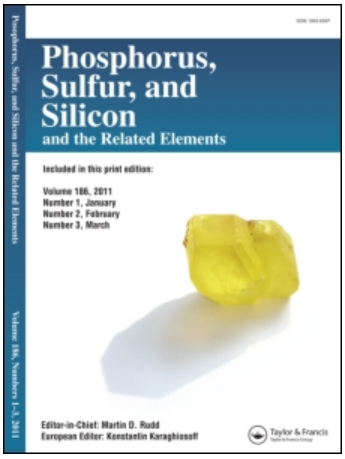

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HETEROCYCLIC SULFUR COMPOUNDS—LXXXV Steric Effects in the Reaction of Primary Amines upon 3,1-Benzothiazine-4-thiones

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HETEROCYCLIC SULFUR COMPOUNDS—LXXXV

Steric Effects in the Reaction of Primary Amines upon 3,1-Benzothiazine-4-thiones

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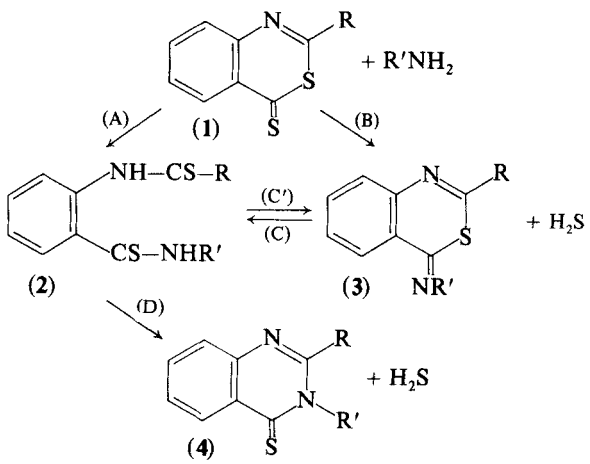
The reaction of primary amines with 3,1-benzothiazine-4-thiones is known to be a good synthesis of 3*H*-quinazoline-4-thiones. This paper shows that, depending on the steric characteristics of the amine group and of the substituent carried in position 2 by the benzothiazinethione, 4-imino-4*H*-3,1-benzothiazines can be obtained.

Preparation and identification of the 3*H*-quinazoline-4-thiones and of their isomers, 4-imino-4*H*-3,1-benzothiazines are described. In acidic ethanol it has been found difficult to isomerize the above mentioned imines into the corresponding thiones and ethyl-2-(thioaroylamino)benzoates have been obtained.

In a paper published in 1960[1] we had shown that reaction of primary amines with 3,1-benzothiazine-4-thiones may be considered as a useful preparative method leading to a wide range of 3*H*-quinazoline-4-thiones. With aliphatic amines, the reaction was performed in boiling ethanol and with aromatic amines at 200°C in an excess of amine.

Later, Walter and Voss[2] found that, in boiling ethanol, primary alkylamines react with 2-*t*-butyl-3,1-benzothiazine-4-thione giving a 2-(thiopivalamido)-*N*-alkyl-thiobenzamide. However, if the reaction is performed at 100–130°C under pressure, a 3-alkyl-2-*t*-butyl-3*H*-quinazoline-4-thione is obtained.

For these reactions, various pathways may be considered:



According to our first results and to those obtained by Walter and Voss, the only proved intermediate was **2** in the sequence **1** → **2** → **4**. The imines **3** had not been identified, and accordingly their isomerization into the thiones **4** could not be studied. In order to study this reaction, Ebel and Lejuez[3] prepared some imines **3** by another method, the action of arylamines on 4-methylthio-3,1-benzothiazinylium fluorosulfates. Imines **3** thus obtained isomerized quantitatively into the corresponding thione **4** in boiling ethanol containing small amounts of sulfuric acid. These results showed that **3** could be an intermediate but did not answer the question whether the imines **3** could be obtained directly from the benzothiazinethiones **1**. In order to solve this problem, we have undertaken a new study of this reaction, varying the experimental conditions and the nature of the reactants, studying more particularly primary amines and 3,1-benzothiazine-4-thiones containing groups liable to have steric effects.

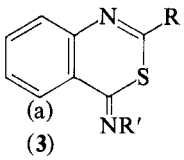
This systematic study led to the conclusion that according to the steric effects of the amine group and of the substituent in position 2, of the 3,1-benzothiazine-4-thione **1**, the imines **3** could be obtained instead of or together with their isomers, the thiones **4**.

CHARACTERIZATION OF THE PRODUCTS

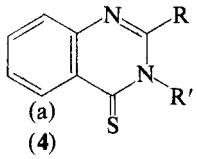
The isomers **3** and **4** were isolated by adsorption chromatography on alumina or silica. Structures

were established by use of nmr and uv spectrometry.

The nmr structure determination is mainly based upon the fact that in naphthalenoid heterocycles, such as 3,1-benzothiazines or quinazolines, having a juxtacyclic double bond in position 4, the chemical shift of the proton in position 5 is clearly affected by the nature of the heteroatom (here nitrogen or sulfur) doubly bonded to the carbon atom numbered 4. This rule has already been shown to have a wide range of application.[4–7] As shown in the following examples, the downfield shift of a proton in position 5, when there is a C=S in position 4, is distinctly larger than when there is a C=N in the same position:



(3)



(4)

R	R'	Nmr shifts for protons (a): (3)	(4)
t-Butyl	Ethyl	8.15–8.31 (m)	8.73–8.87 (m)
Phenyl	2,6-Xylyl	8.15–8.81 (m)	8.51–8.66 (m)
o-Tolyl	Phenyl	8.15–8.31 (m)	8.48–8.58 (m)

The position and intensity of the first absorption band in the near uv clearly differentiate 3*H*-quinazoline-4-thiones **4** from 4-imino-4*H*-3,1-benzothiazines **3**. The former show a strong band near 360–370 nm, between two weaker bands or shoulders, on the other hand, the imines **3** have a clearly stronger absorption band at distinctly shorter wavelengths, about 310–330 nm.

These results are in agreement with the literature,[8–10] as it is known that the $\pi \rightarrow \pi^*$ transition gives an absorption band in thioamides at higher wavelengths than in imines. On the other hand, the absorption related to the $\pi \rightarrow \pi^*$ transition for an imino group is stronger than for a thiocarbonyl. These differences are clearly shown in Figures 1 and 2 giving, respectively, the absorption spectra of three 4-imino-4*H*-3,1-benzothiazines and of the three isomeric 3*H*-quinazoline-4-thiones.

In Table I, the position of these absorption bands are given for the six compounds appearing in Figures 1 and 2 as well as for eight other compounds **3** and **4**.

FACTORS INFLUENCING THE REACTION OF PRIMARY ALIPHATIC AMINES

With a 2-(*t*-butyl) or 2-aryl-3,1-benzothiazine-4-thione in benzene at ordinary temperature, a primary aliphatic amine always leads to a 2-(thioacylamino)thiobenzamide **2**. Although recyclization generally predominates when boiling ethanol is used as solvent, the thioamide **2** may be obtained if the amine group is sterically hindered, as in isopropylamine.

The behavior of thiobenzamides **2** in boiling ethanol depends upon the acidity of the reaction

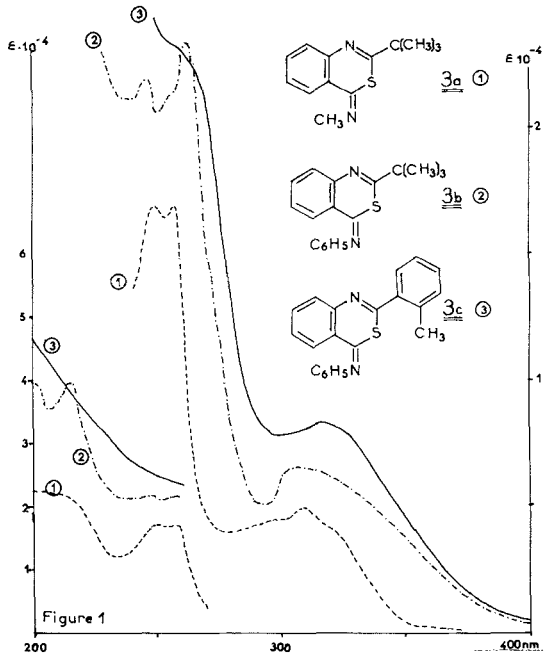


Figure 1

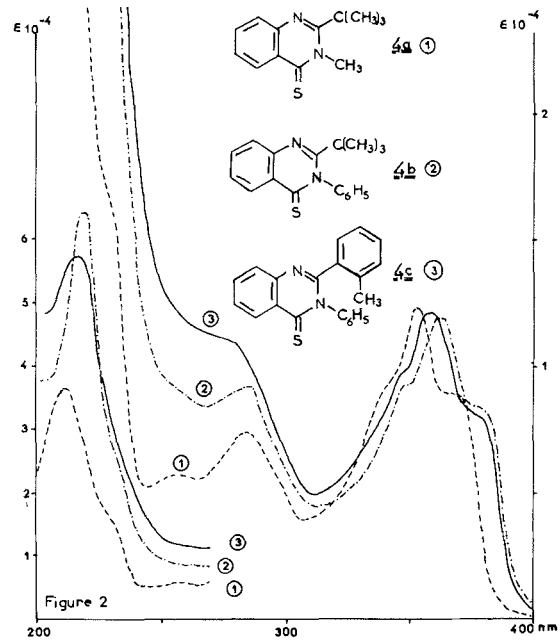
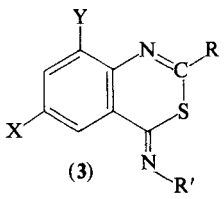


Figure 2

TABLE I

Near uv absorption (in ethanol) of various compounds (**3**) and (**4**)



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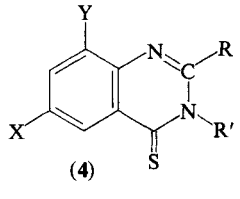
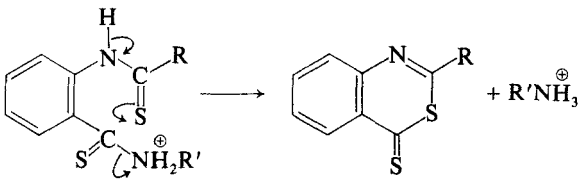


(4)

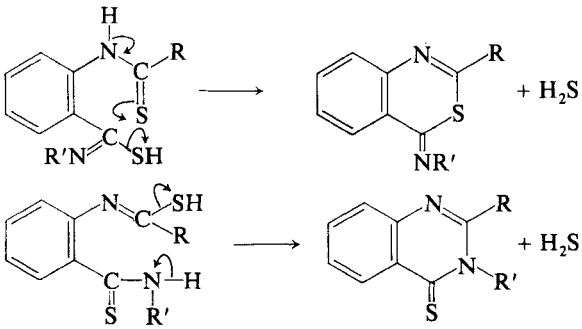
	X	Y	R	R′	(3)	(4)		
(a)	H	H	*t*-Butyl	Methyl	309	340 (sh)	363	370 (sh)
(b)	H	H	*t*-Butyl	Phenyl	312	350 (sh)	363	380
(c)	H	H	*o*-Tolyl	Phenyl	314	347 (sh)	362	380
(d)	Cl	H	*o*-Tolyl	Phenyl	317	353 (sh)	370	389
(e)	H	H	*o*-Tolyl	*o*-Tolyl	316	345 (sh)	361	389 (sh)
(f)	H	H	*o*-Chlorophenyl	Ethyl	311	343 (sh)	358	374
(g)	Cl	Cl	*o*-Chlorophenyl	Phenyl	328	357	374	393

mixture. In the presence of small amounts of hydrogen chloride or sulfuric acid, thiobenzamides **2** lose an amine molecule and revert to the initial 3,1-benzothiazine-4-thione. On the other hand, under neutral conditions, 4-imino-4*H*-3,1-benzothiazines **3** and/or 3*H*-quinazoline-4-thiones **4** are obtained, as shown in Table II. The following equations represent the probable course of the reaction, (a) in the presence of a strong acid, (b) under approximately neutral conditions.

a) Reactions in the presence of strong acids:



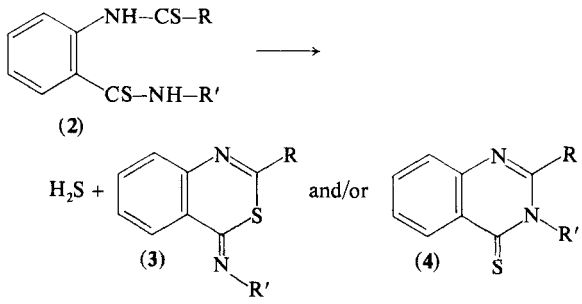
b) Reactions under approximately neutral conditions:



Results given in Table II strongly suggest that steric effects have a significant influence on the cyclization of 2-(thioacylamino)-*N*-alkyl-thiobenzamides. The imine ratio increases when the *N*-

TABLE II

Cyclisation of 2-thioacylamino-thiobenzamides **2**



(2)

(3) and/or (4)

R	R′	Yield of (**3**) (%)	Yield of (**4**) (%)
t-Butyl	Methyl	70	11
t-Butyl	Ethyl	81	—
t-Butyl	Isopropyl	75	—
t-Butyl	Benzyl	65	—
Phenyl	Methyl	—	90
Phenyl	Ethyl	31	65
Phenyl	Isopropyl	83	2
o-Tolyl	Methyl	—	87
o-Tolyl	Ethyl	22	70
o-Tolyl	Isopropyl	82	—
Mesityl	Methyl	87	—
Mesityl	Ethyl	90	—
o-Chlorophenyl	Methyl	—	81
o-Chlorophenyl	Ethyl	54	38
o-Chlorophenyl	Isopropyl	86	—

alkyl substituent is bulkier, as shown by comparison of the corresponding methyl, ethyl and isopropyl derivatives. Similarly, for a given *N*-alkyl substituent on the thiobenzamide functional group, the presence in the thioacylamino group of a *t*-butyl or of a 2,4,6-trimethylphenyl favors imine formation. An *o*-chlorophenyl, compared with phenyl, favors also the imine formation, but to a lesser extent.

FACTORS INFLUENCING THE REACTION OF PRIMARY AROMATIC AMINES

In these cases, reactions have generally been performed in an excess of amine, either at 100°C or at 200°C. Results are given in Table III. The reaction times indicated are defined by the disappearance of the red color of the benzothiazinethione. Here also the amine group or the 3,1-benzothiazine-4-thione substituent in position 2 have a marked effect on the imine ratio: in either case, *t*-butyl, *o*-substituted phenyls and naphthyls favor imine formation whereas a higher temperature increases thione formation, as could be expected if steric hindrance is the prevalent factor favoring the formation of imines **3**.

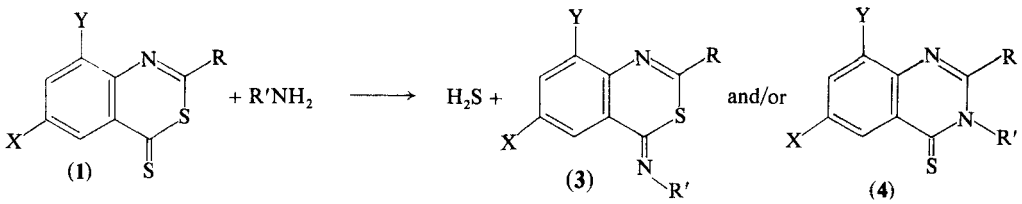
Table IV compares results obtained in various conditions:

A. at 100°C, with an excess of amine
B. at 200°C, with an excess of amine
C. in boiling 1-propanol, with some triethylamine
D. in boiling dimethylformamide.

It appears that triethylamine in 1-propanol favors thione formation, whereas dimethylformamide seems to affect total yields without having a clear influence on the imine ratio. It is also interesting to note that, although in procedures A and B a

TABLE III

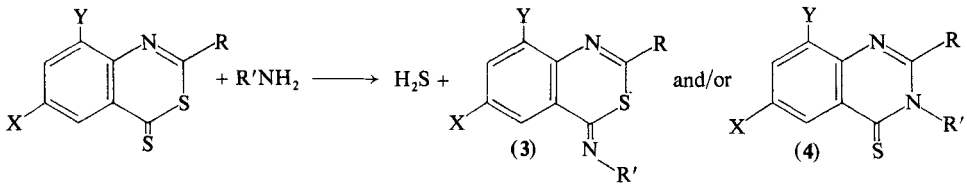
Action of primary aromatic amines on 3,1-benzothiazine-4-thiones (**1**)



X	Y	R	R'	T°C	Time (h)	Yield of (**3**) (%)	Yield of (**4**) (%)
H	H	Isopropyl	Phenyl	100	2	—	83
H	H	*t*-Butyl	Phenyl	100	5	80	—
				200	1	47	26
H	H	Phenyl	Phenyl	100	5	—	85
Cl	Cl	Phenyl	Phenyl	200	1	—	92
H	H	Phenyl	*o*-Tolyl	100	48	4	72
H	H	Phenyl	2,6-Xylyl	200	2	25	41
H	H	Phenyl	*o*-Chlorophenyl	200	3	10	78
H	H	*o*-Tolyl	Phenyl	100	8	52	15
				200	1	32	53
Cl	H	*o*-Tolyl	Phenyl	100	5	75	—
				200	1	76	—
H	H	*o*-Tolyl	*o*-Tolyl	200	2	76	10
H	H	*o*-Tolyl	*o*-Chlorophenyl	200	2	—	85
H	H	*o*-Tolyl	*p*-Chlorophenyl	100	6	33	16
H	H	*o*-Chlorophenyl	Phenyl	100	5	23	42
				200	1	—	62
Cl	Cl	*o*-Chlorophenyl	Phenyl	200	1	46	48
H	H	*o*-Chlorophenyl	2,6-Xylyl	200	2	40	12
H	H	*o*-Methoxyphenyl	Phenyl	100	5	—	70
H	H	*α*-Naphthyl	Phenyl	200	1	80	—
H	H	*β*-Naphthyl	Phenyl	200	1	85	—

TABLE IV

Influence of experimental conditions on the reaction of some 3,1-benzothiazine-4-thiones with aromatic primary amines

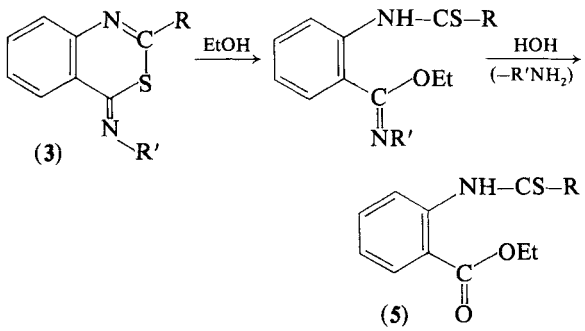


X	Y	R	R'	Procedure	Yield (3) (%)	Yield (4) (%)
H	H	*o*-Tolyl	Phenyl	A (100°, 8 h)	52	15
				B (200°, 1 h)	32	53
				C (PrOH, NEt_3)	32	64
				D (DMF)	28	40
Cl	H	*o*-Tolyl	Phenyl	A (100°, 5 h)	75	—
				B (200°, 1 h)	76	—
				C (PrOH, NEt_3)	2	88
				D (DMF)	70	10
H	H	*o*-Chlorophenyl	Phenyl	A (100°, 5 h)	23	42
				B (200°, 1 h)	—	62
				C (PrOH, NEt_3)	3	91
				D (DMF)	21	60
H	H	*o*-Chlorophenyl	*o*-Chlorophenyl	B (200°, 3 h)	—	20
				D (DMF, 18 h)	35[a]	(traces)

[a] In this case, after 18 h, 15% of unreacted 3,1-benzothiazine-4-thione still remain.

higher temperature clearly favors the formation of 3-phenyl-2-(*o*-tolyl)-3*H*-quinazoline-4-thione, this compound is not appreciably formed by heating the corresponding imine for three hours at 210°C. This shows that the imine ratio depends much more on kinetic control of the reaction than on a possible thermal isomerization of the imine.

Isomerization of imines **3** into thiones **4** is catalyzed by strong acids. Ebel and Lejuez[3] have shown that imines **3** with a non-bulky substituent in position 2 isomerize readily into the corresponding



R = *o*-Tolyl; R' = Isopropyl or Phenyl.

thione **4** by heating in acidic aqueous ethanol. In this case, the ring opening which is necessary for the isomerization probably proceeds through the fixation of an ethoxy group on the carbon 2. On the other hand, under the same conditions, 4-imino-2-(*o*-tolyl)-4*H*-3,1-benzothiazines give mainly or exclusively an ethyl 2-(thioaroylamino)benzoate **5**, probably by acidic transesterification of **3**, which is in fact a cyclic imido-thioester, followed by the hydrolysis of the intermediate imido-ester. Here, the ring opening proceeds by fixation of an ethoxy group on the less hindered carbon 4.

EXPERIMENTAL

3,1-Benzothiazine-4-thiones 1

These compounds have been prepared according to the procedure already published.[11,12] The following compounds had not been already described: 6-Chloro-2-(*o*-tolyl)-3,1-benzothiazine-4-thione. F = 169°C; Yield 74%. 2-Mesityl-3,1-benzothiazine-4-thione. F = 138°C; Yield 51%. 6,8-Dichloro-2-(*o*-chlorophenyl)-3,1-benzothiazine-4-thione. F = 197°C; Yield 85%.

Reaction of Aliphatic Amines on 1

At ordinary temperature, the benzothiazinethione **1** is dissolved in the minimum amount of thoroughly dried benzene. Then a

slight excess of amine, dissolved in benzene, is added. The solution discolours progressively while yellow crystals of 2-(thioacylamino)-thiobenzamide **2** precipitate which are afterwards recrystallized in benzene. Yields are nearly quantitative. The compounds thus obtained are indicated in Table V.

Reaction of Strong Acids on Thiobenzamides **2**

The thiobenzamide **2** (1 g) is dissolved into 50 cm^3 of ethanol to which 0.5 cm^3 of aqueous hydrogen chloride 2N is added. The mixture is refluxed for 15 min. After evacuation of the solvent under reduced pressure, the residue is dissolved in a mixture, in equal amounts, of benzene and petroleum ether. This solution, purified by adsorption chromatography on alumina, gives almost quantitative yields of the corresponding 3,1-benzothiazine-4-thione by elution with a 20:80 benzene/petroleum ether mixture.

Thermal Cyclisation of 2-Thioacylamino-thiobenzamides **2**

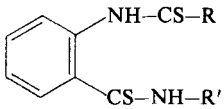
1 g of **2** is dissolved in 50 cm^3 of ethanol and the solution is refluxed during 5 hours. The reaction product is purified as in the preceding paragraph. When two isomers **3** and **4** are present, during the chromatographic elution, the imine **3** generally comes first. Yields in compounds **3** and **4** have been given in Table II. Melting points are respectively given in Tables VI (imines **3**) and VII (thiones **4**).

Reaction of Aromatic Amines on **1**

The products obtained according to the following procedures are described in Table VI (imines **3**) and VII (thiones **4**).

TABLE V

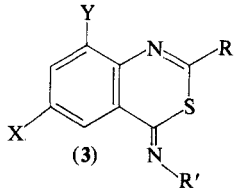
2-Thioacylamino-thiobenzamides



R	R'	Melting point and references (°C)
t-Butyl	Methyl	136[2]
t-Butyl	Ethyl	118
t-Butyl	Isopropyl	121
t-Butyl	Benzyl	122[2]
Phenyl	Methyl	160
Phenyl	Ethyl	190
Phenyl	Isopropyl	137
o-Tolyl	Methyl	191
o-Tolyl	Ethyl	141
o-Tolyl	Isopropyl	145
Mesityl	Methyl	223
Mesityl	Ethyl	166
o-Chlorophenyl	Methyl	192
o-Chlorophenyl	Ethyl	150
o-Chlorophenyl	Isopropyl	177

TABLE VI

4-Imino-4*H*-3,1-benzothiazines



X	Y	R	R'	Melting point (°C)
H	H	*t*-Butyl	Methyl	50
H	H	*t*-Butyl	Ethyl	oil
H	H	*t*-Butyl	Isopropyl	oil
H	H	*t*-Butyl	Benzyl	89
H	H	*t*-Butyl	Phenyl	151
H	H	Phenyl	Ethyl	91
H	H	Phenyl	Isopropyl	70
H	H	Phenyl	*o*-Tolyl	108
H	H	Phenyl	2,6-Xylyl	155
H	H	Phenyl	*o*-Chlorophenyl	180
H	H	*o*-Tolyl	Isopropyl	42
H	H	*o*-Tolyl	Phenyl	110
Cl	H	*o*-Tolyl	Phenyl	105
H	H	*o*-Tolyl	*o*-Tolyl	126
H	H	*o*-Tolyl	*p*-Chlorophenyl	134
H	H	Mesityl	Methyl	113
H	H	Mesityl	Ethyl	130
H	H	*o*-Chlorophenyl	Ethyl	102
H	H	*o*-Chlorophenyl	Isopropyl	78
H	H	*o*-Chlorophenyl	Phenyl	154
H	H	*o*-Chlorophenyl	*o*-Chlorophenyl	137
Cl	Cl	*o*-Chlorophenyl	Phenyl	196
H	H	*o*-Chlorophenyl	2,6-Xylyl	99
H	H	*α*-Naphthyl	Phenyl	180[a]
H	H	*β*-Naphthyl	Phenyl	159

[a] This compound has been previously uncorrectly described as a quinazoline-4-thione.[1]

Procedure A The benzothiazinethione (0.01 mole) and the amine (0.02 mole) are mixed and heated, without solvent, at 100°C until the red colour of the benzothiazinethione disappears. The resulting product is dissolved in benzene and purified by adsorption chromatography on silica. Elution by a 20:80 benzene/petroleum ether mixture generally gives the imine **3** before the thione **4**, but this is not always the case.

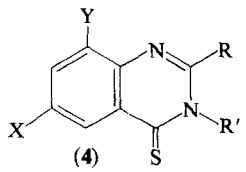
After elution, the products **3** and **4** are purified by crystallization in an ethanol–benzene mixture.

Procedure B This procedure is identical with the preceding one, but for the fact that the reaction temperature is 200°C. Yields of **3** and **4** according to procedures A and B are given in Table III.

Procedure C The benzothiazinethione (0.01 mole) and the aromatic amine (0.02 mole) are dissolved in 50 cm^2 of 1-propanol and 1 cm^3 of triethylamine is added. The solution is refluxed until the red colour of the benzothiazinethione has

TABLE VII

3*H*-Quinazoline-4-thiones



(4)

X	Y	R	R′	Melting point and references (°C)
H	H	Isopropyl	Phenyl	173
H	H	*t*-Butyl	Methyl	79[2]
H	H	*t*-Butyl	Phenyl	176
H	H	Phenyl	Methyl	150[1]
H	H	Phenyl	Ethyl	116[1]
H	H	Phenyl	Isopropyl	173
H	H	Phenyl	Phenyl	149[1]
Cl	Cl	Phenyl	Phenyl	178
H	H	Phenyl	*o*-Tolyl	162
H	H	Phenyl	2,6-Xylyl	179
H	H	Phenyl	*o*-Chlorophenyl	183
H	H	*o*-Tolyl	Methyl	116
H	H	*o*-Tolyl	Ethyl	130
H	H	*o*-Tolyl	Phenyl	162
Cl	H	*o*-Tolyl	Phenyl	168 then 187
H	H	*o*-Tolyl	*o*-Tolyl	198
H	H	*o*-Tolyl	*o*-Chlorophenyl	190
H	H	*o*-Tolyl	*p*-Chlorophenyl	237
H	H	*o*-Chlorophenyl	Methyl	149
H	H	*o*-Chlorophenyl	Ethyl	133
H	H	*o*-Chlorophenyl	Phenyl	198
Cl	Cl	*o*-Chlorophenyl	Phenyl	125 then 170
H	H	*o*-Chlorophenyl	2,6-Xylyl	167
H	H	*o*-Methoxyphenyl	Phenyl	179

disappeared. The solvent is distilled under reduced pressure and water is added to the residue. The aqueous mixture is extracted with benzene. The benzene solution is dried and purifed as in the preceding procedures.

Procedure D This procedure is similar to the preceding one, but 50 cm³ of dimethylformamide are used instead of the mixture of 1-propanol and triethylamine. The yields obtained with procedures C and D are given in Table IV.

Attempted Isomerization of Some Imines **3** *into Thiones* **4**

A 4-imino-2-(*o*-tolyl)-4*H*-3,1-benzothiazine is refluxed during 5 h in 30 cm³ of ethanol containing 1 cm³ of concentrated aqueous hydrochloric acid. Afterwards, the solvent is distilled under reduced pressure and the residue, dissolved in a 50:50 benzene/petroleum ether mixture is fractionated by chromatography on activity 4 alumina. By elution with a 10:90 benzene/petroleum ether mixture, an ethyl 2-(thioacylamino)benzoate **5** is first recovered, sometimes followed by some 3*H*-quinazoline-4-thione **4**.

4-Phenylimino-2-(o-tolyl)-4H-3,1-benzothiazine From the beginning of the elution, pale yellow crystals consisting of ethyl 2-(2-methyl-thiobenzoyl)amino-benzoate are recovered: F = 114°C (ethanol). Yield 66%. Afterwards, yellow crystals of 3-phenyl-2-(*o*-tolyl)-3*H*-quinazoline-4-thione are obtained: F = 162°C. Yield 18%.

4-Isopropylimino-2-(o-tolyl)-4H-3,1-benzothiazine We have obtained only ethyl 2-(2-methyl-thiobenzoyl)amino-benzoate: F = 114°C (ethanol). Yield 70%.

6-Chloro-4-phenylimino-2-(o-tolyl)-4H-3,1-benzothiazine We have obtained only ethyl 5-chloro-2-(2-methyl-thiobenzoyl)amino-benzoate: F = 83°C (ethanol). Yield 75%.

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