, alkyl, benzoyl, acyl)-2-thioureas (IIIa-e), prepared from thioureas and dimethylformamide dimethyl acetal (or dimethylacetamide dimethyl acetal), condensed with

Scheme I



(Reference 5)

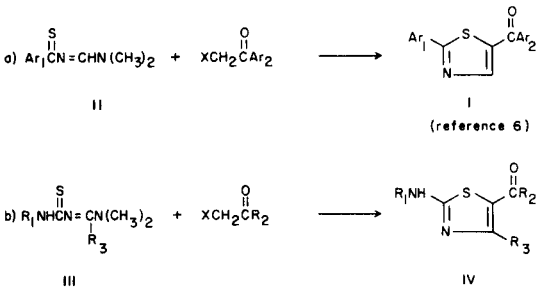
phenacyl halides to give 2-amino-5-thiazolyl aryl (alkyl) ketones (IVa-m) in good yield (Scheme 2, Table I). The same method was extended for the synthesis of compounds with an α-dicarbonyl linkage in that dimethylaminomethylenethioureas condense with 3-bromo-1-phenyl-1,2-propanedione to give Vh,i.

A mechanism for the reaction of thiobenzoylformamidines with phenacyl halides in the presence of triethylamine in benzene was proposed by Meslin and Quiniou (6). As is shown in Scheme 3, two transient intermediates, an open-chained thiopseudourea (V) and a thiazoline (VI), were postulated. We were able to isolate the intermediates Va,b and VIa-c, depending on the nature of R^1, in good yields by the use of milder reaction conditions.

From the reaction of dimethylaminomethylenethioureas with phenacyl halides in acetone at room temperature, one could isolate the thiopseudoureas Va,b (Scheme 4a). These intermediates were then converted into the thiazoles by recrystallization from chloroform or acetic acid or heating to the melting point. The structure assignment of the pseudothioureas rested upon the spectral and analytical data. For example, the pmr spectra of Vb in deuterochloroform showed the dimethylamino moiety at δ 2.66 and only one CH_2 signal for the benzyl group at δ 4.58. A singlet for the formamidine CH= appeared at δ 7.32. The remaining vinyl proton occurs within an aryl multiplet at δ 7.64. As shown in Scheme 4a, the thiopseudoureas Va,b rearranged to the transient thiazoline VI, which immediately lost dimethylamine to give the thiazoles IV.

On the other hand, the reaction of thiobenzoylformamidines with phenacyl halides in acetone gave the thiazolines VIa-c in good yields (Scheme 4b). These were converted into the thiazoles Ia-c by recrystallization from acetic acid. The structure of the thiazolines VIa-c was also determined by spectral and analytical data; for example, the pmr spectra of VIb in deuterated dimethylsulfoxide showed a signal at δ 3.08 for the dimethylamino moiety and a pair of doublets at δ 6.46 and 6.66. The doublets have a coupling constant of J = 4 Hz, which suggested not only the cyclic nature of the product but also a *trans* configuration of the hydrogens. The coupling constant for the *trans* isothiazoline VII (Scheme 4c) is 4 Hz (7). As is

Scheme 2

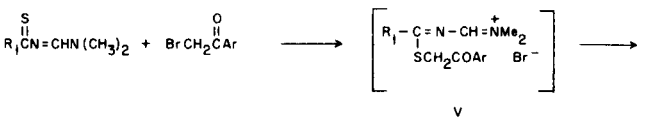


(reference 6)

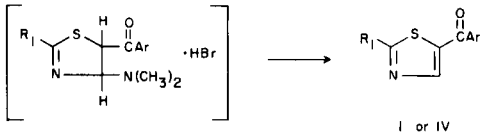
0022-152X/79/071377-07$02.25

evident in Scheme 4b, the charged and reactive thiopseudourea V was not detected.

Scheme 3

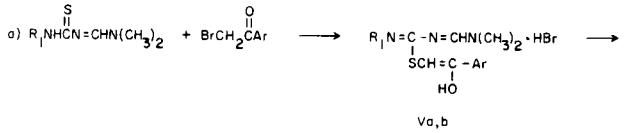


V

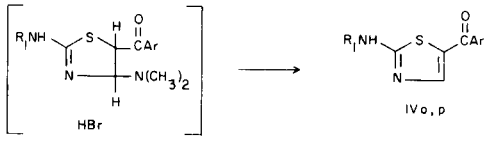


VI I or IV

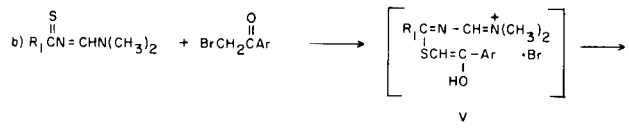
Scheme 4



Va,b

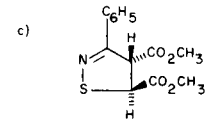


HBr VI IVo,p



V

VIa-c Ia-c

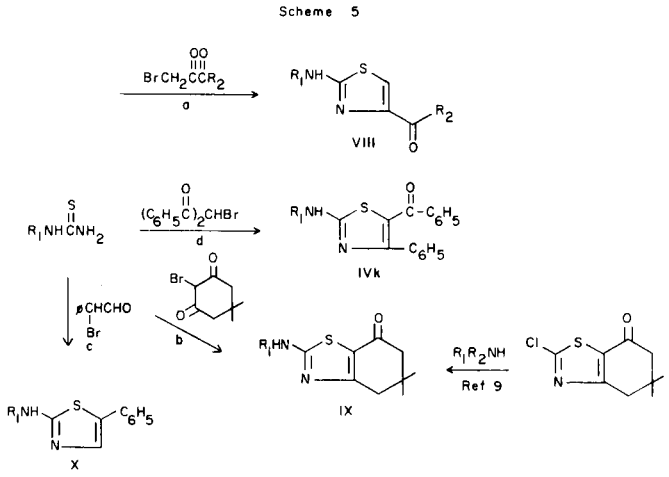


VII (ref. 7)

The condensation of thioureas with phenacyl halides to give 2-amino-4- and 4,5-substituted thiazoles is well known (8). A series of 2-amino-4-thiazolyl aryl (alkyl) ketones (VIIIa-e) was prepared by the condensation of thioureas with 3-bromo-1-phenyl-1,2-propanedione and 1-bromo-2,3-butanedione (Scheme 5a). Thioureas were also condensed with 2-bromo-5,5-dimethyl-1,3-cyclohexanedione to give 2-amino-5,6-dihydro-5,5-dimethylbenzothiazolones (IXa-e, Scheme 5b) in good yield. The literature reported the synthesis of these compounds from 2-chloro-7-(4*H*)benzothiazolones and amines (9). A series of 2-amino-5-substituted thiazoles (Xa-c) was prepared by the condensation of thioureas with α-bromophenylacetaldehyde (Scheme 5c). 2-Amino-4-phenyl-5-thiazolyl phenyl ketones are reported in the literature and have been synthesized by a variety of methods (10-14), including the condensation of thioureas with dibenzoylmethane derivatives (IV*ℓ*,m, Scheme 5d).

The compounds were evaluated for oral activity against lethal *Mycobacterium tuberculosis* H37Rv infections in mice by procedures previously described (2,15,16) and a number of 2-amino-4-(or 5-) thiazolyl phenyl ketones and their oximes possessed moderate activity (2).

Scheme 5



EXPERIMENTAL

All melting points were observed on a Mel-Temp apparatus. Nmr were determined with a Varian HA-100 spectrometer; chemical shifts are reported in ppm relative to internal TMS. DMSO when in association with spectra refers to DMSO-d_6.

1-*t*-Butyl-3-(*p*-fluorobenzyl)-2-thiourea.

p-Fluorobenzylamine (37.5 g., 0.03 mole) was added all at once to a solution of *t*-butylisothiocyanate (34.5 g., 0.03 mole) in 300 ml. of hexane. After stirring for 1 hour, the reaction was stored overnight. The crystals were collected and recrystallized from chloroform-hexane to give 58.3 g. (81%) of white crystals, m.p. 117-119°; nmr (deuteriochloroform): δ 1.40 (*t*-Bu), 4.72 (CH_2), 6.17 (NH), 7.00 (aryl, 2), 7.26 (aryl 2).

Anal. Calcd. for $C_{12}H_{17}FN_2S$ (240.3): C, 60.0, H, 7.13; N, 11.7; S, 13.3; F, 7.91. Found: C, 60.1, H, 7.37; N, 11.7; S, 13.6; F, 8.24.

1-(*p*-Fluorobenzyl)-2-thiourea.

A suspension of 48 g. (0.02 mole) of 1-*t*-butyl-3-(*p*-fluorobenzyl)-2-thiourea in 100 ml. of concentrated hydrochloric acid was heated on a steam bath for 1 hour. The volatiles were removed under reduced pressure. The residue was washed well with 10% aqueous sodium bicarbonate and recrystallized from chloroform-hexane giving 23.2 g. (63%) of white crystals, m.p. 96-98°; nmr (deuteriochloroform): δ 4.67 (CH_2), 6.70 (NH_2), 7.02 (M, 2), 7.32 (M, 2), 7.91 (NH).

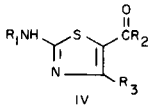
Anal. Calcd. for $C_8H_9FN_2S$ (184.2): C, 52.1; H, 4.92; N, 15.2; S, 17.4; F, 10.3. Found: C, 51.8; H, 4.92; N, 15.1; S, 17.3; F, 10.6.

1-(Dimethylaminomethylene)-3-(*p*-fluorobenzyl)-2-thiourea (IIIa).

A suspension of 18.4 g. (0.1 mole) of 1-(*p*-fluorobenzyl)-2-thiourea in 50 ml. of dimethylformamide dimethyl acetal was heated on a steam bath for 1 hour. The excess reagent was removed under reduced pressure. The residue was recrystallized from chloroform-hexane to give 16.3 g. (68%) of off-white crystals, m.p. 105-107°; nmr (deuteriochloroform): δ 2.96, 3.12 [$(NCH_3)_2$6], 4.64, 4.86 (CH_2d, 2), 7.04, 6.97, 7.26 (aryl 4), 8.82 (s, 1).

Table I

2-Amino-5-thiazolyl Phenyl Ketones

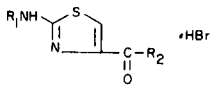


IV

Compound No.	R_1	R_2	R_3	Formula	M.p. °C	Anal. Calcd. Found
IVa	*p*-$FC_6H_4CH_2$	*p*-BrC_6H_4	H	$C_{17}H_{12}BrFN_2OS$	176-178	C, 52.2; H, 3.10; N, 7.17; S, 8.20; F, 4.86; Br, 20.4 C, 52.3; H, 3.19; N, 6.99; S, 7.94; F, 4.89; Br, 20.3
IVb	*p*-$FC_6H_4CH_2$	*m*-$FO_2SC_6H_4$	H	$C_{17}H_{12}F_2N_2O_3S_2$	138-140	C, 51.8; H, 3.07; N, 7.10; S, 16.3; F, 9.63 C, 51.7; H, 3.33; N, 7.42; S, 16.0; F, 9.82
IVc	*p*-$FC_6H_4CH_2$	CH_3	H	$C_{12}H_{11}FN_2OS$	144-146	C, 57.6; N, 4.43; N, 11.2; S, 12.8; F, 7.59 C, 57.7; N, 4.50; N, 11.4; S, 12.6; F, 7.41
IVd	*p*-$FC_6H_4CH_2$	*p*-BrC_6H_4	CH_3	$C_{18}H_{14}BrFN_2OS$	128-130	C, 53.3; H, 3.48; N, 6.91; S, 7.91; F, 4.69; Br, 19.7 C, 53.0; N, 3.53; H, 7.11; S, 8.02; F, 4.55; Br, 19.5
IVe	*m*-$ClC_6H_4CH_2$	*p*-FC_6H_4	H	$C_{17}H_{12}ClFN_2OS$	142-144	C, 58.9; H, 3.49; N, 8.08; S, 9.24; F, 5.48; Cl, 10.2 C, 58.6; H, 3.76; N, 8.28; S, 9.06; F, 5.43; Cl, 10.3
IVf	*m*-$ClC_6H_4CH_2$	*p*-BrC_6H_4	H	$C_{17}H_{12}BrClN_2OS$	147-149	C, 50.1; H, 2.97; N, 6.87; S, 7.86; Cl, 8.70; Br, 19.6 C, 50.3; H, 3.07; N, 7.14; S, 7.80; Cl, 8.97; Br, 19.8
IVg	*p*-ClC_6H_4	*p*-ClC_6H_4	H	$C_{16}H_{10}Cl_2N_2OS$	239-241	C, 55.0; H, 2.89; N, 8.02; S, 9.18; Cl, 20.3 C, 54.7; H, 2.90; N, 8.12; S, 9.22; Cl, 20.3
IVh	*p*-$FC_6H_4CH_2$	C_6H_5CO	H	$C_{18}H_{13}FN_2OS$	155-157	C, 63.5; H, 3.85; N, 8.23; S, 9.42; F, 5.58 C, 63.3; H, 3.92; N, 8.21; S, 9.36; F, 5.47
IVi	C_6H_5	C_6H_5CO	H	$C_{17}H_{12}N_2O_2S$	205-207	C, 66.2; H, 3.92; N, 9.90; S, 10.4 C, 66.4; H, 4.15; N, 9.81; S, 10.3
IVj	*n*-Bu	*p*-ClC_6H_4	H	$C_{15}H_5ClN_2OS$	96-98	C, 57.0; H, 5.13; N, 9.51; S, 10.9; Cl, 12.0 C, 57.2; H, 5.21; N, 9.46; S, 10.9; Cl, 12.0
IVk	$CH_3(CH_2)_{17}$	*p*-BrC_6H_4	H	$C_{28}H_{43}BrN_2OS$	97-99	C, 62.8; H, 8.09; N, 5.24; S, 5.98; Br, 14.9 C, 63.1; H, 8.13; N, 5.34; S, 6.10; Br, 14.7
IVl	*p*-$FC_6H_4CH_2$	C_6H_5	C_6H_5	$C_{23}H_{17}FN_2OS \cdot HBr$	170-172	C, 58.9; H, 3.87; N, 5.97; S, 6.63; F, 4.05; Br, 17.0 C, 58.6; H, 3.61; N, 6.03; S, 6.89; F, 4.25; Br, 16.7
IVm	3-pyridyl	C_6H_5	C_6H_5	$C_{21}H_{15}N_3OS \cdot HBr$	198-200	C, 57.5; H, 3.68; N, 9.59; S, 7.31; Br, 18.2 C, 57.4; H, 3.63; N, 9.68; S, 7.49; Br, 17.9

Table 2

2-Amino-4-thiazolyl Phenyl Ketones

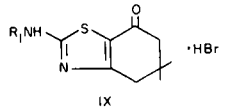


VIII

Compound No.	R_1	R_2	Formula	M.p. °C	Anal. Calcd. Found
VIIIa	*p*-$FC_6H_4CH_2$	CH_3	$C_{12}H_{11}FN_2OS \cdot HBr$	226-229	C, 43.5; H, 3.68; N, 8.46; S, 9.68; F, 5.74; Br, 24.1 C, 43.8; H, 3.89; N, 8.53; S, 9.63; F, 5.92; Br, 24.0
VIIIb	*p*-$FC_6H_4CH_2$	C_6H_5	$C_{17}H_{13}FN_2OS \cdot HBr$	166-168	C, 51.9; H, 3.59; N, 7.12; S, 8.15; F, 4.83; Br, 20.3 C, 52.1; H, 3.58; N, 7.12; S, 8.12; F, 5.01; Br, 20.2
VIIIc	$CH_3(CH_2)_6$	C_6H_5	$C_{17}H_{22}N_2O_3S \cdot HBr$	89-92	C, 67.5; H, 7.33; N, 9.26; S, 10.6 C, 67.3; H, 7.24; N, 9.36; S, 10.3
VIIId	*p*-$ClC_6H_4CH_2$	C_6H_5	$C_{17}H_{13}ClN_2OS \cdot HBr$	170-172	C, 49.9; H, 3.46; N, 6.85; S, 7.85; Cl, 8.67; Br, 19.5 C, 49.7; H, 3.49; N, 6.79; S, 7.61; Cl, 8.40; Br, 19.7
VIIIe	*p*-$ClC_6H_4CH_2$	CH_3	$C_{12}H_{11}ClN_2OS \cdot HBr$	218-220	C, 41.4; H, 3.19; N, 8.06; S, 9.22; Cl, 10.2; Br, 23.0 C, 41.4; H, 3.18; N, 8.05; S, 9.42; Cl, 10.4; Br, 23.2

Table 3

2-Amino-5,6-dihydro-5,5-dimethyl-7(4*H*)benzothiazolones

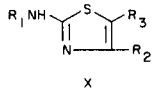


IX

Compound No.	R_1	Formula	M.p. °C	Anal. Calcd. Found
IXa	*p*-$FC_6H_4CH_2$	$C_{16}H_{17}FN_2OS \cdot HBr$	250-252	C, 49.9; H, 4.71; N, 7.27; S, 8.32; F, 4.93; Br, 20.7 C, 50.0; H, 4.85; N, 7.35; S, 8.29; F, 4.88; Br, 20.6
IXb	*p*-$ClC_6H_4CH_2$	$C_{16}H_{17}N_2OS \cdot HBr$	224-227	C, 47.8; H, 4.52; N, 6.97; S, 7.98; Cl, 8.83; Br, 19.9 C, 47.6; H, 4.65; N, 6.95; S, 7.70; Cl, 9.01; Br, 19.8
IXc	3-pyridylCH_2	$C_{15}H_{17}N_3OS \cdot HBr$	230-233	C, 48.9; H, 4.93; N, 11.4; S, 8.70; Br, 21.7 C, 49.2; H, 5.08; N, 11.1; S, 8.64; Br, 21.4
IXd	$C_6H_5CH_2CH_2$	$C_{17}H_{20}N_2OS \cdot HBr$	230-232	C, 53.5; H, 5.55; N, 7.35; S, 8.41; Br, 21.0 C, 53.1; H, 5.52; N, 7.55; S, 8.36; Br, 21.3
IXe	*p*-FC_6H_4	$C_{15}H_{17}FN_2OS \cdot HBr$	204-207	C, 48.5; H, 4.34; N, 7.55; S, 8.64; F, 5.12; Br, 21.5 C, 48.8; H, 4.52; N, 7.71; S, 8.41; F, 5.02; Br, 21.2

Table 4

2-Amino-4(5)-substituted Thiazoles

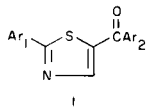


X

Compound No.	R_1	R_2	R_3	Formula	M.p. °C	Anal. Calcd. Found
Xa	*p*-$FC_6H_4CH_2$	H	C_6H_5	$C_{13}H_{16}FN_2S \cdot HBr$	196-198	C, 52.6; H, 3.86; N, 7.67; S, 8.78; Br, 21.9; F, 5.20 C, 52.9; H, 3.89; N, 7.71; S, 8.68; Br, 21.9; F, 5.28
Xb	*p*-$ClC_6H_4CH_2$	H	C_6H_5	$C_{16}H_{13}ClN_2S$	167-170	C, 50.3; H, 3.70; N, 7.34; S, 8.40; Cl, 9.29; Br, 20.9 C, 50.3; H, 3.68; N, 7.08; S, 8.07; Cl, 9.06; Br, 21.1
Xc	*p*-$H_2NO_2SC_6H_4$	H	C_6H_5	$C_{15}H_{13}N_3O_3S_2$	247-249	C, 43.7; H, 3.42; N, 10.2; S, 15.5; Br, 19.4 C, 43.6; H, 3.56; N, 10.0; S, 15.2; Br, 19.3
Xd	3-pyridylCH_2	*p*-ClC_6H_4	H	$C_{15}H_{12}ClN_3S \cdot HBr$	147-150	C, 47.2; H, 3.44; N, 11.0; S, 8.40; Cl, 9.30; Br, 20.9 C, 47.1; H, 3.55; N, 11.3; S, 8.46; Cl, 9.19; Br, 20.7
Xe	*p*-$FC_6H_4CH_2$	C_6H_5	C_6H_5	$C_{22}H_{17}FN_2S \cdot HCl$	237-239	C, 66.6; H, 4.57; N, 7.06; S, 8.08; F, 4.79; Cl, 8.94 C, 66.6; H, 4.75; N, 7.07; S, 8.14; F, 4.79; Cl, 8.96
Xf	3-Pyridyl	C_6H_5	C_6H_5	$C_{20}H_{15}N_3S \cdot HCl$	285-288	C, 65.6; H, 4.41; N, 11.5; S, 8.76; Cl, 9.69 C, 65.6; H, 4.60; N, 11.5; S, 8.74; Cl, 9.81

Table 5

Phenyl 2-Phenyl-5-thiazolyl Ketones



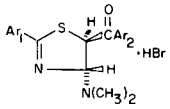
I

Compound No.	Ar_1	Ar_2	Formula	M.p. °C	Anal. Calcd. Found
Ia	C_6H_5	C_6H_5	$C_{16}H_{11}NOS$	117-119	lit. m.p. 117-119 (a)
Ib	C_6H_5	*p*-BrC_6H_5	$C_{16}H_{10}BrNOS$	189-191	lit. m.p. 188-190 (a)
Ic	C_6H_5	*p*-ClC_6H_5	$C_{16}H_{10}ClNOS$	175-178	C, 64.1; H, 3.36; N, 4.67; S, 10.7; Cl, 11.8 C, 64.4; H, 3.59; N, 4.72; S, 10.8; Cl, 11.8

(a) See reference 6.

Table 6

Thiazolines



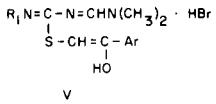
VI

Compound No.	Ar_1	Ar_2	Formula	M.p. °C	Anal. Calcd. Found
VIa	C_6H_5	C_6H_5	$C_{18}H_{18}N_2OS \cdot HBr$	140-144	(a)
VIb	C_6H_5	p-BrC_6H_5	$C_{18}H_{17}BrN_2OS \cdot HBr$		C, 46.0; H, 3.86; N, 5.96; S, 6.82; Br, 34.0 C, 45.8; H, 3.83; N, 6.03; S, 6.71; Br, 33.7
IVc	C_6H_5	p-ClC_6H_5	$C_{18}H_{17}ClN_2OS \cdot HBr$	184-186	C, 50.8; H, 4.26; N, 6.58; S, 7.53 C, 50.6; H, 4.32; N, 6.56; S, 7.73

(a) This compound was *ca.* 95% pure as shown by tlc and nmr analysis. It was also very hygroscopic. Attempts to purify it led to further impurities. The structure is supported by nmr and by comparison with VIb and VIc.

Table 7

Thiopseudoureas

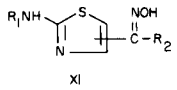


V

Compound No.	R_1	Ar	Formula	M.p. °C	Anal. Calcd Found
Va	m-$ClC_6H_4CH_2$	p-FC_6H_4	$C_{19}H_{19}ClFN_3OS \cdot HCl$	147-148	C, 53.3; H, 4.71; N, 9.82; S, 7.49; F, 4.44; Cl, 16.6 C, 53.5; H, 4.68; N, 9.91; S, 7.61; F, 4.56; Cl, 16.6
Vb	m-$ClC_6H_4CH_2$	p-BrC_6H_4	$C_{19}H_{19}BrClN_3OS \cdot HBr$	149-151	C, 42.8; H, 3.78; N, 7.88; S, 6.01; Br, 30.0; Cl, 9.53 C, 42.5; H, 3.90; N, 8.09; S, 6.15; Br, 29.8; Cl, 9.47

Table 8

2-Amino-4(5)thiazolyl Phenyl Ketone Oximes



XI

Compound No.	R_1	R_2	Formula	M.p. °C	Anal. Calcd. Found
XIa	p-$FC_6H_4CH_2$	5-p-BrC_6H_4	$C_{17}H_{13}BrFN_3OS$	213-215	C, 50.2; H, 3.22; N, 10.4; S, 7.89; F, 4.68; Br, 19.7 C, 49.9; H, 3.28; N, 10.3; S, 7.96; F, 4.71; Br, 19.9
XIb	$pFC_6H_5CH_2$	4-C_6H_4	$C_{17}H_{14}FN_3OS$	173-175	C, 62.4; H, 4.31; N, 12.8; S, 9.79; F, 5.80 C, 62.1; H, 4.58; N, 13.0; S, 9.79; F, 5.69

p-Bromophenyl 2-(*p*-fluorobenzylamino)-5-thiazolyl Ketone (IVa).

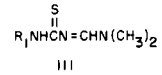
A suspension of 4 g. (0.017 mole) of 1-(dimethylaminomethylene)-3-(*p*-fluorobenzyl)-2-thiourea and 4.6 g. (0.017 mole) α,*p*-dibromoacetophenone in 75 ml. of acetone was stirred overnight. The acetone was removed and the residue washed with 10% aqueous sodium bicarbonate. The residue was extracted with boiling chloroform. Hexane was added to the point of incipient cloudiness and the solution was cooled, yield 4.9 g. (73%), m.p. 176-178°; nmr (deuteriochloroform-DMSO-d_6): δ 4.54 (CH_2), 7.02 (m, 2), 7.36 (m, 2), 7.40 (m, 4), 7.44 (s, 1), 9.04 (NH).

2-(*p*-Fluorobenzylamino)-4-thiazolyl Phenyl Ketone Hydrobromide (VIIIb).

A solution of 3-bromo-1-phenyl-1,2-propanedione (17) (6.8 g., 0.03 mole) and 1-(*p*-fluorobenzyl)-2-thiourea (5.5 g., 0.03 mole) in 100 ml. of ethanol was refluxed for 2 hours. The solvent was removed and the residue recyrstallized from ethanol-ethyl acetate to give 6.6 g. (56%) of crystals, m.p. 166-168°; nmr (deuteriochloroform-DMSO): δ 4.70 (CH_2), 7.31-7.87 (aryl, 9) 7.71 (s, 1), 8.51 (NH).

Table 9

1-(Dimethylaminomethylene)-3-substituted-2-thioureas



III

Compound No.	R_1	Formula	M.p. °C	Anal. Calcd. Found
IIIa	p-$FC_6H_4CH_2$	$C_{11}H_{14}FN_3S$	105-107	C, 55.2; H, 5.90; N, 17.6; S, 13.4; F, 7.94 C, 55.0; H, 6.09; N, 17.4; S, 13.3; F, 7.96
IIIb	m-$ClC_6H_4CH_2$	$C_{11}H_{14}ClN_3S$	127-130	C, 51.7; H, 3.52; N, 16.4; S, 12.5; Cl, 13.9 C, 51.7; H, 5.49; N, 16.5; S, 12.7; Cl, 14.0
IIIc	C_6H_5	$C_{10}H_{13}N_3S$	154-156	
IIId	$CH_3(CH_2)_{17}$	$C_{22}H_{45}N_3S$	60-62	C, 68.9; H, 11.8; N, 11.0; S, 8.36 C, 68.5; H, 11.6; N, 11.0; S, 8.46

2-(p-Fluorobenzylamino)-4-thiazolyl Methyl Ketone Hydrobromide (VIIIa).

A solution of 1-(p-fluorobenzyl)-2-thiourea (5.5 g., 0.03 mole) and 1-bromo-2,3 propanedione (17) (4.9 g., 0.03 mole) in 100 ml. of ethanol was refluxed for 2 hours. The solvent was removed and the residue recrystallized from ethanol-ethyl acetate to give 5.9 g. (60%) of white crystals, m.p. 226-229°; nmr (DMSO): δ 2.49 (s, 3), 4.64 (CH_2), 7.20 (m, 2), 7.40 (m, 2), 7.92 (s, 1).

3-[[[4-(p-Chlorophenyl-2-thiazolyl]amino]methyl]pyridine Hydrobromide (Xd).

A suspension of α-bromo-p-chloroacetophenone and 1-(3-pyridylmethyl)-2-thiourea (5.0 g., 0.03 mole) in 50 ml. of 1-propanol was refluxed for 2 hours. The solvent was removed and the residue recrystallized from ethanol-ethyl acetate to give 9.4 g. (0.82%) of light yellow crystals, m.p. 147-150°; nmr (DMSO): δ 4.76 (CH_2), 6.56 (NH), 7.14 (s, 1), 7.36 (d, 2), 7.70 (d, 2), 8.06 (t, 1), 8.62 (d, 1), 8.84 (d, 1), 9.01 (s, 1).

p-Bromophenyl 2-(p-fluorobenzylamino)-5-thiazolyl Ketone Oxime (XIa).

A solution of 4 g. of ketone and 2 g. of hydroxylamine hydrochloride in 15 ml. of pyridine and 15 ml. of ethanol was refluxed for 2 hours. The solvents were removed under reduced pressure and the residue partitioned between water and hot chloroform. The chloroform was removed and the residue recrystallized from chloroform-hexane to give 3 g. of off white crystals, m.p. 213-215°; mmr (DMSO): δ 4.57 (CH_2), 7.27-7.70 (aryl, 8), 7.60 (s, 1), 8.51 (NH and OH).

2-(p-Fluorobenzylamino)-5-phenylthiazole Hydrobromide (Xa).

A solution of α-bromophenylacetaldehyde (18) (6 g., 0.03 mole) and 1-(p-fluorobenzyl)-2-thiuorea in 100 ml. of ethanol was refluxed for 2 hours. The solvent was removed and the residue recrystallized from ethanol-ethyl acetate to give 4.8 g. (44%) of white crystals, m.p. 196-198°; nmr (deuteriochloroform-DMSO): δ 4.70 (CH_2), 7.33-7.43 (aryl 9), 7.48 (s, 1).

2-(p-Fluorobenzylamino)-4-phenyl-5-thiazolyl Phenyl Ketone Hydrobromide (IVℓ).

A solution of 1-(p-fluorobenzyl)-2-thiourea (5.5 g., 0.03 mole) and 2-bromodibenzoylmethane (9.1 g., 0.03 mole, Parish Chem. Co.) in 100 ml. of ethanol was refluxed for 2 hours. The solvent was removed and the residue recrystallized from ethanol-ethyl acetate to give 5.6 g. (45%) of white crystals, m.p. 211-214°; nmr (DMSO): δ 4.56 (CH_2), 7.08 (m, 2), 7.13 (m, 5), 7.44 (m, 5), 7.52 (m, 2), 8.79 (NH).

2-(p-Fluorobenzylamino)-5,6-dihydro-5,5-dimethyl-7-(4H)benzothiazolone Hydrobromide (IXa).

A solution of 1-(p-fluorobenzyl)-2-thiourea (5.5 g., 0.03 mole) and 2-bromo-5,5-dimethyl-1,3-cyclohexanedione (6.6 g., 0.03 mole, Eastman) in 100 ml. of ethanol was refluxed for 2 hours. The solvent was removed and the residue recrystallized from ethanol-ethyl acetate to give 5.5 g. (47%) of white crystals, m.p. 250-252°; nmr (DMSO): δ 1.08 (s, 6), 2.32 (s, 2), 3.75 (s, 2), 4.56 (CH_2), 7.32 (m, 2), 7.43 (m, 2), 8.64 (NH) m/e 304, 209, 183, 181, 109 (p-F-$C_6H_4CH_2$).

4,5-Diphenyl-2-(p-fluorobenzylamino)thiazole Hydrochloride (Xe).

A solution of 5.5 g. (0.03 mole) of 1-(p-fluorobenzyl)-2-thiourea and 6.9 g. (0.03 mole) of desyl chloride in 100 ml. of n-propanol was refluxed for 2 hours. The solvent was removed and the residue recrystallized from ethanol-ethyl acetate to give 10.3 g. (88%) of white crystals, m.p. 237-339°; nmr (DMSO): δ 4.67 (CH_2), 7.3-7.5 (aryl 14).

[2-(p-Fluorobenzylamino)-5-thiazolyl]phenyl Glyoxal (IVh).

A suspension 1-(dimethylaminomethylene)-3-(p-fluorobenzyl)-2-thiourea (2.4 g., 0.01 mole) and 3-bromo-1-phenyl-1,2-propanedione (17) (2.3 g., 0.01 mole) in acetone was stirred overnight. The acetone was removed, the residue washed with 10% sodium bicarbonate and extracted with chloroform. The chloroform was removed and the residue recrystallized from chloroform-hexane to give 6.3 g. (62%) of white crystals, m.p. 155-157°; nmr (DMSO): δ 4.56 (CH_2) 7.11 (m, 2), 7.40 (m, 3), 7.60 (m, 2), 7.75 (s, 1), 7.92 (m, 2), 9.05 (NH); ms: 340, 235 (M-C_6H_5CO), 109 ($FC_6H_4CH_2$).

2-(p-Bromo-β-hydroxystyryl)-1-(m-chlorobenzyl)-3-dimethylaminomethylene-2-thiopseudourea Hydrobromide (Vb).

1-(m-Chlorobenzyl)-3-dimethylaminomethylene-2-thiourea (2 g., 0.008 mole) and α,p-dibromoacetophenone (2.3 g., 0.008 mole) were mixed in acetone (75 ml.). A precipitate was evident within 5-10 minutes and this was collected by filtration and air dried, yield 4 g., m.p. 149-151°; nmr (deuteriochloroform): δ 2.66 (NMe_2), 4.58 (CH_2), 7.28 (aryl, 4), 7.32 (m, 1), 7.64 (5), 9.08 (NH).

p-Bromo-4-dimethylamino-2-phenyl-2-thiazolin-5-yl Ketone Hydrobromide (IVb).

A mixture of N-thiobenzoyl-N',N'-dimethyl acetamidine (7.69 g., 0.04 mole) and α,p-dibromoacetophenone in 100 ml. of acetone was refluxed for 1.5 hours and then stored at 0° overnight. Colorless crystals were collected and washed with acetone to give 14.5 g. (77%).

p-Chlorophenyl 2-Phenyl-5-thiazolyl Ketone (Ic).

p-Chlorophenyl 4-dimethylamino-2-phenyl-2-thiazolin-5-yl ketone hydrobromide (8.6 g.) was recrystallized from acetic acid to give 5.95 (98%) of off white crystals, m.p. 185-187°; nmr (deuteriochloroform): δ 7.50 (aryl, 5), 7.80 (aryl 2), 8.00 (aryl 2), 8.23 (s, 1).

Acknowledgement.

We wish to thank Dr. W. Gore and staff for the spectra data, and Mr. L. Brancone and staff for microanalyses.

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