RING TRANSFORMATIONS OF OXAZOLES AND THEIR BENZO ANALOGUES. NEW SYNTHETIC ROUTE FOR 2H-IMIDAZO[2,1-b][1,3,4]THIADIAZINE AND N-HETEROARYL-o-AMINOPHENOL

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Abstract - Ring transformations of certain functionalized oxazoles and their benzo analogues were studied. The α-(oxazol-2-ylthio) ketones 3a, b, c, and e gave 2H-imidazo[2,1-b][1,3,4]thiadiazines (4a, b, c, and e) on treatment with hydrazine hydrate in acetic acid. Similar treatment of ketones 3d and f-h resulted in the formation of the complex mixtures. The α-(benzoxazol-2-ylthio) ketones 5a and b reacted with ammonium acetate in acetic acid to give 2-(2-hydroxyphenylamino)thiazoles 6a and b in quantitative yields. With hydrazine, 5a afforded thiazoline derivative 7 while 5b provided 1,3,4-thiadiazine derivative 8 under the similar conditions. Aminophenols 6a and b were further converted into 1,4-benzoxazines 10a and b by treating with chloroacetone followed by phosphorus pentoxide in benzene. Mechanisms for these transformations are proposed.

Bridgehead nitrogen heterocycles are commonly synthesized by the intermolecular conventional condensation reactions.[1] For this criterion, we have investigated an alternative route which involves the intramolecular ring transformation. We have recently established a new entry to fused s-triazoles such as 7H-s-triazolo[3,4-b][1,3,4]thiadiazine (1) and thiazolo-[2,3-c]-s-triazole (2) by intramolecular displacement of oxygen in the oxadiazole ring with the hydrazone or imine nitrogen.[2] To make the intramolecular ring transformation an accepted basic strategy for the construction of bridgehead nitrogen heterocycles, we have further studied the possibility of intramolecular ring transformations in similarly functionalized oxazoles, α-(oxazol-2-ylthio) ketones (3). The reaction of oxazole with ammonia affording imidazole was first reported in 1888.[3] 2H-Imidazo[2,1-b][1,3,4]thiadiazine ring system, which is expected our final product, was first synthesized by Waschk and his co-workers[4]

from 1-amino-2-mercapto-4-phenylimidazole and phenacyl bromide. Recently Pfeiffer and his co-worker[5] prepared such a ring system from 2-amino-5-phenyl-1,3,4-thiadiazine and α-halo-ketones. These methods rest upon the condensation reactions. We also report herein the introduction of thiazole on the nitrogen of o-aminophenol by the analogous ring transformation of benzo analogues (5).

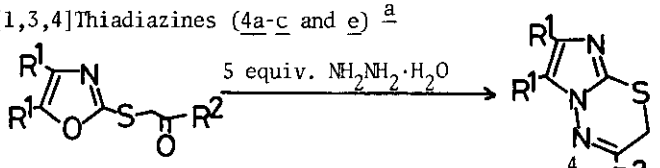
RESULTS AND DISCUSSION

Reaction of α-(Oxazol-2-ylthio) Ketones 3a-h with Hydrazine.

Starting mercapto ketones 3a-h were prepared according to the reported procedure.[6] The structures of unknown ketones 3c-f were determined on the spectral correlations with known 3a, b, g, and h as shown in Table IV and V. Attempts to effect ring closure of 3a were carried out successfully by treating 3a with 5 equimolar amounts of hydrazine hydrate in refluxing acetic acid and gave imidazothiadiazine 4a in 63 % yield. Under the neutral conditions, none of the desired products were isolated. The solvent effect is similar to that observed previously in the reaction of α-(1,3,4-oxadiazol-2-ylthio) ketones.[2] The structure 4a was definitely confirmed by comparison with an authentic sample[5] prepared from 2-amino-5-phenyl-1,3,4-thiadiazine[7] and desyl bromide.[8] Under the same conditions as for 3a, related 3b-h were treated with hydrazine hydrate. As summarized in Table I, phenyl ketones (3a, c, e, and g) gave more favorable yields than methyl ketones (3b, d, f, and h).[9] This discrepancy was not observed in the previous oxadiazole case. Furthermore, the existence of aryl substituent of the oxazole (i.e. 1a-f) gave more satisfactory yields than methyl substituent (i.e. 1g and h). This observation agrees with the reported results that aryl groups at 4 position promote the ring conversion into imidazole in the intermolecular reaction of oxazoles with ammonia.[10] With the spectral data for 4a in hand, the structures 4b, c, and e were readily determined as given in Table II; The ring closure was verified by disappearance of carbonyl absorption in the IR spectra and by the upfield shift of methylene protons in the ^{1}H NMR. The mechanism for the transformation of 3 to 4 is the same as proposed for α-(1,3,4-oxadiazol-2-ylthio) ketones to 1:[2] Initially, condensation of the ketone function with hydrazine gives hydrazone 11a. A subsequent attack of the terminal nitrogen of hydrazone on the carbon-nitrogen double bond of the oxazole ring affords the spiro derivative 12a, which collapses to 13a. Tautomerization of 13a to the keto-form 14, followed by condensation gives 4 (Scheme II).

With an expectation that 3 would also provide imidazo[2,1-b]thiazole ring system, we attempted to effect the ring closure of 3 with ammonia. However, in contrast to the successful con-

Table I. Yields and Melting Points of 2H-Imidazo[2,1-b]-[1,3,4]Thiadiazines (4a-c and e) [a]



3 4

a, R^1=Ph; R^2=Ph
b, R^1=Ph; R^2=CH_3
c, R^1=4-ClC_6H_4; R^2=Ph
d, R^1=4-ClC_6H_4; R^2=CH_3
e, R^1=4-$CH_3OC_6H_4$; R^2=Ph
f, R^1=4-$CH_3OC_6H_4$; R^2=CH_3
g, R^1=CH_3; R^2=Ph
h, R^1=CH_3; R^2=CH_3

compd	reaction conditions	yield(%)	mp(°C) (Lit.)
4a	AcOH reflux 20 min	63	205[b] (192[5])
4b	AcOH reflux 30 min	20	210-212[c]
4c	AcOH reflux 50 min	41	207-210[c]
4e	AcOH reflux 1 h	35	203-205[c]

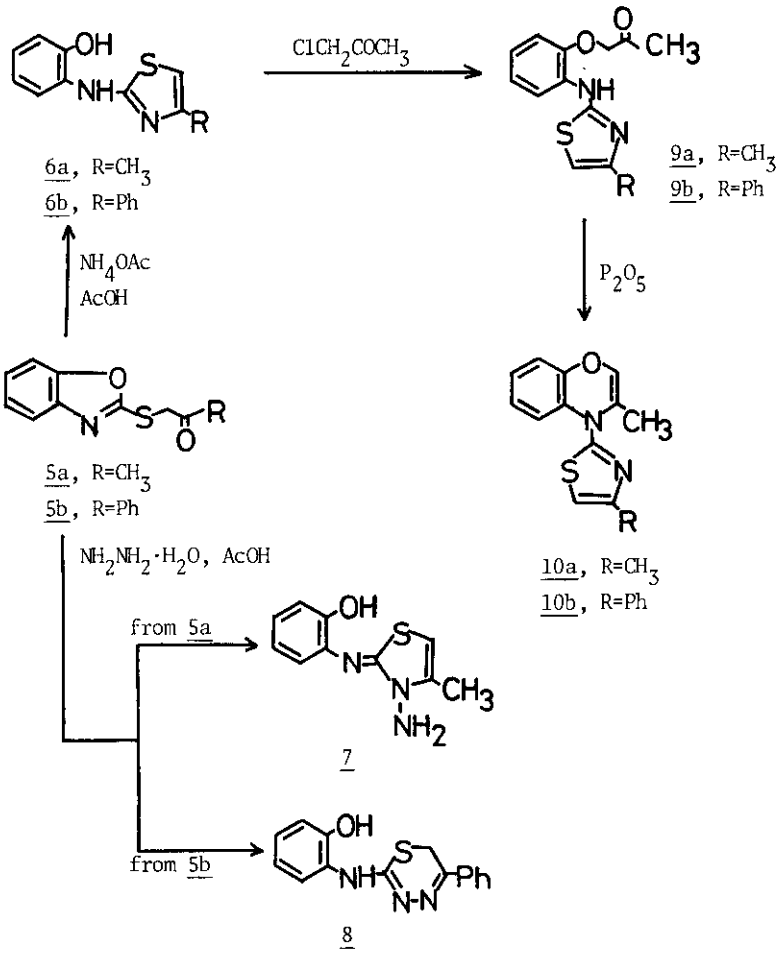
[a] All microanalyses were within 0.4% of the theoretical values. [b] Purified on a silica gel column using $CHCl_3$ as the eluent [c] Recrystallized from EtOH

Table II. IR and ^1H NMR Data of Compounds 4a-c and e

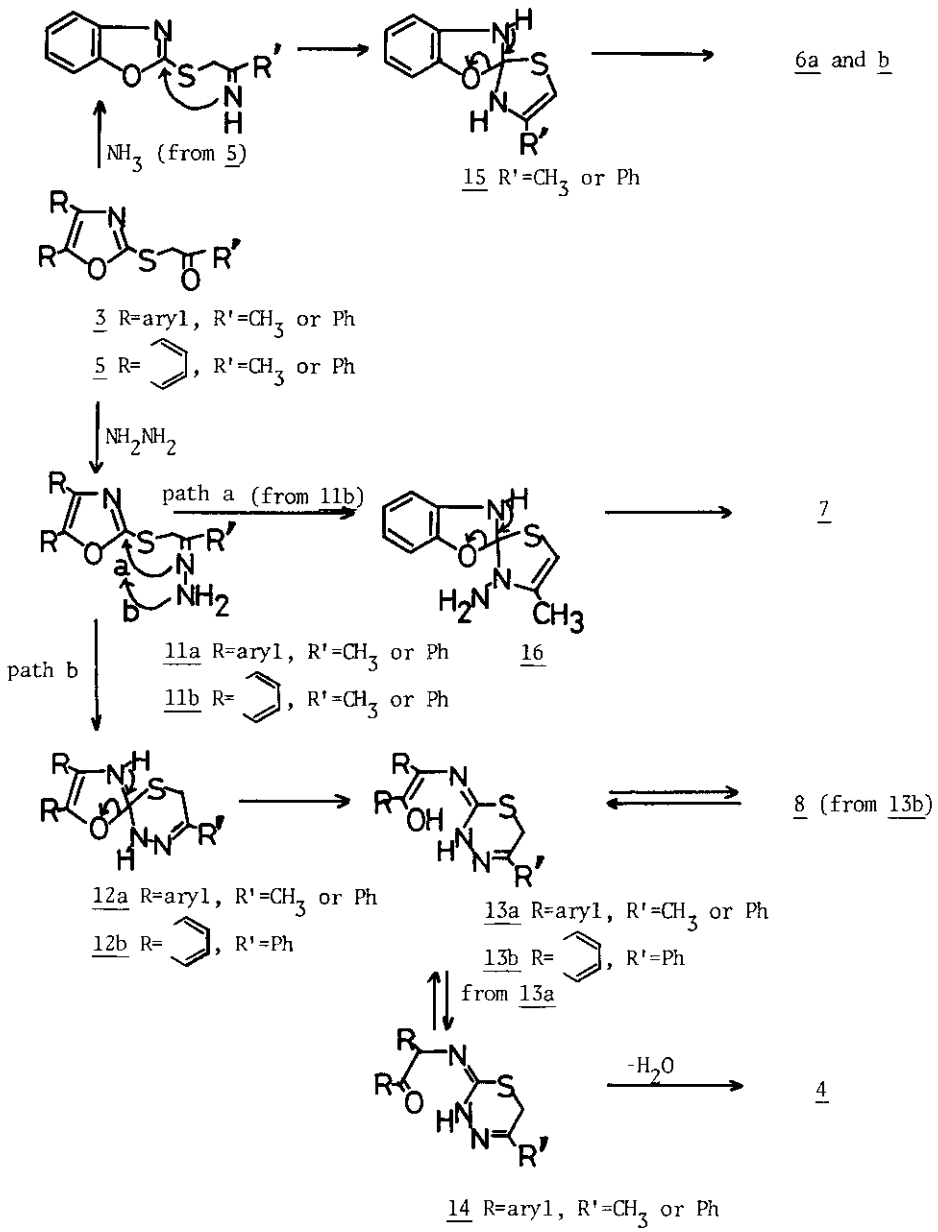
compd	IR (cm^{-1})[a]	^1H NMR (δ)[b]
4a	3080, 1606, 1510	3.94(s, 2H, CH_2)
	1490, 1463, 1450	7.11-7.97(m, 15H, Ar)
4b	3070, 1607, 1514	2.23(s, 3H, CH_3)
	1490, 1460, 1443	3.44(s, 2H, CH_2)
		7.10-7.79(m, 10H, Ar)
4c	3080, 2920, 1510	4.00(s, 2H, CH_2)
	1492, 1474, 1410	7.09-7.91(m, 13H, Ar)
4e	3090, 2960, 1620	3.75(s, 3H, OCH_3)
	1535, 1510, 1470	3.81(s, 3H, OCH_3)
		3.94(s, 2H, CH_2)
		6.70-7.90(m, 13H, Ar)

[a] KBr [b] $CDCl_3$

Scheme I.


ClCH2COCH3
6a, R=CH3
6b, R=Ph
9a, R=CH3
9b, R=Ph
NH4OAc
AcOH
P2O5
5a, R=CH3
5b, R=Ph
10a, R=CH3
10b, R=Ph
NH2NH2·H2O, AcOH
from 5a
from 5b
7
8

Scheme II.


NH3 (from 5)
6a and b
15 R'=CH3 or Ph
3 R=aryl, R'=CH3 or Ph
5 R= , R'=CH3 or Ph
NH2NH2
path a (from 11b)
7
11a R=aryl, R'=CH3 or Ph
16
path b
11b R= , R'=CH3 or Ph
8 (from 13b)
12a R=aryl, R'=CH3 or Ph
13a R=aryl, R'=CH3 or Ph
12b R= , R'=Ph
13b R= , R'=Ph
from 13a
-H2O
4
14 R=aryl, R'=CH3 or Ph

version of α-(1,3,4-oxadiazol-2-ylthio) ketones to 2,[2] the similar type of reaction of 3 resulted in the formation of complex mixtures.

Reactions of α-(Benzoxazol-2-ylthio) Ketones 5a and b with Ammonia and Hydrazine.

Mercapto ketones 5a and b were prepared in high yields (94-97 %) by the reaction of sodium salt of 2-mercaptobenzoxazole with chloroacetone and phenacyl bromide, respectively. Treatment of 5a and b with 5 equimolar amounts of ammonium acetate in refluxing acetic acid for 1-2 h afforded 2-(2-hydroxyphenylamino)thiazoles 6a and b both in quantitative yields. This transformation was verified by disappearance of a carbonyl absorption, by appearance of a broad absorption (3200-2400 cm^{-1}) of phenol in the IR spectra, and by an overlapping signal due to NH and OH protons (6a, δ 9.69; 6b, δ 9.55) and a signal due to olefinic proton (δ 6.33), which was coupled to the 4-methyl substituent (J = 1.20 Hz) in the ^1H NMR spectra. Interestingly, 5a and b gave the different types of products with hydrazine hydrate: While phenyl ketone 5b gave 1,3,4-thiadiazine derivative 8 in 53 % yield by treating with 5 equimolar amounts of hydrazine hydrate in acetic acid at room temperature, methyl ketone 5a afforded thiazoline derivative 7 in 86 % yield under the same conditions (Scheme I). The above reactions carried out at refluxing temperature gave only an intractable mixture. The structures 7 and 8 were assigned based on spectral data and elemental analyses. In the ^1H NMR, 7 showed NH_2 and OH protons (δ 5.48 and 8.12 respectively) and olefinic proton (δ 5.85, J = 1.20 Hz), while 8 exhibited an overlapping broad signal due to NH and OH protons (δ 9.90) and methylene protons (δ 3.90) shifted to upfield compared with 5b. Table III shows the UV data of starting ketones 5a and b and those of products 6a, b, 7, and 8; the absorption

Table III. UV Data of Compounds 5a, b, 6a, b, 7, and 8[a]

compd	λ nm (log ε)
5a	244(4.14), 276(4.10), 283(4.08)
5b	245(4.42), 277(4.18), 283(4.15)
6a	280(3.99), 303(4.10)
6b	272(4.17), 302(4.21)
7	290(3.89), 330(3.98)
8	290 sh (3.96), 330(4.07)

[a] MeOH

around 245 and 280 nm region due to benzoxazole[11] changed to give new absorption assignable for products (6a and b, around 300 nm; 7 and 8, around 330 nm). The overall reaction paths from 5 to 6, 7, and 8 can be explained in the same way as 3 to 4. With hydrazine, the product

7 and 8 are derived depending on the direction of the ring closure of hydrazone 11b (path a or b in Scheme II). Considering the results that 3 gave only thiadiazine derivatives, 7 is rather unusual product; the employed reaction temperature was somewhat different. In these cases, further condensation of 6, 7, and 8, resulting from the collapse of the corresponding spiro derivatives (15, 16, and 12b, respectively) is naturally impossible because of the formation of phenol. Nevertheless these transformation established a new route to introduce heterocycles to the nitrogen of o-aminophenol. Thus obtained aminophenols 6a and b were converted to 1,4-benzoxazine derivatives by the ring closure with chloroacetone. Very recently a convenient one-step synthesis of 3-aryl-2H-1,4-benzoxazines from o-aminophenols and phenacyl bromide was reported.[12] However, under these reported conditions, 6a and b gave the intermediate keto-ether 9. Finally desired 10a and b were obtained in 41-44 % yields by dehydrating the crude 9 with phosphorus pentoxide in refluxing benzene. Conversion of 6 to 10 was verified by appearance of a signal due to olefinic proton (10a, δ 6.06; 10b, δ 6.17), coupled to 3-methyl substituent (J = 1.50 Hz) in the ^{1}H NMR. However, attempted ring closure of 8 was unsuccessful.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micromelting-point apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 B elemental analyzer. UV spectra were determined with a Hitachi spectrophotometer (Model 200-10). The ^{1}H NMR spectra were taken at room temperature with a JEOL C-60-HL spectrometer with tetramethylsilane as an internal standard. The IR spectra were taken with a JASCO-IRA-1 spectrometer.

α-(Oxazol-2-ylthio) Ketones (3a-f). - 3a, b, g, and h were prepared by the procedure of Bradsher and Jones.[6] 3c-f were prepared similarly from the corresponding 2-mercaptooxazoles[13] and α-haloketones. A general procedure is the following: To a solution of 2-mercaptooxazole, an equimolar amount of sodium methoxide, and dry methanol, was added an equimolar amount of α-haloketone (chloroacetone or phenacyl bromide) in one portion at room temperature. After stirring for 1 day at room temperature, methanol was evaporated under reduced pressure and the product was washed with water, filtered, and recrystallized from ethanol affording 3c-e. 3f was extracted with chloroform after the reaction mixture was concentrated and poured into water. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give a yellow oil, which was purified on a silica gel column with EtOH/$CHCl_3$=1/30 as the eluent. Yields and physical properties of 3c-f are summarized in Table IV and V.

2H-Imidazo[2,1-b][1,3,4]thiadiazines (4a-c and e). - A mixture of 3 (1 mM), hydrazine hydrate

Table IV. Yields and Melting Points of α-(Oxazol-2-ylthio) Ketones 3c-f[a]

compd	yield(%)	mp(°C)[b]
3c	73	118-119
3d	77	103-105
3e	92	89-91
3f	100	oil

[a] All microanalyses were within 0.4 % of the theoretical values. [b] 3c-e were recrystallized from EtOH. 3f was purified on a silica gel column with $EtOH/CHCl_3$=1/30 as the eluent.

Table V. IR and ^1H NMR Data of Compounds 3c-f

compd	IR;$\nu_{C=O}(cm^{-1})$[a]	^1H NMR (δ)[b]
3c	1680	4.79(s, 2H, CH_2)
		7.13-8.21(m, 13H, Ar)
3d	1720	2.39(s, 3H, CH_3)
		4.13(s, 2H, CH_2)
		7.21-7.64(m, 8H, Ar)
3e	1680	3.80(s, 6H, OCH_3×2)
		4.80(s, 2H, CH_2)
		6.72-8.20(m, 13H, Ar)
3f	1730	2.39(s, 3H, CH_3)
		3.80(s, 6H, OCH_3×2)
		4.10(s, 2H, CH_2)
		6.70-8.05(m, 8H, Ar)

[a] 3c-e, KBr; 3f, neat [b] $CDCl_3$

(5 mM), and acetic acid (4 ml) was heated under reflux for 20 min - 1 h as listed in Table I. After removal of acetic acid, the residue was washed with water, filtered, and purified as listed in Table I. Yields and physical properties of 4a-c and e are summarized in Table I and II.

2-Acetonylthiobenzoxazole (5a). - To a solution of 2-mercaptobenzoxazole (6.0 g, 39.8 mM), sodium hydroxide (1.6 g, 40.0 mM), and water (60 ml), was added chloroacetone (3.2 ml, 39.8 mM) in one portion at room temperature. After stirring for 1 day at room temperature a precipitate was filtered to give 8.0 g (97 %) of 5a. An analytical sample was obtained as light yellow crystals by recrystallization from ethanol: mp 78-80°C; IR (KBr) 1720 (C=O)

cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 7.18-7.80 (m, 4H, Ar). Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76. Found: C, 57.84; H, 4.39; N, 6.86.

2-Phenacylthiobenzoxazole (5b). - 5b was prepared similarly as 5a from 2-mercaptobenzoxazole and phenacyl bromide: 94 % yield; mp 124-125°C (yellow needles, EtOH); IR (KBr) 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (s, 2H, CH_2), 7.18-8.20 (m, 9H, Ar). Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.90; H, 4.12; N, 5.20. Found: C, 67.08; H, 4.20; N, 5.22.

2-(2-Hydroxyphenylamino)-4-methylthiazole (6a). - A solution of 5a (300 mg, 1.4 mM), ammonium acetate (500 mg, 6.5 mM), and acetic acid (6 ml) was heated under reflux for 1 h. After removal of the solvent, the resulting mixture was neutralized with 20 % sodium hydroxide solution to give an oily product, which solidified on standing at room temperature for half a day. Filtration gave 300 mg (100 %) of 6a, which was purified by recrystallization from ethanol: mp 158-160°C; IR (KBr) 3390, 3200-2400 (broad) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.18 (d, J = 1.20 Hz, 3H, CH_3), 6.33 (q, J = 1.20 Hz, 1H, =CH), 6.55-8.02 (m, 4H, Phenyl), 9.60 (br s, 2H, OH and NH). Anal. Calcd for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.53; H, 4.95; N, 13.57.

2-(2-Hydroxyphenylamino)-4-phenylthiazole (6b). - 6b was obtained similarly as 6a by refluxing 5b and 5 equimolar amounts of ammonium acetate in acetic acid for 2 h: 100 % yield; mp 192-194°C (light brown cystals, EtOH); IR (KBr) 3370, 3200-2400 (broad) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.17-8.56 (m, 10H, Ar), 9.55 (br s, 2H, OH and NH). Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.00; H, 4.59; N, 10.50.

2-(2-Hydroxyphenylimino)-3-amino-4-methyl-4-thiazoline (7). - To a solution of 5a (600 mg, 2.9 mM) and acetic acid (20 ml), hydrazine hydrate (730 mg, 14.6 mM) was added slowly at room temperature. Gradually a white precipitate formed. On standing at room temperature it slowly dissolved and after 2 days the resulting clear solution was poured into 20 ml of saturated brine. Neutralization with 20 % sodium hydroxide solution gave 550 mg (86 %) of 7 as a light yellow precipitate. An analytical sample was obtained as light yellow crystals by recrystallization from ethanol: mp 153-155°C; IR (KBr) 3320, 3120, 3070, 1620, 1570 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.13 (d, J = 1.20 Hz, 3H, CH_3), 5.48 (s, 2H, NH_2), 5.85 (q, J = 1.20 Hz, 1H, =CH), 5.70-7.20 (m, 4H, Phenyl), 8.12 (s, 1H, OH). Anal. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.09; H, 5.06; N, 19.13.

2-(2-Hydroxyphenylamino)-5-phenyl-1,3,4-thiadiazine (8). - To a solution of 5b (500 mg, 1.9 mM) and acetic acid (20 ml), hydrazine hydrate (460 mg, 9.2 mM) was added slowly at room temperature. The reaction solution was stirred at room temperature for 4 days and poured into

10 ml of saturated brine and neutralized with 20 % sodium hydroxide solution to give an oily product, which solidified on standing at room temperature for 1 day. Filtration and recrystallization from ethanol gave 280 mg (53 %) of 8 as yellow crystals: mp 153-154°C; IR (KBr) 3500, 3400, 3200, 1590, 1560 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.90 (s, 2H, CH_2), 6.70-8.05 (m, 9H, Ar), 9.90 (br s, 2H, NH and OH). Anal. Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.39; H, 4.81; N, 14.83.

3-Methyl-4-(4-methylthiazol-2-yl)-4H-1,4-benzoxazine (10a). - A mixture of 6a (500 mg, 2.4 mM), anhydrous potassium carbonate (300 mg), chloroacetone (0.20 ml, 2.4 mM), and dry acetone (15 ml) was heated under reflux for 9 h. The reaction mixture was filtered and the inorganic material was washed with acetone. Combined acetone was then evaporated and the residue was dissolved in 30 ml of chloroform. The organic solution was washed with water 3 times, dried over anhydrous magnesium sulfate, and concentrated to give a brown oil, which was dried well under reduced pressure. The brown oil was dissolved in 20 ml of dry benzene and to this solution was added phosphorus pentoxide (580 mg, 4.1 mM) and heated under reflux for 7 h. The reaction mixture was filtered and the insoluble product was washed with benzene. The organic solution was washed with saturated sodium hydrogen carbonate solution once, with water 3 times, dried over anhydrous magnesium sulfate, and concentrated to give crude 10a, which was purified on a silica gel column using benzene as the eluent to afford 240 mg (41 %) of pure 10a as a yellow oil: IR (neat) 3120, 3000, 1690, 1600, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (d, J = 1.50 Hz, 3H, CH_3 on 1,4- benzoxazine), 2.35 (d, J = 1.20 Hz, 3H, CH_3 on thiazole), 6.06 (q, J = 1.50 Hz, 1H, =CH), 6.46 (q, J = 1.20 Hz, 1H, =CH), 6.58-7.30 (m, 4H, Ar). Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.92; H, 4.96; N, 11.45.

3-Methyl-4-(4-phenylthiazol-2-yl)-4H-1,4-benzoxazine (11b). - 10b was obtained similarly as 10a. Crude 10b was purified on a silica gel column using benzene as the eluent: 44 % yield; yellow oil; IR (neat) 3100, 2950, 1690, 1600, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (d, J = 1.50 Hz, 3H, CH_3), 6.17 (q, J = 1.50 Hz, 1H, =CH), 6.65-8.05 (m, 10H, Ar). Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.61; N, 9.14. Found: C, 70.78; H, 4.66; N, 9.13.

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Received, 7th July, 1982