Benzothiazole From Aryl thioalkylamides (11)
Studies on Influences of Substituents upon the Ring Formation of Aryl Thioacetamides.

By Yoshihisa Mizuno* and Kikuo Adachi.

Introduchion

An examination of the literature dealing with the preparation of l-alkyl benzothiazoles shows that methods of prepparing the compound can be divided into two main classes: the one (Jacobson method) consists in transforming N-aryl thioalkylamides into benzothiazole derivatives by the action of potassium ferricyanide in alkaline solution and the other method consists in treating aminothiophenoles with acid andydrides.

For the former method (Jacobson method), some improvement in procedure and yield has been devised by the present authors (1).

However, an investigation of the mechanaism of the ring formation and an ex-amination of the scope and limitations still remained untouched.

In this paper the effect of substituents on the benzene nucleus upon the ring formation of aryl thioamides will be described and based on the results obtained, discussions will be made on the mechanism of the ring formation.

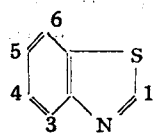
Resultsobtained

Nineteen of N-aryl thio-alkylamides including thioformyl anilide were prepared according to the improved methd reported before(2). Yield of bases in the ring formation of the aryl thio-alkylamides were determined along with absorption maxima in alkaline media.

Results obtained were shown in the following tables, so that the data may be easily available for the subsequent discussion.

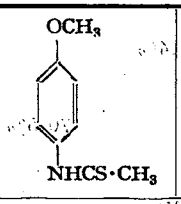
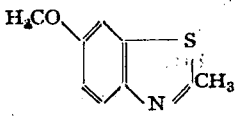
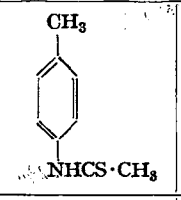
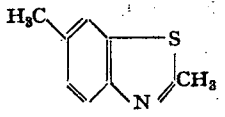
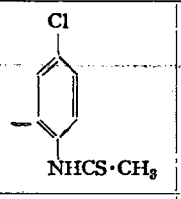
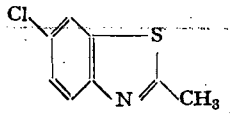
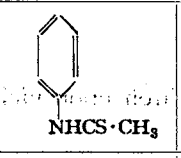
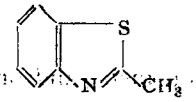
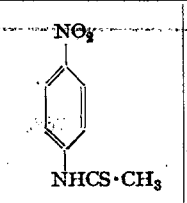
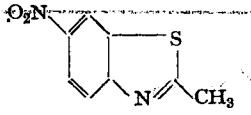
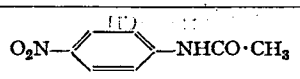
(I) Effect of substituent groups at para position upon the yield of bases.

Nomenclacturb of oenzothiazole:



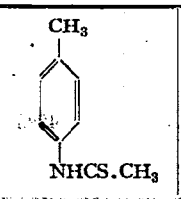
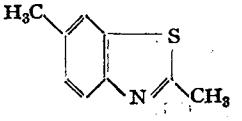
(*) Department of pharmacy, University of Kanazawa: Tokugawa Institute for Biological Research.

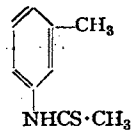
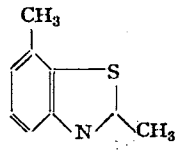
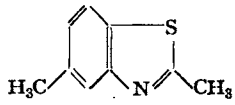
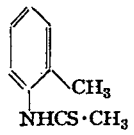
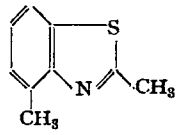
Table I

		76.3%
		73·1%
		72.0%
		67.5%
		0 %
		95 %

(II) Effect of methyl group at ortho, meta, and para position upon yield.

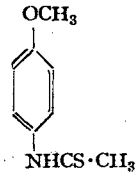
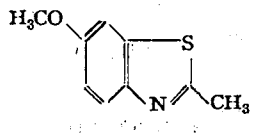
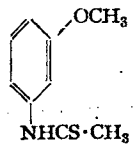
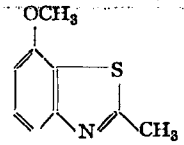
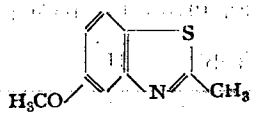
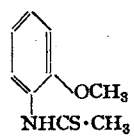
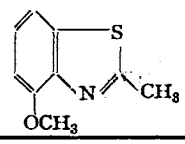
Table II

		73.1%

		6.4%	70.5%
		64%	
			52%

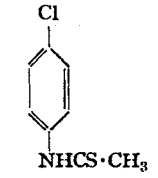
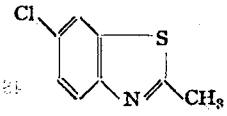
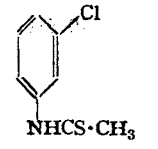
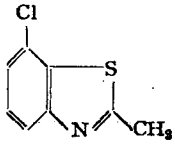
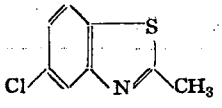
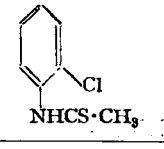
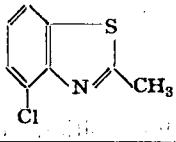
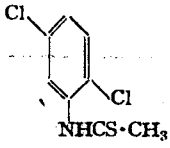
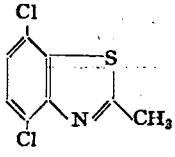
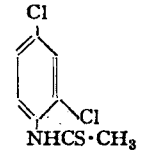
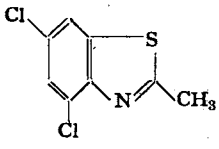
(III) Effet of methoxy group at para, meta, and ortho position upon yield.

Table III

			76%
		11.2%	59.5%
		48.3%	
			42%

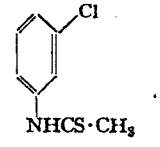
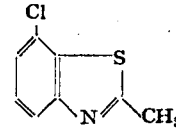
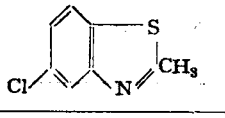
(IV) Effect of chlorine atom at para, meta, and ortho position.

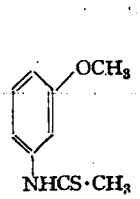
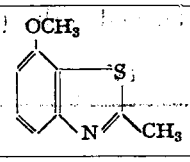
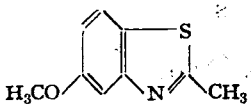
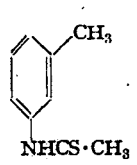
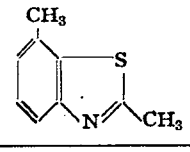
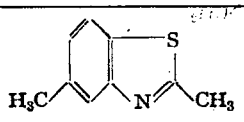
Table IV

			72%
		42.6%	71%
		28.4%	
			45%
			59%
			36.5%

(V) Effect of various at meta position upon yield.

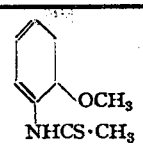
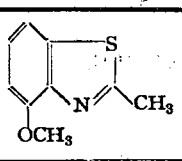
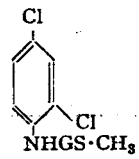
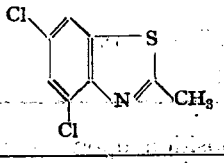
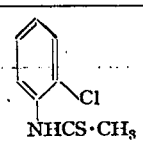
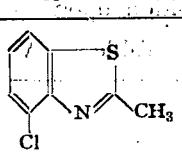
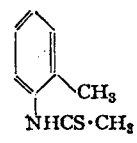
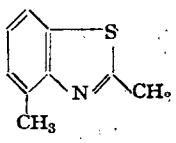
Table V

		42.6%	71%
		28.4%	

		11.2%	59.5%
		48.3%	
		6.4%	70.5%
		64.1%	

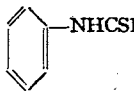
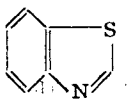
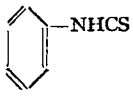
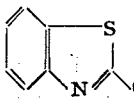
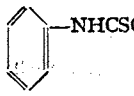
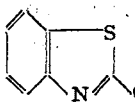
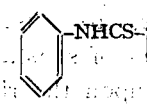
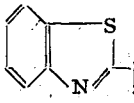
(VI) Effect of various substituents at ortho position upon yield.

Tadle VI

		42%
		36.5%
		45%
		52%

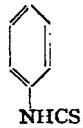
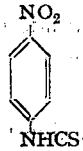
(VII) Effect of substituent in $C_6H_5NH{\cdot}CS{\cdot}R$.

Table VII

R	Thiamide	base	yield
H			0 %
CH_3			67%
C_3H_7			39%
C_6H_5			87%

(VIII) Result obtained in determination of absorption maxima in alkaline media.

Table VIII

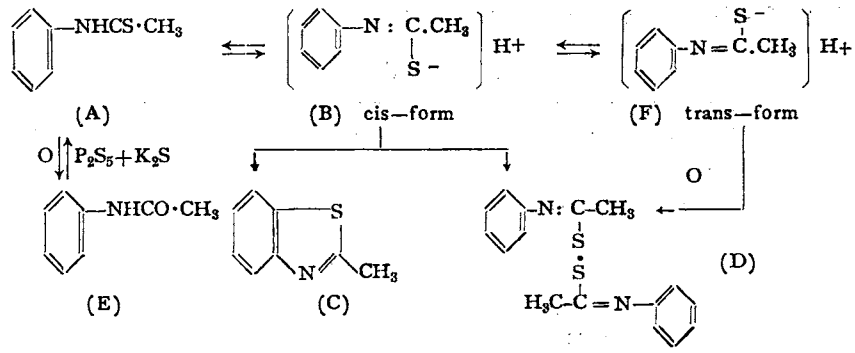
				2950	2780	2650	2500		2460
	3370	3350	3150	2930		2850	2600	2540	2460

Discussion

Thioacetanilide can be derived from acetanilide and which dissolves in alkaline solution where it undergoes almost complete enolisation. It has been known that thioacetanilide, when oxidized, is largely transformed into 1–methyl benzothiazole by way of the enole form and is partially converted into the acetanilide.

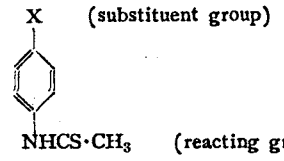
It was found in the present studies that a part of thioacetanilide was oxidized to form a sulphur-sulphur linkage intermolecularly.

Of course, the reaction conditions are sometimes critical or may have an extrinsic and secondary effect on the course of ring closure.



Now, in this place, a discussion of the effect of substituent groups on the benzene nucleus upon the formation of benzothiazoles by the ring closure of aryl substituted aliphatic thioamide will be presented.

The common rules of orientation regarding aromatic substitution may be extended to this ring closure. However, on account of the situation which the reacting group (-NH-CS-R) is directly attached to the benzene nucleus, the chemical nature of the group, especially the ease with which the reacting group (-NH-CS-R) is enolized, may be influenced by subsrituent group (X).



It is, therefore, convenient for present purposes, to discuss classifying the influences of substituents on the benzene nucleus upon the ring formation reaction into three: effect of substituent groups upon enolisation, influence upon electron density of the carbon atom ortho to thioaceamide group, and effect of steric hindrance.

Consideration of Effect of Substituent Group at para Position. to -NHCS.-CH$_3$

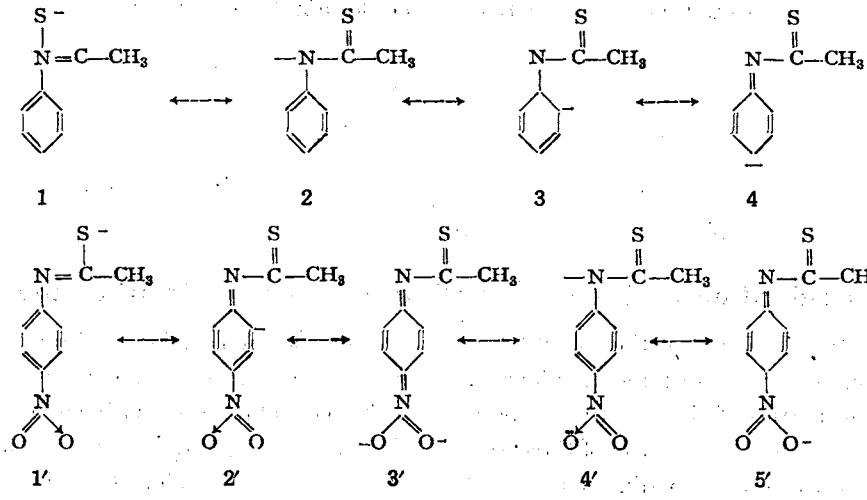
It is generally accepted that electronic influences of substituent on benzene ring is approximately limited to the carbon atoms, ortho and para to the substituent concerned.

In case of para-substituted thioacetanilide, therefore, the substituent (X) at the para position has little influence over electron density of the two carbon atoms orth to the thioacetamide group, that is, the carbon meta to that substituent (X). The substituent can be assumed on the basis of structural chemistry to have no steric effect on the reaction. Accordingly, its influenec, if any, may be associated with enolisation of the thioaceamide group :

$$(-NHCS-CH_3 \rightleftarrows N=\underset{\displaystyle SH}{\overset{\displaystyle |}{C}}-CH_3).$$

Yields obtained with five p-substituted thioacetanilides are satisfactory and almost indifferent to properties of substituent introduced, except in the casc of P-nitro thioacetanilide (Table I). Therefore, it may be concluded that the effect of the substituents except p-nifro group upon the enolisotion is not so powerful as to alter the rate of the ring formation. The exception obtained with p-nitro thioacetanilide may be explained in terms of "Paulings canonical structures". In case of thioace-

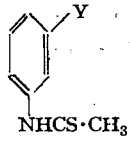
tanilide in basic solution where its molecule is ionized, the contributing structures to resonance consist of four different structures (2, 3, and 4), but in case of p-nitro-thioacetanilide, contributing structures consist of five. When compared with the contribution of structures 3' 4', and 5', the contribution of structure 1' which is involved in the ring formation may be relatively small on account of the precence of the nitro group.



That is, in the case of P-nitro-thioacetenilide, enolisation is so difficult that the ring closure of the thioanilide via the enol form is surpressed, and instead the formation of P-nitro-acetanilide becomes favorable.

This view is substentiated by the fact that P-nitrothioacetanilide absorbs light of longer wave length than thioacetanilide does. That is, bathochromic shift could be seen in passing from thioacetanilide to p-nitrothioacetanilide (Table VIII).

Consideration of Influence of Radical at meta Position. to NHCS. CH_3.

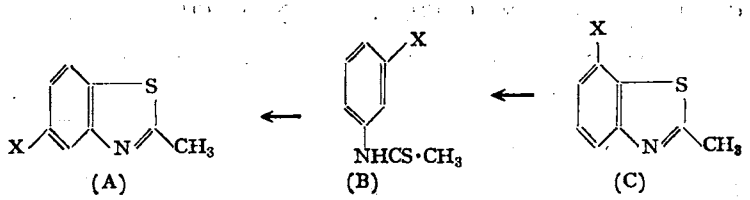


Some suggestion can be obtained on the problem as to whether or not the electron dentity of the two carbon atoms ortho to the radical (-NHCS • CH_3) has influence upon the ring formation, by comparing the yield of various meta · substituted thioacetamides with one another. As can be seen from table V, the order of decreasing vields of basses, afforded by these compounds is 71% for m-chloro-thioacetamide, 79.5% for m-thiotoluide 59.5% for m-thioanisidide, and 47.3% for m-nitro-thioacetanilide.

This shows that the electron density of the carbon atoms has something to do with ring formation and the yield of base is not favored owing to too much electronegativity on the carbon stoms. This also infers that the ring formation involves non-ionized cis-form(-N=C-CH_3).
SH

In the second place, by comparing the yields of A-type bases with those of B-type bases formed from m-substituted aryl thioacetamides (C), information as to whether steric hindrance exists or not, can be obtained, beceause the equal yields may be expected as far as electron density is concerned.

The ratio of yield of A-type base to that of B-type base is 5 : 1 for m-thioacetanilisidide, 10 : 1 for m-thiotoluidide and 2 : 3 for m-chlorothioacetanilide (Table III). Considerable steric hindrance could not be observed.



(A) (B) (C)

Consideration of Effect of Substituent Groups at Ortho Position.

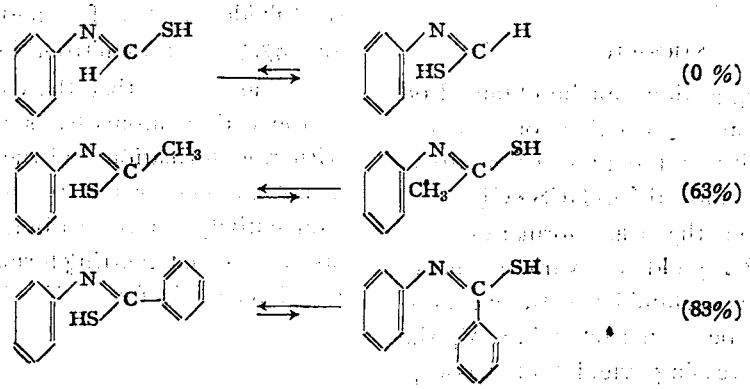
Yields obtained with ortho-substituted thioacetanilides are almost independent of chemical properties of the substituents, but the yields are about two thirds of those obtained with the corresponding para- and mete-substituted compounds (Table VI).

It is probably due to the fact that one of the two ortho positions available in the case of meta- and para-substituted aryl thioacetamibes has been occupied by the substituent, and accordingly, a numder of positions at which the thioacetamide radical can attack is one less than that of meta- or para-substituted molecule.

Consideration of Effect of Substituent R in C_6H_5NH-CS-R.

Table VII shows that yield of base increases in proportion to the increases of the number of carbon in R groups, more precisely in proportion to the increase of effective volume of the R radical conrned.

It may be, therefore, concluded that enolisation in the thioacetamide molecule can occur in two forms : cis-form and trans-form, and the ratio of cis-form to trans-form depends upon the relative size of R radical compared SH group. The situation can be described with in the following diagram.



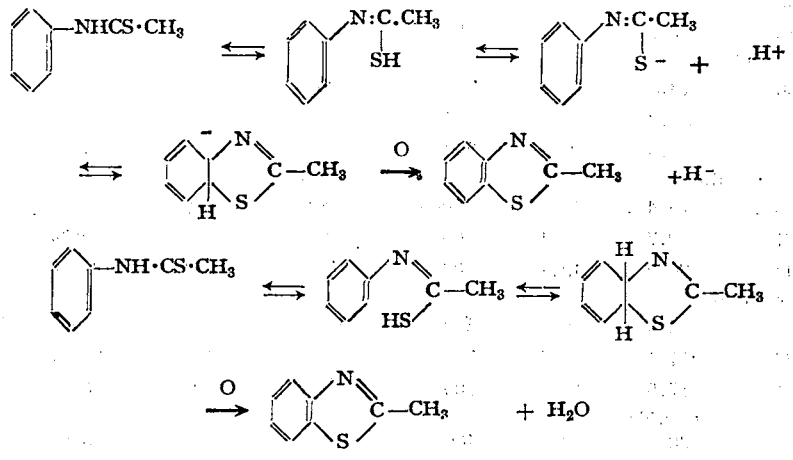
Conclusion

(I) Except in the case of P-nitrothioacetanilide, the ring formation of aryl thioacetamides is not inflnenced considerably by substituents present in the benzene ring. That is, improved procedure devised by the present authors can give satisfactory results, especially for para-substituted aryl thioacetamides.

(II) The ring formation of N-aryl thioalyalyamides suffers steric hindrance by such sudstituents as methoxy and methyl at the meta carbon, but it is not so powerful in the casa of chlorine atom at the meta position.

(III) Yield of base increases in proportion to an increase of the effective volum of the R radical in $C_6H_5NH{\cdot}CS{\cdot}R$. It may infer that enolisation of the thioamide molecule can occur in two forms: that is, cis-form and trans-form and the ratio of cis-form to trans-form depends upon the relative size of R radical to SH group.

(IV) The mechanism of the ring formation could not be made entirely clear. However, the ring formation of aryl thioacetamides probably proceeds in the following way.



Experimental

(I) Preparation of thioacetanilide derivatves.

Thioacetanilide was prepared by modifying the method of Jacobson(3).

In a 500 ml. three-necked flask fitted with a mercury-sealed stirrer and a thermometer, was placed 90 g. of acetanilide and 250 ml. of dry xylene. The flask was heated under stirring in an oil bath until the acetanilide was dissolved(about 80°). Under vigorous stirring the mixture of 35 g. of phosphorous penta-sulfide and 53 g. of powdered potassium sulfide was added in portions to the solution at the temperature of 115° during the course of thirty minutes. After all the mixture was added, the content of the flask was kept stirring for another thirty minutes at the same temperature. The pale yele yellow solution thus obtained was removed from the deposit by decantation.

The residue was washed with two portions of 50 ml. of dry xylene. Xylene solution was washed with two portions ot 50 ml. of dry xylene. Xylene solution and two extract were combined. On cooling, yellow amorphous crystals separated. The crystals (crude thioacetanilide) were collected in filtering by suction. Xylene was removed from the mother liquor under the reduced pressure at the temperature of no more than 70°. The oily residue and the amorphous crystals mentioned above were combined and exhaustedly extracted with 300 ml. of 8% alkaline solution. The alkaline extract was neutralized with carbon dioxide. Amorphous crystals separated were collected and washed with 50 ml. of water. If necessary, crude materials were recrystalized by the same procedure. The yield was 81 g. (80%) m. p. 68°. The crude material was suitable for the subsebuent ring formation.

Substituted phenyl thioacetanilides were prepared by similar procedure, unless otherwise mentioned.

Material		K_2S	P_2S_5	Xylene	8% alkali	Yield	M.P.	Remark	
Thioacettoluidide									
P–	50g.	26g.	17.0g	250ml.	250ml.	47.5g.	86.7%	118C.	
m–	32	22	15.4	200		21	57%	58–9°	
O–	18	12.7	8.7	200	625	15	75%	67–8°	
Thioacetanisidide									
P–	30	18.5	12.7	200	300	30.5	91%	112C.	
m–	68	52.3	28.7	400		42	56.5%	43–4°	
O–	22	13.5	9.2	200		15	62.5%	48°	
Chlorothioaceteanilide									
p–	50g.	25.4g.	16.9g.	350ml.	300ml	38g.	81%	143C.	
m–	21	10.7	7.1	200	328	15.7	68%	62–3°	(b)
o–	44	26.2	18.1	400		35.0	72.5%	53–5°	(b)
Nitrothioacetanilide									
p–	25	12.0	8.0	650	300	20.2	73.5%	173–4 C.	(a)
m–	20	11.4	7.7	750		19	87.3%	91–2	(c)
o–	31	17.5	12	700		20	59%	79–80	(c)
2,5–Dichlorothioacetanilide									
	55	30	18.7	400		50	85.5%	118–9°	
2,4–Dichlorothioacetanilde									
	42	21.5	14.4	400		33.5	74%	94–5°	
Thioformyl anilide									
	45	26.5	17.4	220	400	24.5	50.3%	138–9°	
Thiobutyl anilide									
	31	19.2	12.5	500		33	86.5%	32°	(c)
P–Methoxythiobenzanilide									
	10	4.5	3.1	500		7.5	71.5%	153–4°	
P–Nitrothiodenzanilide									
	10	4.3	2.8	700		8	76%	141–2°	
Thiobenzanilide									
	15	7.5	5.3	700		12.5	72%	96°	

Remark (a): In this case, the mother liquor (from which crude thioacetanilide separated) was discarded, because the thioacetenilide is barely soluble in xylene at 10°.

Remark (b). In this case, the thioacetanilide was extracted from the mother lignor with 8% alkaline solution, because the thioacetanilide was prone to be resinified at the temperature of 80°C.

Remark (c). In this case, the solide base separated from the reaction mixture was not treated with 8% alkali, but instead was recrystalized from alcohol.

Assay:

1.	m-Thioanisidide.	$C_9H_{11}O\ N\ S$	requires	N:	7.73
			Found.	N:	7.51
2.	m-Thiotoluidide.	$C_8H_1N\ S$	requires	N:	8.47
			Found.	N:	8.52
3.	m-Nitrothio-acetanilide	$C_8H_8O_2N_2S$	requires	N:	4.29
			Found.	N:	4.15
4.	o-Chlorothioacet-tanilide.	$C_8H_8N\ SCl$	requires	N:	7.75
			Found.	N:	7.63
5.	o-Ni1rothioacet-anilide.	$C_8H_8O_2NS$	requires	N:	4.29
			Found.	N:	4.25
6.	2,4-Dichloro-thioacetanilide.	$C_8H_7NSCl_2$	requires	N:	6.39
			Found.	N:	6.11
7.	2,5Dichloro-thioacetanilide	$C_8H_7NSCl_2$	requires	N:	6.37
			Found.	N:	6.32

In case of p-methoxythioacetanilide, the reaction was carried out at the temperature of 120° to 125°. At the lower temperature (80° to 110°), the yield was very poor.

In case of o-nitro-acetanilide, a substance containing sulphur and insoluble in 8% alkaline solution was obtained along with thioacetanilide.

Calculated for	$C_{16}H_{14}S_2N_4O_4$	N:	11.35
Found.		N:	11.27

(2) Preparation of 1-methyl benzothiazole: In a three-necked flask fitted with a thermometer, a separatory funnel, and a mechanical stirrer. were placed 88 g. of powdered ferri cyanide and 136 ml. of water. The stirrer as started and a solution of 20.0 g. of thioacetanilide in 8% alkaline solution prepared by dissolving 14.5g. of potasium hydroxide in 298ml. of water and flltering, was poured into the flask at 40° dunring the course of an hour and a half. After the whole solution was poured, 58g. of anhydrous sodium carbonate was added for salting-out under stirring. After that, the reaction mixture was extracted with three portions of 100 ml of ether. The ether was removed and the residue was sudjected to steam distillation. The distillate was extracted with three portions of 210 ml. of ether. The etherial solution was dried over calcium chloride overnight. The ether was removed and the residue was distilled under the reduced pressure. The yield was 13.8g. (67.3%), b. p. 238-240°. The picrate melted at 153.5°.

Preparation of substituted 1-methyl benzothiazoles.

Substituted 1-methyl benzothiazoles were prepared approximately by similar prooedure, unless otherwise mentioned. That is, one mole of substituted phenyl thioacetamide was dissolved in alkaline solution prepared by dissolving 2.4 moles of sodium hydroxide in 1500 ml. of water. The solution prepared was added to the

mixture of 2.4 moles of potassium ferricyanide and 1400 ml. of water at 40° during the course of a hour and a half. The base formed was isolated by means of one of the following three procedures according to physical properties of the base obtained.

(1) In the case where the method of steam distillation was available, the base formed was isolated in the same procedure as in the case of 2-methyl benzothiazole.

(2) In the case where steam distillation method could not be applied for isolation and the base was obtained as liquid, the base was extracted with ether and the residue obtained by removing the ether was extracted exhaustedly with ca. 34% hydrochloric acid and hydrochloric acid neutralized with conc. ammonium hydroxyde to separate the base.

(3) In the case where the method of steam distillation could not be applied, and the base was a soiid, the base separated in the supernatant layer was collected by filtration and extracted with ca. 34% hydrochloric acid and then neutralized with conc. ammonium hydroxide to separate the base.

Material	NaOH	Water	$K_3Fe(CN)_6$	Water	Na_2CO_3 for salting-out	Ether for extract.	yild of base	
Thioacettoluidede							g	%
p-38.5g.	40g.	580ml.	220g.	440ml.	100g.	470ml.	27.5g.	71.3
m-16.5	11.2	150	79	140			11.5	70.5
o-21.00	15	217	82.5	150	58	230	9.95	52.0
Thioacetanisidide								
p-41	24.9	395	152	235	90	300	28.1	70.3
m- 9	2.8	60	40	80			5.3	59.5
o-15	11.2	150	79	140	60		6.3	42.0

Material	NaOH	Water	$K_3Fe(CN)_6$	water	$NaCO_3$ for salting-out	Ether for extract	Base yield	
Chlorothioacetanilide							g	%
p-18.5	11.2	150	94.8	140			13.2	72
m-18.5	11.2	150	80.0	140			13.9	71
o- 9.2	2.8	60	40	80			4.1	45
Nitrothioacetanilide								
p-18.0	9.9	143	60	94				none
m-								
o-								
2,5-Dichlorothioacetanilide								
22	11.2	150	79	140			13.0	59
2,4-Dichlorothioacetanilide								
11.0	5.6	75	40	70			4.0	36.5
Thioformylanilide								
2.7	17.3	200	95	157				none
Thiobutyranilide								
9.5	5.6	70	40	75			3.4	39

Separation and Identification of two Isomers in the case where two Isomers can be expected (m-Substituted Phenyl Thioacetamides)

I. m-chloroacetanilides.

(a) 4-chlohloro 1-methyl benzothiazole.

13.5g. of the substance, prepared from 18.0g. of m-chlorothioacetanilide and soluble in hydrochloric acid, was distilled under the reduced pressure. (3mm.) The first run of the distillate solidified on standing at the temperature (aount 15°). It weighed 5.50g. (42.6% calculated for the strating material), melted at 67–8°. The melting point is identical to that of 4-chloro, 1-methyl benzothiazole prepared by means of D.R.P. method (D.R.P. 36744, and 360690). It was converted into picrate, which melted at 161–2°.

(b) 6-Chloro 2-methyl benzothiazole.

The second run of the distillate remained unsolidified on standing. It was converted into its picrate. It weighed 7.56g. (28.4%) and melted at 115–6°, after it was recrystalized from benzene.

The mixed melting point was 150°.

Yield-ratio of 6-isomer to 4-isomer is 2 : 3.

2. m-Methoxy thioacetanilides.

5.3g. of base was transformed to its picrate and the picrate was recrystallized from benzene.

Picrate obtained from the comparatively less soluble part, melted at 155–6°, and weighed 1.44g. (11.2%) 6.32g. (48.3%) of picrate was recovered from the mother liquor and it melted at 159°. The mixed melting point was 135°. The ratio of one isomer to the other is 1 : 5.

3. m-Thiotoluidides.

11.5g. of base was converted into its picrate and the picrate was recrystallized from benzene. The picrate which was separated first melted at 167–8°. and weighed 1.5g. (6.4%). The picrate obtained from the mother liquor melted at 127–9°. and weighed 21.8g. (64.1%).

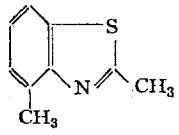
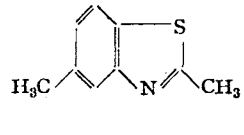
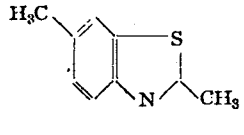
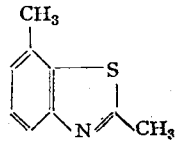
The ratio of the base of lower melting point to that of higher melting point is 1 : 10.

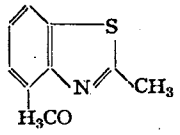
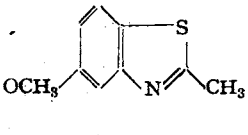
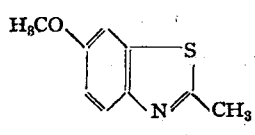
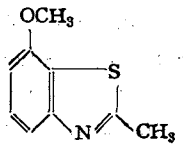
(5) Substituted 1-methyl benzothiazole newly prepared.

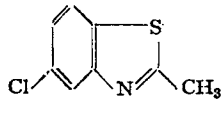
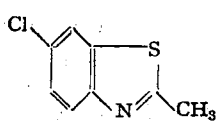
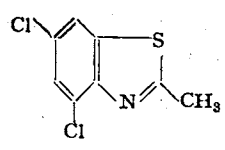
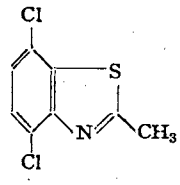
1. 1,4-dimethyl benzothiazole. (b.p. 95–105/3mm); m.p. (picrte) 127—9 C.
   $C_{15}H_{12}O_7SN_4$ (picrate) requires C; 45.80 H; 2.89 N; 14.23
   Found. C; 45.60 H; 3.01 N; 14.32
2. 1,6-dimethyl benzothiazole. (b.p. 95-105/3); picrate 167—8 C.
   $C_{15}H_{12}O_7SN_4$ (piorane) repuires C; 45.80 H; 2.89 N; 14.23
   Found. C; 45.62 H; 2.71 N; 14.20
3. 1-methyl, 4-methoxy benzothiazole. (b.p. 125–135/3); picrate 153—4 C.
   $C_{15}H_{12}O_8SN_4$ (picrate) requires C; 44.13 H; 2.93 N; 13.73
   Found. C; 44.00 H; 2.82 N; 13.70
   C_9H_9OsO S N requires C; 60.19 H; 5.07
   Found C; 60.00 H; 4.93
4. 1-methyl, 6-methoxy benzothiazole.
   (m.p. 48–50 C., b.p. 125–135/3); picrate 159 C.
   $C_{15}H_{12}O_7SN_4$ (picrate) requires C; 44.13 H; 2.93 N; 13.73
   Found C; 44.01 H; 2.73 N; 14.01
5. 1-methyl, 3,5-dichloro benzole. picrate 140—142 C.
   C^8H^5N S Cl_2 requires C; 44.24 H; 2.30 N; 6.45

	Found	C;	44.20	H;	2.40	N; 6.50
6. 1-methyl, 3,6-dichloro benzothiazole. (m.p. 131-2 C.)						
$C_8H_5N\ S\ Cl_2$	requires	C;	44.24	H;	2.30	N; 6.45
	Found	C;	44.20	H;	2.30	N; 6.35

(6) Table of the Benzothiazole prepared.

				
m.p.	34°C.	—	—	—
b.p.	105/8mm	95-105/3	120/11.5mm.	—
m.p. forpicrate	153-4°C.	127-9°C.	173-4°C.	167-8°C.
literature	(2)	(none)	(15)	(none)

				
m.p.	88-9°C.	—	—	48-50
b.p.		125-135/3mm.	284/760mm. 170/20mm.	125-135/3mm.
mp. for picrate	155-6°C.	153-4°C.	176°C.	[159°]
literature	(2)	(none)	(16)	(none)

				
m.p.	67-8°C.	85-7°C.	146°	131-2°C.
m.p. for picrate	161-2°C.	141-2°C.	115-6°C.	
literature	(17)	(17), (8) and (1)		

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2) **Y.Mizuno et. al:** Journ. Pharm. Soc. Japan 70 10

3) **Y.Mizuno et. al:** ibid.

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