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Studies on Isothiazoles. III.[1] A Novel Ring Closure to Isothiazoles by the Reaction of α-Amino Ketones with Thionyl Chloride or Sulfur Monochloride

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New compounds, 4-hydroxyisothiazoles, have been prepared by the reaction of α-amino ketones with thionyl chloride or sulfur monochloride, which is a novel procedure for cyclization to an isothiazole ring. Polar solvents, especially dimethylformamide (DMF), were preferable for this cyclization. The reaction hardly proceeded in a nonpolar solvent such as benzene, but was accelerated by an addition of a small amount of DMF.

Mononuclear isothiazoles have been unknown until Adams and Slack[2] obtained in 1956 isothiazole-4,5-dicarboxylic acid by oxidation of 5-aminobenzisothiazole. Since then, many isothiazole derivatives have been prepared by several routes: oxidative ring closure of β-iminothioamides[3] or β-iminothioketones,[4] reaction of olefins with sulfur dioxide and ammonia in the presence of activated alumina,[5] cyclization with liquid ammonia of the addition product from acetylenic ketones and thiosulfate or thiocyanate,[6] cyclization of dicyanoethylene-thiolate with sulfur, chlorine or chloramide,[7] treatment of dithiolium salts with ammonia[8] and reaction of nitriles with sulfur and morpholine.[9] Now we wish to report a novel procedure for formation of the isothiazole ring from open-chain compounds and the resulting products, 4-hydroxyisothiazoles, which have been hitherto undescribed.

1) Part II: T. Naito, S. Nakagawa and K. Takahashi, *Chem. Pharm. Bull.*, **16**, 160 (1968).

2) A. Adams and R. Slack, *Chem. & Ind. (London)*, **1956**, 1232.

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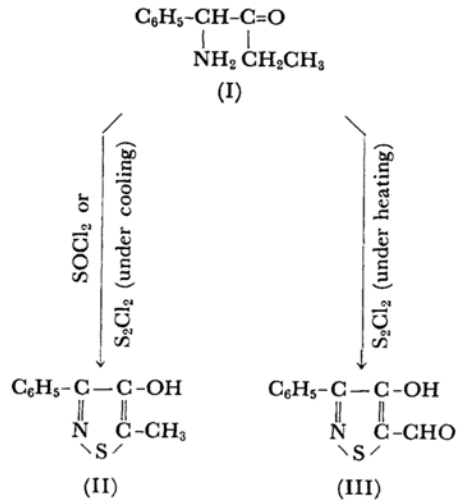
8) a) D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc.*, **1962**, 252. b) E. Fanghänel, *Z. Chem.*, **5**, 386 (1965). c) R. A. Olofson, J. M. Landesberg, R. O. Berry, D. Leaver, W. A. H. Robertson and D. M. McKinnon, *Tetrahedron*, **22**, 2119 (1966). d) G. Purrello, *Gazz. Chim. Ital.*, **96**, 1000 (1966).

9) A. Brund and G. Purrello, *Gazz. Chim. Ital.*, **96**, 986 (1966).



1-Amino-1-phenyl-2-butanone (I) readily reacted with thionyl chloride in dimethylformamide (DMF) to give an acidic product melting at 153—153.5°C, which showed the characteristics expected for those of 4-hydroxy-5-methyl-3-phenylisothizaole (II). The product is soluble in dilute sodium hydroxide, but insoluble in neutral or acid water. The IR spectrum shows a band at about 3200 cm^{-1}, but no band in the carbonyl region. Its NMR spectrum*1 in dimethylsulfoxide-d_6 has a singlet due to a phenolic hydroxyl proton at 9.62[10] together with a singlet of C_5-methyl protons at 2.46,[11] a multiplet due to meta- and para-protons of phenyl ring at 7.56—7.86 and a multiplet due to ortho-protons at 8.24—8.50. Acetylation of the product with acetic anhydride gave a neutral colorless oil, which showed a carbonyl band due to enol acetate at 1755 cm^{-1} in the IR spectrum. The NMR spectrum of the acetate in deuteriochloroform shows two methyl singlets at 2.24 and 2.34 and phenyl proton multiplets at 7.32—7.52 and 7.68—7.90. Methylation with diazomethane afforded a colorless oil which showed complete absence of hydroxy stretching band and appearance of new bands due to an aromatic ether at 1250 cm^{-1} and 1000 cm^{-1} in the IR spectrum. When I was allowed to react with sulfur monochloride in DMF under cooling, the same product (II) was obtained in 44% yield. However, the reaction under heating gave another acidic compound melting at 104—105°C, which was determined to be 5-formyl-4-hydroxy-3-phenylisothiazole (III). It shows a hydroxyl band at about 3400 cm^{-1} and a carbonyl band at 1655 cm^{-1}, and gives the corresponding 2,4-dinitrophenylhydrazone having an absorption maximum at 391 mμ. By acetylation the carbonyl band remains and the hydroxyl band disappears with an appearance of a new band due to enol acetate at 1770 cm^{-1}. The NMR spectrum of the acetate in carbon tetrachloride shows a methyl singlet at 2.46, multiplets of five phenyl protons at 7.54—7.82 and 7.94—8.18 and a singlet due to a formyl proton at 10.14.

TABLE 1. PREPARATION OF 4-HYDROXYISOTHIAZOLES

Starting ketone	Cyclization reagent, eq.	Method	Product	Yield, %
I	$SOCl_2$ 4	B	II	78
I	$SOCl_2$ 4	A	II	74
I	$SOCl_2$ 3	A	II	70
I	$SOCl_2$ 2	B	II	73
I	$SOCl_2$ 2	A	II	54
I	$SOCl_2$ 1	B	II	41
I	S_2Cl_2 4	B	III	34
I	S_2Cl_2 3	A	II	44
IV	S_2Cl_2 3	A	II	17
IV	$SOCl_2$ 4	B	*	—
VI	$SOCl_2$ 4	A	IX	22
VI	$SOCl_2$ 2	A	VIII	74
VI	S_2Cl_2 4	B	VII	43
VI	S_2Cl_2 3	A	VII	70
X	S_2Cl_2 3	A	VII	14
XIa	$SOCl_2$ 4	B	XIIa	66
XIa	S_2Cl_2 4	B	XIIa	37
XIb	$SOCl_2$ 2	A	XIIb	7
XIb	S_2Cl_2 2	A	XIIb	9
XIc	$SOCl_2$ 4	A	XIIc	7
XIc	S_2Cl_2 4	A	XIIc	19
XId	$SOCl_2$ 3	A	XIId	42

* An oxazole derivative (V) was obtained (see, experimental section).

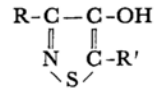
The reaction of I with thionyl chloride was investigated under various conditions. As shown in Table 1, the reaction under cooling (Method A) gave more than 70% yield of the product (II) with three equivalents or more of thionyl chloride. The reaction without thermal control (Method B) proceeded with nearly the same yield as Method A when two equivalents or more of thionyl chloride was used, while the yield decreased considerably with an equimolar of the reagent. As shown in Table 4, the solvent, DMF, can be substituted by other polar solvents, but with decrease of the yield. The reaction in dimethylsulfoxide gave only an unidentified tarry product with mercaptan-like odor. A nonpolar solvent such as benzene was not suitable for this reaction, but the addition of a small amount of DMF accelerated the reaction considerably.

*1 All NMR spectra in this paper were run with a Varian A-60 spectrometer, for which the authors are indebted to Assistant Professor M. Goto and Dr. Urushibara of Gakushuin University. Chemical shifts are represented in ppm from an internal reference, TMS.

10) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

11) T. Naito, S. Nakagawa and K. Takahashi, *Chem. Pharm. Bull.*, **16**, 148 (1968).

TABLE 2. 4-HYDROXYISOTHIAZOLES



No.	R	R′	Mp., °C	λ_{max}^{EtOH} mμ(ε)	Molecular formula		Anal, % C	H	N	S	Cl
II	C_6H_5	CH_3	153—153.5	249(6500) 296(13700)	$C_{10}H_9NOS$	Calcd Found	62.79 62.79	4.74 4.40	7.32 7.09	16.78 17.28	
III	C_6H_5	CHO	104—105	235(21600) 284(7550) 342(9850)	$C_{10}H_7NO_2S$	Calcd Found	58.54 58.02	3.44 3.38	6.83 7.00	15.62 15.59	
VIII	C_6H_5	H	156—158	218(10700) 243.5(6500) 302(14000)	C_9H_7NOS	Calcd Found	61.00 61.01	3.98 3.66	7.91 7.58	18.09 18.35	
VII	C_6H_5	Cl	175(dec)	299(12800)	C_9H_6ClNOS	Calcd Found	51.07 51.59	2.86 2.82	6.62 6.57	15.09 14.61	16.69 16.93
XIIa	C_6H_5	C_6H_5	112.5—113.5	238(21500) 310(15400)	$C_{15}H_{11}NOS$	Calcd Found	71.12 71.81	4.38 4.68	5.53 5.92		
XIIb	CH_3	CH_3	106—108	217(4660) 269(6850)	C_5H_7NOS	Calcd Found	46.49 47.03	5.46 5.05	10.84 10.50		
XIIc	CH_3	Cl	150—155	225(3670) 271(6200)	C_4H_4ClNOS	Calcd Found	32.63 32.11	2.87 2.70	9.11 9.36	20.21 20.43	23.70 24.34
XIId	CH_3	C_6H_5	144—147	293(11900)	$C_{10}H_9NOS$	Calcd Found	62.79 62.70	4.74 4.96	7.32 7.51		
IX	C_6H_5	*	220—223	220(14750) 313(10600)	$C_{18}H_{12}N_2O_2S_3$	Calcd Found	56.23 56.64	3.44 3.12	7.29 7.47	25.02 25.30	

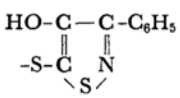
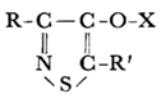
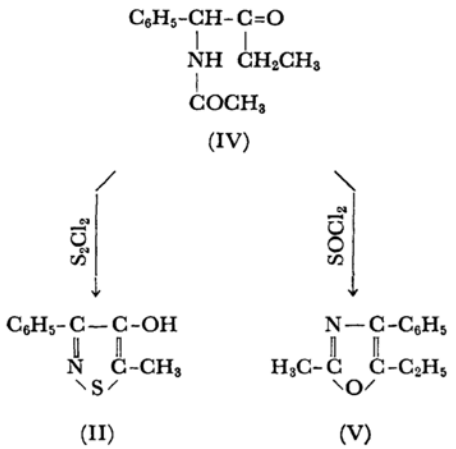
* 

TABLE 3. 4-ACETOXYISOTHIAZOLES AND 4-METHOXYISOTHIAZOLES



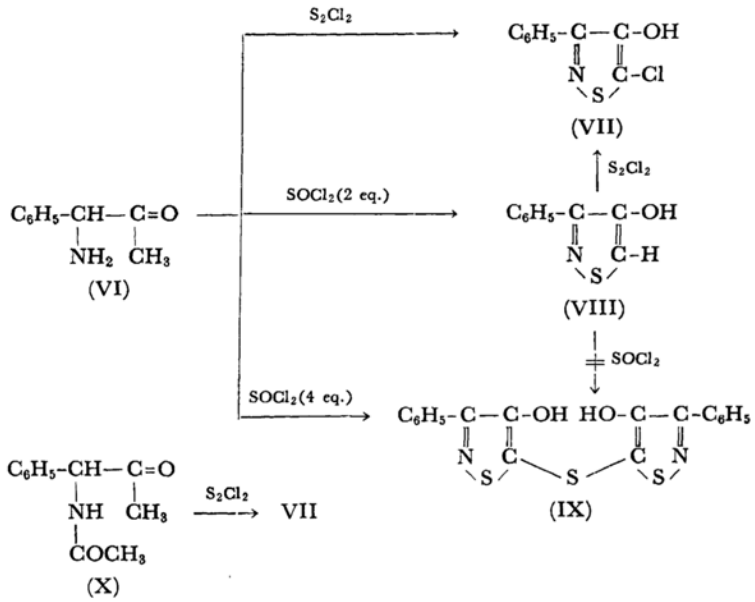
X	R	R′	Yield %	Bp °C/mmHg	$\nu_{C=O}$ cm^{-1}	λ_{max}^{EtOH} mμ(ε)	Molecular formula		Anal, % C	H	N
$COCH_3$	C_6H_5	CH_3	53	142—143/1.2	1775	272.5(16600)	$C_{12}H_{11}NO_2S$	Calcd Found	61.79 61.85	4.75 4.77	6.00 6.25
$COCH_3$	C_6H_5	CHO	60	mp 80—81.5	1770 1660	235(10000) 299(14500) 422(3800)	$C_{12}H_9NO_3S$	Calcd Found	58.29 58.10	3.67 3.72	5.67 5.75
$COCH_3$	C_6H_5	H	55	132—134/1.0	1780	239(5780) 275(14200)	$C_{11}H_9NO_2S$	Calcd Found	60.25 60.24	4.14 3.91	6.39 6.23
$COCH_3$	C_6H_5	Cl	79	mp 43—45	1785	218(15500) 275(14500)	$C_{11}H_8ClNO_2S$	Calcd Found	52.07 52.45	3.18 3.52	5.52 5.88
$COCH_3$	C_6H_5	C_6H_5	76	mp 72—73	1785	243(22000) 279(21000)	$C_{17}H_{13}NO_2S$	Calcd Found	69.13 69.82	4.44 4.99	4.74 4.88
$COCH_3$	CH_3	C_6H_5	57	132—134/1.2	1780	266(16800)	$C_{12}H_{11}NO_2S$	Calcd Found	61.79 62.06	4.75 4.93	6.00 5.90
CH_3	C_6H_5	CH_3	37	118/3	—	280(15800)	$C_{11}H_{11}NOS$	Calcd Found	64.39 64.30	5.40 5.36	6.83 7.22
CH_3	C_6H_5	H	54.5	124—126/0.7 (mp 58—61)	—	240(5700) 297.5(13300)	$C_{10}H_9NOS$	Calcd Found	62.80 62.96	4.74 4.52	7.32 7.25
CH_3	C_6H_5	Cl	61	115/1.0	—	217(16200) 283(14500)	$C_{10}H_8ClNOS$	Calcd Found	53.21 52.97	3.57 3.82	6.21 6.46



(IV) (II) (V)

Treibs and Suter[12] have reported that 3-acetamido-2-butanone was reacted with thionyl chloride to give 2,4,5-trimethyloxazole. Similarly 1-acetamido-1-phenyl-2-butanone (IV) was dehydrated by thionyl chloride to afford 5-ethyl-2-methyl-4-phenyloxazole (V). The reaction with sulfur monochloride did not give the oxazole derivative (V) but the above-mentioned isothiazole (II) in 17% yield by cyclization accompanied with *N*-deacetylation.

1-Amino-1-phenyl-2-propanone (VI) was subjected to a similar reaction with sulfur monochloride either under cooling or under heating. In both cases, the product was the same chlorine-containing acidic compound, 5-chloro-4-hydroxy-3-phenylisothiazole (VII). The mass spectrograph*2



(VI) (VII) (VIII) (IX) (X)

TABLE 4. PREPARATION OF 4-HYDROXY-5-METHYL-3-PHENYLISOTHIAZOLE (II) WITH 2.0 eq. OF THIONYL CHLORIDE IN VARIOUS SOLVENTS

Exp. No.	Solvent	Reaction condition	Yield (%)
(1)	DMF	overnight at room temp.	73
(2)	Nitromethane	overnight at room temp., then 25 hr at 65—70°C	40
(3)	Acetonitrile	overnight at room temp., then 7 hr at 30—40°C	30*
(4)	THF	overnight at room temp., then 2.5 hr at 50—60°C	55
(5)	Benzene	5 hr at 60°C	trace**
(6)	Benzene+DMF(0.18 g, 0.1 eq)	5 hr at 60°C	56
(7)	Benzene+DMF(1.82 g, 1.0 eq)	5.5 hr at 60°C	43
(8)	Benzene+DMF(3.7 g, 2.0 eq)	3 hr at 60°C	43

* 6.3% of the starting amino ketone was recovered.
** 83% of the starting amino ketone was recovered.

*2 Mass spectra were run with a Hitachi RMU-6 spectrometer by a heating inlet system (Chember voltage, 80 V; reservoir temp., 120°C; electron multiplier voltage 2000 V), for which the authors are indebted to Professor S. Hishida of Nihon University.

12) A. Treibs and W. Suter, *Chem. Ber.*, **84**, 96 (1951).

of VII showed a molecular peak at *m/e* 211/213 with characteristic isotopic abundance and the NMR spectrum in dimethylsulfoxide-d_6 solution indicated signals of phenyl protons and a phenolic hydroxyl proton. 1-Acetamido-1-phenyl-2-propanone (X) was reacted similarly with sulfur monochloride to afford VII by cyclization accompanied with *N*-deacetylation and chlorination.

The reaction of VI with 2 equivalents of thionyl chloride in DMF gave the expected product, 4-hydroxy-3-phenylisothiazole (VIII), which showed a singlet of C-5 proton at 8.12[11] along with singnals of phenyl protons and a phenolic hydroxyl proton. On the other hand the reaction with 4 equivalents of thionyl chloride gave another acidic product which showed a molecular peak at *m/e* 384. The structure was established as bis-(4-hydroxy-3-phenyl-5-isothiazole) sulfide (IX) by lack of C-5 proton and elemental analysis. It was found that a minor amount of VIII was also present in a reaction mixture of VI with sulfur monochloride under mild condition. Moreover, VIII was converted into VII by sulfur monochloride, while treatment with thionyl chloride gave neither VII nor IX, but the starting material (VIII) was recovered.

(XI) (XII)

a : R=R'=C_6H_5 a : R=R'=C_6H_5
b : R=R'=CH_3 b : R=R'=CH_3
c : R=CH_3, R'=H c : R=CH_3, R'=Cl
d : R=CH_3, R'=C_6H_5 d : R=CH_3, R'=C_6H_5

1-Amino-1,3-diphenyl-2-propanone (IXa) was expected to give 4-hydroxy-3,5-diphenylisothiazole (XIIa) as a sole product, because substitution or oxidation would be blocked in the 5-position in XIIa. In fact, none of by-product was obtained when XIa was allowed to react with thionyl chloride or sulfur monochloride under the condition same as that yielding the abnormal products such as IX, III and VII. 2-Amino-3-pentanone (XIb) was reacted similarly with either one of the cyclization reagents to afford 3,5-dimethylisothiazole (XIIb), although the yield was poor. Also, 3-amino-1-phenyl-2-butanone (XId) was cyclized to 4-hydroxy-3-methyl-4-phenylisothiazole (XIId) by thionyl chloride. On the other hand, the reaction with 3-amino-2-butanone (XIc) gave only a chlorine-containing product (XIIc).

Experimental

α-Amino Ketones. According to the procedure of Dakin and West,[13-17] α-amino ketones were prepared by heating an α-amino acid or α-acetamido acid with an acid anhydride in the presence of pyridine followed by hydrolysis of the resulting α-acylamido ketone with 6 N hydrochloric acid. The results and properties are shown in Table 5.

4-Hydroxyisothiazoles. 4-Hydroxyisothiazoles were prepared by the following two methods and the results are shown in Table 1. The properties and analyses of the products are shown in Table 2.

Method A. There was added 0.1—0.2 mol of thionyl chloride or sulfur monochloride to 50 m*l* of DMF below 0°C with stirring. To the stirred solution was added 0.05 mol of an appropriate α-amino ketone hydrochloride with cooling in an ice-salt bath to maintain the temperature below 10°C. After an exothermic reaction had ceased, the bath was removed and the stirring continued for two hours. The reaction mixture was allowed to stand overnight at room temperature, then poured into 100 m*l* of ice water and extracted with three 50-m*l* portions of ether. The combined ethereal extracts were washed with two 50-m*l* portions of water and then back-extracted with two 50-m*l* portions of 5% aqueous sodium hydroxide solution. The combined alkaline extracts were evaporated under reduced pressure to remove low boiling materials and then acidified whit 20% hydrochloric acid with cooling to give the product which was collected by filtration and recrystallized from ligroin or benzene-ligroin.

Method B. There was added 0.05—0.2 mol of thionyl chloride or sulfur monochloride to 50 m*l* of DMF below 0°C and the solution was mixed with 0.05 mol of an appropriate α-amino ketone hydrochloride in one portion. An exothermic reaction began soon and the temperature of the mixture rose to 50—80°C. When the reaction had ceased, the reaction mixture was heated on a water bath at 60—90°C for 1.5—2 hr, then allowed to stand overnight at room temperature. The product was isolated by the procedure described in Method A.

4-Acetoxyisothiazoles. Acetylation of 4-hydroxyisothiazoles was carried out with acetic anhydride by a usual manner. The yields and properties of the resulting 4-acetoxyisothiazoles are shown in Table 3.

4-Methoxyisothiazoles. 4-Hydroxyisothiazoles were converted into the corresponding 4-methoxy derivatives with diazomethane in ether. The yields and properties are shown in Table 3.

Reaction of 1-Acetamido-1-phenyl-2-butanone (IV) and Thionyl Chloride. To a cold suspension of 5 g (0.025 mol) of IV in 25 m*l* of ligroin was added 12 g (0.1 mol) of thionyl chloride in one portion. The mixture was stirred overnight at room temperature and heated at 80—90°C for four hours. The reaction mixture was evaporated under reduced pressure, the residual oxazolium salt was washed with three 30-m*l* portions of ether and added to 30 m*l* of water to convert it to the oily free oxazole. The oil was extracted with two 30-m*l* portions of ether and the extracts were washed with 30-m*l* of water, two 30-m*l* portions of 2.5% sodium

13) H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91 (1928).

14) P. A. Levene and R. E. Steiger, *ibid.*, **79**, 95 (1928).

15) R. H. Wiley and O. H. Borum, *J. Am. Chem. Soc.*, **70**, 2005 (1948); "Organic Syntheses," Coll. Vol. 4, p. 5 (1963).

16) G. H. Cleland and C. Nieman, *J. Am. Chem. Soc.*, **71**, 841 (1949).

17) S. Searles and G. J. Cvejanovich, *ibid.*, **72**, 3200 (1950).

TABLE 5. α-AMINO KETONES (HYDROCHLORIDE)

Compd. No.	Yield** %	Mp °C	Lit. mp °C	$\nu_{C=O}$ cm^{-1}
I	(a) 86	166—170	***	1730
	(b) 76			
IV*	(b) 93	bp 162—169/3		1730, 1655
VI	(a) 81	205—207	204—208[13]	
			203[14]	
X*	(a) 90	100—102	103—104[13]	1715, 1640
			100—101[14]	
XIa	(b) 36	181—182(dec.)	****	1730
XIb	(b) 36	123—128(dec.)	128(dec.)[18]	1725
XIc	(a) 76	108—110(dec.)	111(dec.)[19]	1725
XId	(b) 13	143—145		1730

* *N*-Acetyl derivative.
** Overall yield from (a) α-amino acid or (b) α-acetamido acid.
*** Found: C, 59.83; H, 6.83; N, 7.44%. Calcd for $C_{10}H_{13}ON \cdot HCl$: C, 60.15; H, 7.07; N, 7.02%.
**** Found: C, 68.55; H, 6.22; N, 5.68%. Calcd for $C_{15}H_{15}ON \cdot HCl$: C, 68.83; H, 6.16; N, 5.35%.

hydroxide solution and finally with two 30-m*l* portions of water and then treated by active carbon. The filtrate was evaporated and the residue distilled under reduced pressure to give 1.9 g (41%) of V as a pale yellow oil boiling at 150—152°C/13 mmHg (lit.,[20] bp 146—148°C/12 mmHg). NMR (ppm, in CCl_4): 1.30 (3H, triplet), 2.42 (3H, singlet), 2.87 (2H, quartet), 7.25—7.75 (5H, multiplet).

Reaction of 4-Hydroxy-3-phenylisothiazole (VIII) with Sulfur Monochloride. To a stirred solution of 1.24 g (0.007 mol) of VIII in 10 m*l* of DMF was added dropwise 2.84 g (0.021 mol) of sulfur monochloride with cooling. The mixture was stirred for four hours and allowed to stand overnight at room temperature. The reaction mixture was poured into 100 m*l* of ice water and extracted with three 30-m*l* portions of ether. The combined ethereal solution was extracted with 5% sodium hydroxide solution and the aqueous extracts were acidified with hydrochloric acid to afford 1.09 g (74%) of white precipitate, which was identical to an authentic sample of VII by IR spectrum and acetylation.

Reaction of 4-Hydroxy-3-phenylisothiazole (VIII) with Thionyl Chloride. A solution of 1.24 g (0.007 mol) of VIII in 10 m*l* of DMF was allowed to react with 2.5 g (0.021 mol) of thionyl chloride by the procedure described above. Acidification with hydrochloric acid gave 0.98 g (79%) of the starting material (VIII) which was confirmed by mixed melting point and IR spectrum.

Reaction of 1-Amino-1-phenyl-2-butanone (I) and Thionyl Chloride in Various Solvents (Table 4). To a mixture of 5.0 g (0.025 mol) of I in 15 m*l* of an appropriate solvent listed in Table 4 was added dropwise 6.0 g (0.05 mol) of thionyl chloride at room temperature with stirring. An exothermic reaction occurred and the temperature rose to 30—40°C. The mixture was allowed to react under the condition shown in Table 4. In Exp. Nos. (1) and (2), the reaction mixture was a homogeneous solution and the product was isolated by the same procedure as Method A described above. In. Exp Nos. (3) and (5), the reaction mixture contained insoluble precipitate which was the unreacted starting ketone (I). The ketone was removed by filtration and the filtrate was worked up by the same procedure as Method A to give the product (II). In Exp. Nos. (4), (6), (7) and (8), the reaction mixture contained insoluble precipitate or oil, which appeared to be the isothiazolium salt by IR spectrum. The salt was collected by filtration or decantation and converted into, the corresponding isothiazole (II) by treating with cold water. The filtrate or the supernatant was poured into ice water and extracted with ether. To the ethereal extracts was added the crude II which was obtained from the isothiazolium salt. The solution was treated by the same procedure as described in Method A.

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