Synthesis of 2-Amino-5,6-dihydro-4*H*-1,3-thiazines and Related Compounds by Acid Catalyzed Cyclization of Allylic Isothiuronium Salts

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Several allylic isothiuronium salts **6** have been shown to yield 4-substituted 2-amino-5,6-dihydro-4*H*-1,3-thiazines (**2**; R^3 = H) and the 2-phenylimino compound **10** on exposure to trifluoroacetic acid or trifluoroacetic acid-stannic chloride. The overall process constitutes a convenient transformation of readily available ketones or aldehydes **3** into the target heterocycles. The scope and limitations of this approach are discussed in terms of carbenium ion intermediates (**7**). Whereas this method successfully led to the imidazo[2,1-*b*][1,3]thiazine **13** (93% from **12**), its application to the synthesis of 2-amino-2-thiazolines (*eg.* **14** → **15**) or imidazo-[2,1-*b*]thiazoles (*eg.* **16** → **17**) was unsuccessful. The 2-acetylimino derivatives **9** were found to be useful for purification of the 2-aminothiazines.

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The spirothiazinepyrans represented by structure **1** (1) constitute a novel class of heterocycles, many examples of which exhibit analgesic activity (2). In an effort to develop certain structure-activity relationships in this area, we sought a general synthetic method for preparing related 2-amino-5,6-dihydro-4*H*-1,3-thiazines, in particular, 4-substituted compounds, such as **2**, in which the spiroannulated ether ring in **1** has been replaced by other appendages.

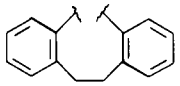
Although 2-amino-5,6-dihydro-4*H*-1,3-thiazine and its derivatives are readily available by cyclization of *N*-(3-halogenopropyl)thioureas or related compounds (3-9), it occurred to us that thiazines having the substitution pattern present in **2** might be most expeditiously prepared starting from allylic isothiuronium salts such as **6**. We reasoned that protonation of the olefinic double bond in **6** with a strong acid should give rise to a carbenium ion intermediate **7** which could react intramolecularly with a nitrogen atom of the isothiourea moiety. Neutralization of the resulting dication **8** should then afford the desired amino thiazine **2** (10). This approach seemed particularly attractive given the ready availability, in wide structural diversity, of the required salts **6**. These substances are easily prepared by vinylation of a ketone or aldehyde **3** followed by allylic rearrangement of the resultant vinyl carbinol **4** and subsequent treatment of the allylic intermediate **5** with a thiourea. In certain cases the rearrangement of **4** can be carried out in the presence of the thiourea thus leading directly to **6** without isolation of **5** (11).

Our initial experiments utilizing this approach and involving the known isothiuronium salt **6a** (11) (Table I) have been reported previously (12). In this case the desired thiazine **2a** (Table II) was obtained in 41% yield by simply dissolving **6a** in neat trifluoroacetic acid and quenching the resulting green solution with alkali after 4.5 hours at room temperature. Given this encouraging first result, we next turned our attention to an examination of the scope and limitations of this thiazine synthesis, the outcome of which is described herein.

A variety of allylic isothiuronium salts (**6a-j**) were prepared starting from the ketones or aldehydes **3** by standard methods as described in Table I and the experimental section. The cyclizations of compounds **6b-d** and

Table I

Isothiuronium Salts (a)

Compound	Starting Material	R^1	R^2	R^3	X	Method (b)	Yield (%)	M.p. °C	Formula	Analyses (%) Calcd. C	H	N	S	Found C	H	N	S
6a (c)	**4a** (c)			H	OAc	A	98 (c)	125-127 (c)	$C_{14}H_{18}N_2OS \cdot C_2H_4O_2$ (d)								
6b (i)	**4b** (j)	C_6H_5	CH_3	H	Cl	C	69.7	175-176.5	$C_{11}H_{14}N_2S \cdot HCl$	54.42	6.23	11.54	13.21	54.21	6.13	11.58	13.34
6c (e)	**4c** (j)	p-$CH_3OC_6H_4$	CH_3	H	OAc	A	78.7	147-148.5 (e)	$C_{12}H_{16}N_2OS \cdot C_2H_4O_2$	56.74	6.80	9.45	10.82	56.96	6.61	9.41	10.94
6d	**4d** (k)	3,4-$(CH_3O)_2C_6H_3$	C_2H_5	H	OAc	A	57.7	131-132.5	$C_{14}H_{20}N_2O_2S \cdot C_2H_4O_2$	56.45	7.10	8.23	9.42	56.17	7.05	8.08	9.37
6e (f)	**5e** (l)	C_6H_5	H	H	Br	B	84.5	196-197 (f)	$C_{10}H_{12}N_2S \cdot HBr$ (d)								
6f (g)	**4f**	p-$CH_3OC_6H_4$	H	H	OAc	A	64.1	149-149.5	$C_{11}H_{14}N_2OS \cdot C_2H_4O_2$	55.30	6.42	9.92	11.35	55.49	6.36	9.76	11.44
6g	**5g** (m)	C_6H_5	C_6H_5	H	Br	B	60.8	189-190	$C_{16}H_{16}N_2S \cdot HBr$	55.02	4.91	8.02	9.18	55.05	4.93	8.03	9.44
6h	**5h** (n)			H	Br	B	69.2	194-195	$C_{18}H_{18}N_2S \cdot HBr$	57.60	5.10	7.46	8.54	57.46	4.92	7.33	8.72
6i (h)	**5i** (o)	$(CH_2)_5$		H	Cl	B	66.2	168.5-169.5	$C_9H_{16}N_2S \cdot HCl$	48.97	7.76	12.69	14.52	48.89	7.92	12.71	14.75
6j	**5b** (p)	C_6H_5	CH_3	C_6H_5	Cl	B	74.2	157.5-159	$C_{17}H_{18}N_2S \cdot HCl$	64.03	6.00	8.79		64.20	5.93	8.82	

(a) All compounds exhibited compatible uv and nmr spectra. (b) See experimental section. (c) See reference 11. (d) Microanalysis not obtained in this work. (e) Reported m.p. 145-147°; H. Schick and G. Hilgetag, *J. Prakt. Chem.*, 312, 837 (1970). (f) Reported m.p. 187°; Z. El-Hewehi and M. S. E. Saleh, *J. Prakt. Chem.*, 7, 286 (1959). (g) The picrate salt is known: A. Burger and S. E. Zimmerman, *Arzneim.-Forsch.*, 16, 1571 (1966). (h) *Chem. Abstr.*, 78, p 136537y (1973) (East German Patent 84180). (i) The acetate has been reported: *Chem. Abstr.*, 72, 21521x (1970) (German Patent 1,900,658, Syntex). (j) I. M. Nazarov and V. F. Ryabchenko, *Izv. Akad. Nauk. SSSR., Ser. Khim*, 1370 (1956). (k) Prepared from 3,4-dimethoxypropiophenone (**3d**; C. W. Perry, M. V. Kalnins and K. H. Deitcher, *J. Org. Chem.*, 37, 4371 (1972)) which was generously supplied by Dr. Clark Perry. (l) X = Br; Commercially available. (m) X = Br; prepared from **4g** (P. Martinet and H. Doupeux, *C. R., Acad. Sci., Paris, Ser. C.*, 259, 2241 (1964)) using the method of reference 20. (n) See reference 20. (o) X = Cl; M. C. Chaco and B. H. Iyer, *J. Org. Chem.*, 25, 186 (1960); 1-Vinyl-1-cyclohexanol (**4i**; W. Reppe and co-workers, *Ann. Chem.*, 596, 38 (1955)) was obtained by partial hydrogenation of commercially available 1-ethynyl-1-cyclohexanol. (p) X = Cl; E. G. E. Hawkins and R. D. Thompson, *J. Chem. Soc.*, 370 (1961).

Table II

4-Substituted-2-amino-5,6-dihydro-4*H*-1,3-Thiazines and Salts (a)

Compound (b)	Starting Material	Method (c)	Yield % (d)	Crystallized from (e)	M.p. °C	Formula	Analyses (%) Calcd. C	H	N	S	Found C	H	N	S
2a	**6a**	D	41	(f)	193-194	$C_{14}H_{18}N_2OS$ (h)	64.10	6.92	10.68	12.20	64.31	6.81	10.54	12.36
2b	**6b**	D	(72)	A	117.5-119	$C_{11}H_{14}N_2S$ (h)	64.04	6.84	13.58	15.54	64.09	6.92	13.60	15.58
				(M-E)	(230-231)	$(C_{11}H_{14}N_2S \cdot HCl)$ (j)	(54.42)	(6.23)	(11.54)	(13.21)	(54.70)	(6.27)	(11.51)	(13.26)
2c	**9c**	E	(72.5)	A	152-153.5	$C_{12}H_{16}N_2OS$ (h)	60.99	6.82	11.85	13.57	60.78	6.86	11.91	13.62
				(M-E)	(255-256.5)	$(C_{12}H_{16}N_2OS \cdot HCl)$ (j)	(52.84)	(6.28)	(10.27)	(11.75)	(53.08)	(6.18)	(10.22)	(11.87)
2d	**9d**	E	87.3	B-H	90-91.5	$C_{14}H_{20}N_2O_2S$ (h)	59.97	7.19	9.99	11.45	59.77	7.19	9.87	11.54
				(M-E)	(190.5-192)	$(C_{14}H_{20}N_2O_2S \cdot HCl)$ (j)	(53.07)	(6.68)	(8.84)	(10.12)	(53.10)	(6.76)	(8.77)	(10.20)
2e (i)	**9e**	E	80.5	(M-E)	(159-162) (i)	$(C_{10}H_{12}N_2S \cdot HCl)$ (g,j)								
2f (k)	**9f**	E	(42.8)	(M-E)	(211-213) (k)	$(C_{11}H_{14}N_2OS \cdot HCl)$ (g,j)								
2g	**6g**	D	0 (l)											
2h	**6h**	D	0 (m)											
2i	**9i**	E	92.5	A	81-82.5	$C_9H_{16}N_2S$ (h)	58.65	8.75	15.20	17.39	58.45	8.98	15.09	17.53
				(EA)	(153.5-155)	$(C_9H_{16}N_2S \cdot C_4H_4O_4)$ (j,n)	(51.98)	(6.71)	(9.32)	(10.67)	(52.04)	(6.79)	(9.25)	(10.66)

(a) Data in parentheses refer to salts. (b) R^1 and R^2 as in Table I; R^3 = H. (c) See experimental section. (d) Data given refer to essentially pure materials obtained by recrystallization. (e) A = acetonitrile; B = benzene; E = ethyl ether; EA = ethanol; H = hexane; M = methanol. (f) Purified by trituration with acetonitrile. (g) Microanalysis not obtained in this work. (h) This compound exhibited compatible ir, nmr, uv and mass spectra. (i) See reference 4, reported m.p. 159-162°. (j) Compound exhibited compatible uv and nmr spectra. (k) *Chem. Abstr.*, 61, p12013f (1964) (German Patent No. 1,176,148, Bayer) reported m.p. 210-213°. (l) Free base of starting isothiuronium salt isolated in 93% yield. (m) Free base of starting isothiuronium salt isolated in 89% yield. (n) Maleic acid salt.

Table III
2-Iminothiazines and Salts (a)

Compound (b)	Starting Material	Method (c)	Yield (d) %	Crystallized from (e)	M.p. °C	Uv max, ε (f,g)	Formula	Analyses (%) Calcd. C	H	N	S	Found C	H	N	S
9b (h)	**2b**		83.3		O (i)	264, 13100	$C_{13}H_{16}N_2OS$	62.87	6.50	11.28	12.91	62.62	6.63	11.06	12.85
				(A)	(208-212)		$(C_{13}H_{16}N_2OS \cdot HCl)$	(54.82)	(6.02)	(9.83)	(11.26)	(54.92)	(6.17)	(9.82)	(11.18)
9c	**6c**	F	63.5		O (i)	264, 13600	$C_{14}H_{18}N_2O_2S$	60.40	6.52	10.06	11.52	60.23	6.27	9.85	11.18
				(M-E)	(191-192.5)		$(C_{14}H_{18}N_2O_2S \cdot HCl)$	(53.41)	(6.08)	(8.90)	(10.18)	(53.26)	(6.06)	(8.85)	(10.25)
9d	**6d**	F	48.6 (k)		O (i)	264, 16250	$C_{16}H_{22}N_2O_3S$	59.60	6.88	8.69		59.25	6.98	8.47	
9e (l)	**6e**	G	44.4		O (i)	262, 12300	$C_{12}H_{14}N_2OS$	61.51	6.02	11.95	13.68	61.28	6.13	11.52	13.74
9f	**6f**	G	13.3		O (i)		$C_{13}H_{16}N_2O_2S$ (j)								
9i	**6i**	G	29.5	B-H	89-90.5	261, 19100	$C_{11}H_{18}N_2OS$	58.37	8.01	12.37	14.16	58.36	8.02	12.35	14.24
10	**6j**	D	86.2	EA	135-136	260, 11640	$C_{17}H_{18}N_2S$	72.30	6.42	9.92	11.35	72.32	6.51	9.90	11.13

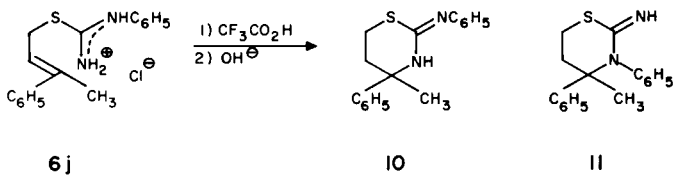
(a) Data in parentheses refer to salts. (b) R^1 and R^2 as in Table I. (c) See experimental section. (d) Data given refer to essentially pure materials obtained by column chromatography. (e) Solvents as in Table II. (f) 95% Ethanol. (g) Compound exhibited compatible ir, nmr and mass spectra. (h) Compound prepared by acetylation of **2b** with acetic anhydride/pyridine and purified by column chromatography. (i) Pale-yellow, viscous oil. (j) Microanalysis not obtained. (k) A 62.3% yield was obtained in a larger run. (l) *Chem. Abstr.*, **61**, p12013f (1964) (German Patent No. 1,176,148, Bayer).

6j were carried out using the simple procedure mentioned above for conversion of **6a** to **2a** (method D). Generally highly colored trifluoroacetic acid solutions were produced, varying from dark green to burgundy, which yielded the desired thiazines **2b-d** and **10** in good yield upon quenching with alkali (Tables II, III). The transformations of **6b,c** to **2b,c** could easily be followed by ^{1}H nmr examination of the cyclization solutions. It was found that the doublet-triplet (-SCH_2CH=) and vinyl CH_3 resonance patterns characteristic of the isothiuronium salts gave way to new, higher field resonances, most significantly a singlet, arising from the quaternary CH_3 in cation **8.** These cyclizations were quite rapid; the formation of **8b** and **8c** being essentially complete after 60 and 20 minutes, respectively. Due to the simplicity of and success observed with the trifluoroacetic acid procedures, alternative cyclization media were not examined. It is interesting to note, in this regard, that although the salt **6b** was prepared under strongly acidic conditions (hydrochloric acid/acetic acid), its cyclization under these conditions was not observed. Neat trifluoroacetic acid (pK_a 0.2) appears to be an excellent medium for the protonation of certain olefins (13).

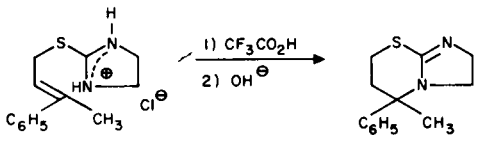
It was frequently most convenient to acetylate the crude cyclization products for purification purposes (method F). This procedure transformed the amino thiazines **2** (R^3 = H) into the 2-acetylimino derivatives **9** (Table III) and converted the main impurity, namely the starting isothiourea, into neutral substances which could be separated by extraction of **9** into aqueous acid. The derivatives **9** were also easily purified by column chromatography on silica gel. Regeneration of the amino compounds **2** (R^3 = H) was effected by hydrolysis of **9** in dilute hydrochloric acid at reflux (method E).

Conversion of the salts **6e,f,i** to the thiazines **2e,f,i** did not proceed with facility. In these examples, a Lewis acid, stannic chloride, was added to the cyclization mixtures in an effort to promote carbenium ion formation. In addition, the reactions were carried out at reflux temperature. By these modifications, the desired products were obtained in poor to moderate yields after purification *via* the corresponding acetyl derivatives (method G).

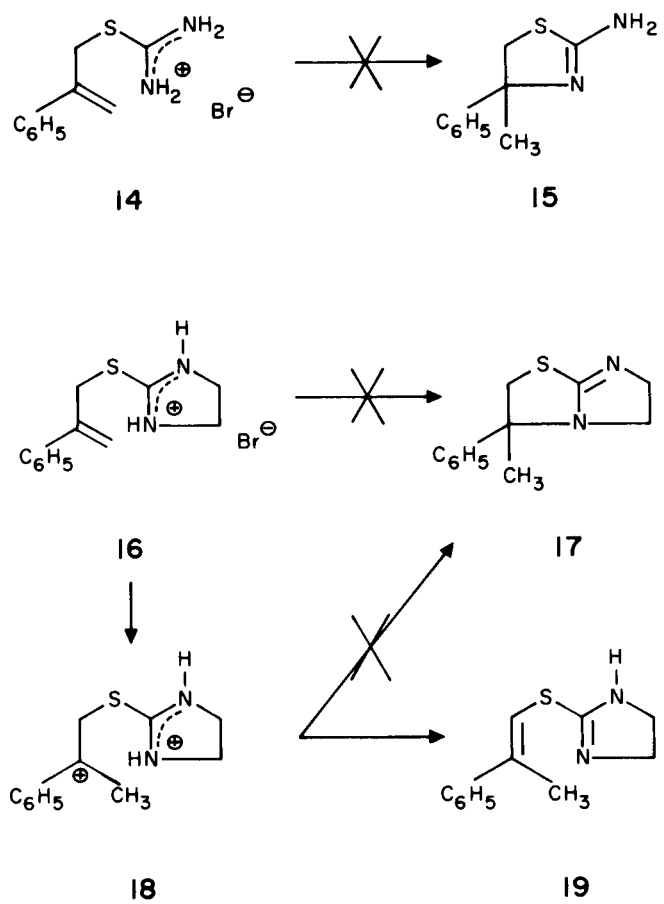
The diaryl isothiuronium salts **6g,h** gave none of the corresponding amino thiazines upon exposure to trifluoroacetic acid or trifluoroacetic acid-stannic chloride. When



6j **10** **11**



12 **13**



14 15

16 17

18 19

the reactions were conducted at 0° to room temperature, only the free bases derived from the starting salts were isolated. At reflux temperature, the isothiourea moiety was destroyed, and mixtures rich in the corresponding allylic disulfides were obtained.

On a more positive note, the cyclization process could be extended to the synthesis of certain fused thiazines. Thus the salt **12** afforded the imidazo[2,1-*b*][1,3]thiazine **13** in 93% yield when treated with trifluoroacetic acid (14).

Confirmation of the 2-amino- or 2-imino-1,3-thiazine structures for the cyclization products obtained by this process was achieved by ir, uv, ^{1}H nmr and mass spectroscopic as well as microanalytical means. In particular, the products generally exhibited an M-28 peak in the mass spectra corresponding to loss of ethylene *via* a retro Diels-Alder process, a mode of fragmentation characteristic of 2-amino-5,6-dihydro-4*H*-1,3-thiazines (15). The uv maximum at 260 nm (ϵ, 11,640) exhibited by compound **10** confirmed the exocyclic double bond arrangement (16) and eliminated the regioisomeric structural possibility **11**.

From the results obtained, it is evident that the success of this cyclization process is dependent upon the balance between stability and reactivity of the carbenium ion intermediates **7**. At one extreme are the very highly stabilized ions such as **7g,h** in which the positive charge is delocalized by two aryl groups. These ions would be expected to form rapidly; however, the equilibrium between **7** and **8** heavily favors the former and cyclization is not observed. At the other extreme, in the examples studied, lie series **e**, **f**, and **i** in which the ions **7** are relatively unstable being either aryl alkyl secondary or trialkyl tertiary. In these cases although cyclization of **7** to **8** should be facile, the initial carbenium ion formation is slow; thus only poor to moderate yields of thiazines are observed. Highest yields of thiazines are obtained when **7** is an aryl dialkyl tertiary carbenium ion of intermediate relative stability as in series **a-d** and **j**. Here the formation of **7** is rapid, but the equilibrium between **7** and **8** now favors the latter. Thus the optimum combination of reactivity and stability factors is achieved. The presence of substituents in the isothiourea moiety (*eg.* **6j** → **10**; **12** → **13**) appears to offer no hindrance to cyclization and, in view of the relatively high yields observed in these examples, may, in fact, facilitate thiazine formation.

Finally, an effort was made to extend this approach to the synthesis of 2-amino-2-thiazolines and the related imidazo[2,1-*b*]thiazoles. To this end, the isothiuronium salts **14** (17) and **16** were prepared, in straightforward manner by treatment of α-bromomethylstyrene (18) with thiourea and 2-imidazolidinethione, respectively. Unfortunately, exposure of these salts to trifluoroacetic acid failed to yield detectable amounts of the desired products **15** and **17**. In the case of **16** an unstable material was isolated which appeared to be the isomerized isothiourea **19** on the basis of its spectral properties. Clearly, the required carbenium ion **18** had formed (13) but failed to cyclize. Recently, and after our studies were completed, Baldwin published a series of rules for ring closure (19). In this communication, it was noted that whereas cationic ring closures of the 6-*Endo-Trig* type (*eg.* **7** → **8**) are favored, those of the 5-*Endo-Trig* variety (*eg.* **18** → **17**) are not. Thus our success in forming thiazines but not thiazolines by the above processes is consistent with Baldwin's formulations.

In summary, the isothiuronium salt cyclizations described herein, as hoped for initially, have allowed the synthesis of various 4-substituted 2-amino-1,3-thiazines and related compounds, frequently in quite satisfactory yields. This approach, therefore, complements the existing synthetic routes to this class of heterocycles (3-9, 14).

EXPERIMENTAL

General.

All reactions were carried out under an atmosphere of dry nitrogen. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. The "usual work-up" consists of extraction with 3 portions of the specified solvent. The extracts were combined, washed with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated at

40-50° at water aspirator pressure. The residue was dried to constant weight under high vacuum. Thin layer chromatography (tlc) was performed using Merck (Darmstadt) Silica Gel G. For the 2-imino-1,3-thiazines (**9,10**), plates were developed with 1:1 benzene-ethyl acetate (system A). Analysis of the more basic products was carried out on plates developed with 9:1 benzene-triethylamine (system B). Spots were detected with uv light, iodine vapor or *p*-toluenesulfonic acid spray followed by heating. Column chromatography was performed on Merck Silica Gel G 0.2-0.5 mm. Columns were packed in benzene. Varian A-60, HA-100 or Jeolco C-60H spectrometers were used to obtain the ^{1}H nmr spectra. Chemical shifts are reported relative to TMS as an internal standard. Ultraviolet spectra were recorded in 95% ethanol solution on a Cary 14M spectrophotometer. Infrared spectra were obtained on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. Low-resolution mass spectra were determined on CEC 21-110 or JMS-01SG spectrometers. Tetrahydrofuran (THF) and pyridine were dried by slurrying over Woelm grade I neutral alumina just prior to use. MC and B trifluoroacetic acid, b.p. 71-73°, was employed for the cyclization reactions.

Vinyl Alcohols **4**.

A solution of 0.083 mole of the ketone, or aldehyde **3** in 50 ml. of anhydrous ether was added dropwise over 20 minutes to a stirred solution of 55 ml. (0.167 mole) of 3*M* vinylmagnesium chloride in THF in 50 ml. of dry ether keeping the internal temperature at -20 - -25°. The resulting gelatinous mixture was stirred at -20 - -25° for 10 minutes, then allowed to warm to room temperature, and stirring was continued for 2 hours. The reaction mixture was poured into a mixture of ice and saturated ammonium chloride solution and worked up with ether in the usual manner. The vinyl alcohols **4b-d,f,g,** and **4h** (20) were isolated in essentially quantitative yield as oils which were used without further purification. These materials exhibited compatible ir and nmr spectra. The starting carbonyl compounds **3b,c,f,g,h** were commercially available.

Allylic Halides **5**.

Compounds **5g** (X = Br) and **5h** (X = Br) were prepared starting from **4g** and **4h**, respectively, using the method of Wendler, *et al*, (20). The crude allylic bromides were used without further purification. The chlorides **5b** (X = Cl) and **5i** (X = Cl) were obtained as follows from **4b** and **4i**, respectively: a solution of 0.125 mole of the vinyl alcohol in 150 ml. of hexane was stirred with ice-bath cooling while 17.5 ml. of thionyl chloride was added in one portion. Gas was evolved and the resulting yellow solution was stirred at 0-5° for 2 hours then concentrated at reduced pressure. The residual oily chlorides were used without further purification.

Isothiuronium Salts **6**.

Method A.

The procedure of Kuo, *et al*, (11) was employed for conversion of the vinyl alcohols **4a,c,d,f** into the corresponding isothiuronium acetates.

Method B.

A mixture of the crude allylic halide **5** and an equimolar quantity of the thiourea in acetonitrile (0.25-1*M* solution) was stirred at room temperature until reaction was complete (0.5-20 hours). The precipitated salt was filtered with suction, washed with acetonitrile and ether, and dried under high vacuum.

Method C.

A mixture of the crude vinyl carbinol **4** (0.25 mole) and an equimolar amount of thiourea in 220 ml. of 1*M* hydrochloric acid in glacial acetic acid was stirred at room temperature for 4 hours. To the resulting slurry was added 500 ml. of anhydrous ether; then the solid was filtered, washed with ether, and dried under high vacuum.

Since the intermediates **4** and **5** were used without purification (except for series **a** and **e**), the yields given in Table I are overall yields based on **3** (**4** in series **i**).

2-Amino-5,6-dihydro-4*H*-1,3-thiazines **2**.

Method D. Allylic Isothiuronium Salt Cyclization.

A 1*M* solution of the isothiuronium salt **6** in trifluoroacetic acid (prepared by adding the salt to the trifluoroacetic acid with ice-bath cooling - these solutions were generally dark green or burgundy in color) was stirred at 0-5° for 0.5 hour and at room temperature for 4.5 hours. At the end of this time, the solution was poured into a mixture of ice and excess 10% sodium hydroxide solution. After stirring for several minutes, the mixture was worked up with dichloromethane in the usual manner. Compound **2a** was purified by digestion with hot acetonitrile whereas the crude **2b** was converted to the hydrochloride salt which was then purified by recrystallization. Compound **10** was purified by chromatography (silica gel-20 parts-eluted with 9:1 benzene-ether).

Method E. Hydrolysis of the Acyl Derivatives **9**.

A mixture of 0.01 mole of the acyl derivative **9** and 25 ml. of 2*N* aqueous hydrochloric acid was stirred and refluxed for 2 hours. After cooling, the mixture was made alkaline with 10% sodium hydroxide and worked-up with dichloromethane in the usual manner. The resultant aminothiazine was purified by recrystallization or by conversion to a salt which was then recrystallized. In the case of **2c**, the hydrochloride salt crystallized from the acidic hydrolysis mixture and was directly isolated by filtration.

2-Acetylimino-3,4,5,6-tetrahydro-2*H*-1,3-thiazines **9**.

Method F. Allylic Isothiuronium Salt Cyclization Followed by Acetylation.

The cyclization of **6** in trifluoroacetic acid was carried out as described above in procedure D. The crude basic product consisting of the thiazine **2** (major) and the free base of **6** (minor), as indicated by tlc analysis (system B), was directly acetylated using acetic anhydride-pyridine as described previously for related compounds (1). The acetylated product, freed of neutral impurities by extraction from ether into 1-3*N* hydrochloric acid and regeneration by basicification with sodium carbonate, was chromatographed on 20-30 parts of silica gel. Elution with 1:1 benzene-ether to 1:1 ether-ethyl acetate gave the pure acetylimino compounds **9**, usually isolated as pale-yellow oils.

Method G. Cyclization of **6** with Trifluoroacetic Acid-Stannic Chloride followed by Acetylation.

A mixture of 0.09 mole of **6** and 0.9 ml. of stannic chloride in 90 ml. of trifluoroacetic acid was prepared at 0-5°, stirred at that temperature for 5 minutes, and then refluxed for 16 hours. After cooling, the reaction mixture was worked-up as described above in procedure D. The crude amine product was then acetylated and the crude **9** was freed of neutral impurities and tarry matter by extraction into dilute hydrochloric acid, then purified by column chromatography as in procedure F.

Acetylation of 2-[3-(4-Methoxyphenyl)but-2-en-1-yl]isothiourea (**6c** free base).

A suspension of 1 g. (3.38 mmoles) of salt **6c** in 10 ml. of water was stirred at 0-5° while 2 ml. of 10% aqueous sodium hydroxide was added. The mixture was stirred for 15 minutes at

0-5° then filtered. The solid was washed with water and a small amount of acetone and dried giving 0.6 g. of the free base of **6c** as a colorless solid. This material was treated with 10 ml. of pyridine and 2 ml. of acetic anhydride and the resulting solution was stirred at room temperature for 4 hours, then concentrated under reduced pressure. The residue was dissolved in ether and the ether solution was washed 3 times with 1*N* aqueous hydrochloric acid, then processed in the usual manner giving 0.875 g. of a yellow oil; tlc, 2 major spots, Rf 0.48 and 0.56 (system A); ir (film): 3100-3500 (br NH), 1730, 1630, 1615, 1550, 1520 cm^{-1} (C=O and C=N). This neutral material was not further characterized but apparently consists of a mixture of di- and tri-*N*-acetyl derivatives of **6c**. Basification of the aqueous acidic extracts and work-up with dichloromethane gave no residue. This experiment demonstrates that any starting isothiourea present in the crude cyclization products is converted to non-basic materials upon acetylation.

Attempted Cyclization of 2-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohept-5-ylidene)ethyl Isothiuronium Bromide (**6h**).

A 1.87 g. (5 mmoles) sample of **6h** was added to 5 ml. of cold trifluoroacetic acid. The resulting mixture was stirred and heated at reflux for 16 hours. On heating, the brown solution changed in color to dark green. The solution was quenched in cold 10% aqueous sodium hydroxide and worked-up with dichloromethane in the usual manner giving 1.05 g. (83.5%) of a dark-brown foam composed mainly of di-2-(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohept-5-ylidene)ethyl disulfide; tlc, Rf 0.55 (system B); uv: max 209 nm (ε, 71,800), 245 (19,500), 282 (11,000), sh. 302 (7100), 339 (2,880), 355 (220); mass spectrum: m/e 502 (M^+, $C_{34}H_{30}S_2$), 219 ($C_{17}H_{15}$); ir: no N-H or C=N.

Attempted cyclization of **6h** at temperatures below reflux gave a light brown solid composed mainly of the corresponding isothiourea; tlc, Rf 0.08 (system B); uv max: 205 nm (44,500), 245 (16,850).

2-(3-Phenylbut-2-en-1-ylthio)-2-imidazoline Hydrochloride (**12**).

This material was prepared from chloride **5b** (X = Cl) and 2-imidazolidinethione, in 67% yield using method B above. The salt was obtained as a tan solid, m.p. 150-152°; uv: max 245 nm (ε, 18,250); nmr (deuteriochloroform): δ 10.62 (br s, 2, NH^+), 7.26 (s, 5, C_6H_5), 5.83 (t, 1, J = 8 Hz, -CH=), 4.27 (d, 2, J = 8 Hz, $-SCH_2CH=$), 3.85 (s, 4, $-(CH_2)_2-$), 2.08 ppm (br s, 3, $CH_3C=$).

Anal. Calcd. for $C_{13}H_{16}N_2S \cdot HCl$: C, 58.09; H, 6.37; N, 10.42; S, 11.93. Found: C, 57.83; H, 6.40; N, 10.39; S, 11.61.

rac. 5-Methyl-5-phenyl-2,3,6,7-tetrahydro-5*H*-imidazo[2,1-*b*][1,3]-thiazine (**13**).

A 19.4 g. (0.0723 mole) sample of salt **12** was cyclized in 73 ml. of trifluoroacetic acid using method D above. The crude product was taken up in 3*N* aqueous hydrochloric acid and the acidic solution was washed twice with benzene and once with ether to remove neutral impurities. The aqueous solution was then made alkaline with 10% sodium hydroxide and the precipitated amine was isolated by extraction with dichloromethane in the usual manner. There was obtained 15.6 g. (93%) of **13** as a brown solid which was essentially homogeneous on tlc analysis (system B). This material was treated with 7.8 g. of maleic acid in 100 ml. of hot ethanol. The solid obtained on cooling was isolated by filtration and recrystallized from ethanol, using decolorizing charcoal, giving 13.7 g. of **13** maleate as a colorless solid, m.p. 148-149.5°.

Anal. Calcd. for $C_{13}H_{16}N_2S \cdot C_4H_4O_4$: C, 58.60; H, 5.79; N, 8.04; S, 9.20. Found: C, 58.57; H, 5.73; N, 8.04; S, 8.89.

A sample of **13** was regenerated from this salt with 10% sodium hydroxide giving a colorless solid, m.p. 101-103°; ir: 1560 cm^{-1} (C=N), no NH; uv: max 205 nm (ε, 15,650), sh. 235 (6,600); nmr (deuteriochloroform): δ 7.30 (s, 5, C_6H_5), 3.62 (m, 4, $-(CH_2)_2-$), 2.67 (m, 2, $-CH_2-$), 2.23 (m, 2, $-CH_2-$), 1.72 ppm (s, 3, CH_3); mass spectrum: m/e 232 (M^+).

Anal. Calcd. for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06. Found: C, 66.57; H, 6.99; N, 11.90.

2-(2-Phenylprop-2-en-1-yl)isothiuronium Bromide (**14**).

A mixture of α-bromomethylstyrene (18) (67%) and 1-bromo-2-phenylpropene (33%) (18 g. total; 0.061 mole α-bromomethylstyrene; percentage composition determined by nmr analysis; obtained by NBS bromination of α-methylstyrene (18)) and 4.65 g. (0.061 mole) of thiourea in 100 ml. of acetonitrile was stirred at room temperature for 18 hours. The precipitated salt was filtered, washed with acetonitrile and ether and dried under high vacuum giving 14.3 g. (85.9%) of **14** as a colorless solid, m.p. 118-119.5°; uv: max 231 nm (ε, 12,400); nmr (DMSO-d_6): δ 9.17 (br s, 4, $-NH^+$), 7.43 (m, 5, C_6H_5), 5.63, 5.58 (2s, 2, $CH_2=$), 4.55 ppm (s, 2, $-SCH_2-$).

Anal. Calcd. for $C_{10}H_{12}N_2S \cdot HBr$: C, 43.96; H, 4.80; N, 10.25; S, 11.74. Found: C, 43.89; H, 4.75; N, 10.32; S, 11.85.

2-(2-Phenylprop-2-en-1-ylthio)-2-imidazoline Hydrobromide (**16**).

This material was prepared in 92.3% yield from 2-imidazolidinethione and α-bromomethylstyrene as described in the preceding experiment. There was obtained a colorless solid, m.p. 168.5-170°; uv: max 232 nm (ε, 15,120); nmr (DMSO-d_6): δ 10.28 (m, 2, NH^+), 7.38 (m, 5, C_6H_5), 5.65 (s, 2, $CH_2=$), 4.65 (s, 2, $-SCH_2-$), 3.88 ppm ($-(CH_2)_2-$).

Anal. Calcd. for $C_{12}H_{14}N_2S \cdot HBr$: C, 48.17; H, 5.05; N, 9.36; S, 10.72. Found: C, 48.14; H, 5.03; N, 9.46; S, 10.77.

E-2-(2-Phenylprop-1-en-1-ylthio)-2-imidazoline (**19**).

Attempted cyclization of **16** (3.0 g., 0.01 mole) was carried out using method D above with the modification that the trifluoroacetic acid solution was refluxed for 4.5 hours. The crude product (2.0 g.) was a gummy solid which was triturated with ethyl acetate. The colorless solid was isolated by filtration and dried affording 0.45 g. of **19**, m.p. 75-77.5°; uv: max 220 nm (ε, 15,600), 275 (17,200); nmr (deuteriochloroform): δ 7.30 (m, 5, C_6H_5), 6.92 (br s, 1, -CH=), 5.15 (s, 1, NH), 3.63 (s, 4, $-(CH_2)_2-$), 2.15 ppm (br s, 3, CH_3); mass spectrum: m/e 218 (M^+).

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