A CONVENIENT SYNTHESIS OF *N*-SUBSTITUTED 2,3-DIHYDRO-3-OXOISOTHIAZOLO[5,4-*b*]PYRIDINES IN ACIDIC CONDITIONS

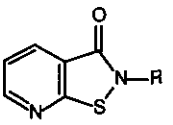
Hideo Terauchi,* Akihiko Tanitame, Keiko Tada, and Yoshinori Nishikawa

Discovery Research Laboratories II, Dainippon Pharmaceutical Co., Ltd., Enoki 33-94, Suita, Osaka 564, Japan

Abstract - A novel and convenient synthesis of *N*-substituted 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridines which possess potent *in vitro* inhibitory activity against gastric (H^+/K^+)-ATPase is reported. Compared with the methods reported previously, the compounds were synthesized more readily in relatively high yields by conversion of *N*-substituted 2-(benzyl-, 1-phenylethyl-, and benzhydrylsulfinyl)nicotinamides (**17d-l**) in a diluted hydrochloric acid-methanol solution at room temperature.

Recently, gastric (H^+/K^+)-ATPase inhibitors represented by 2-[(2-pyridylmethyl)sulfinyl]benzimidazoles (PSBs) such as omeprazole[1] have been shown to be potent antiulcer agents. It is well known that the PSBs act as prodrugs, being chemically transformed to biologically active intermediates, sulfenamides, in acidic condition.[2]

On the basis of random screening, we have found that *N*-substituted 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridines[3] (**1**) and (**2**) inhibited the (H^+/K^+)-ATPase irreversibly,[4] but did not exhibit inhibitory

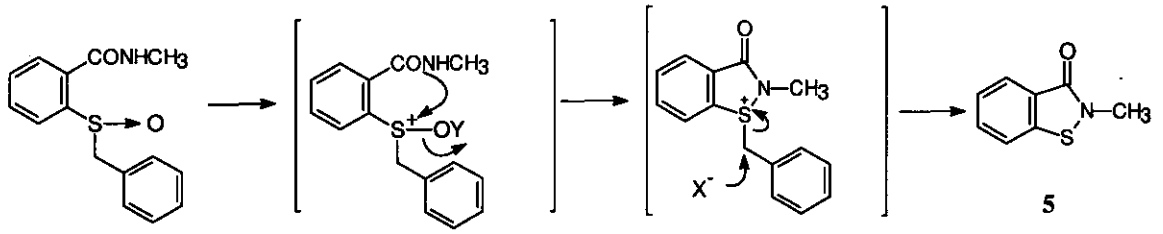


1: R = $-CH_2CH(CH_3)_2$

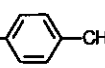
2: R = 

activity against gastric acid secretion *in vivo*. We speculated that this might be because **1** and **2** reacted with thiol groups of other proteins before the compounds reached the target enzyme, gastric (H^+/K^+)-ATPase. To get good *in vivo* efficacy, it appeared to be necessary to find out prodrugs which are converted into the active forms, the isothiazolopyridines like **1** and **2**, only in stomach in a manner similar to omeprazole and its analogues. The present study was undertaken to develop a synthetic method by which the isothiazolopyridines were readily prepared in acidic conditions.

There are several methods of preparing 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridines. For example, the compounds are prepared by cyclization of the 2-mercaptonicotinamides with potassium hexacyanoferrate(III),[5] iodine,[5,6] or thionyl chloride.[7] However, these cyclization must not occur in the acid compartments of the parietal cell. Recently, Uchida *et al.*[8] reported that benzyl *o*-(*N*-methylcarbamoyl)phenyl sulfoxide (**3**) was converted into *N*-methyl-1,2-benzisothiazol-3(2*H*)-one (**5**) by treating with electrophiles such as thionyl chloride, acetyl chloride, and *p*-toluenesulfonyl chloride, and speculated that the mechanism for the conversion might involve the formation of intermediate sulfonium

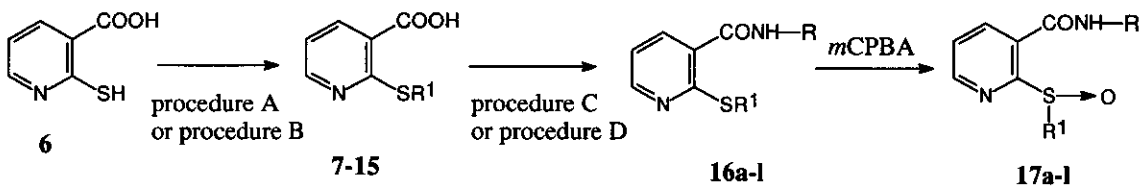


3 **4** **5**

Y=$COCH_3$, X=$OCOCH_3$
Y=$COCH_3$, X=Cl
Y=SOCl, X=Cl
Y=SO_2-  -CH_3, X=Cl

Scheme 1

salt (**4**) as shown in Scheme 1. On the other hand, Wright *et al.*[9] reported that *N*-substituted 2-benzylsulfinylnicotinamides were converted into *N*-substituted 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]-pyridines by treating with trichloroacetic anhydride (TCAA). This conversion may also proceed in a manner similar to that of the conversion of **3**. We assumed that the conversion into 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridines and 1,2-benzisothiazol-3(2*H*)-ones may occur by treating in hydrochloric acid instead of using the electrophiles if the nicotinamides possess a leaving group having a more stable carbonium ion than that of the benzyl group.

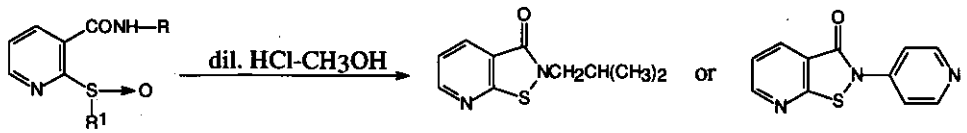


Scheme 2

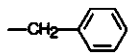
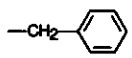
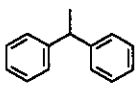
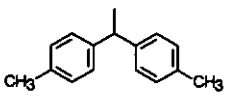
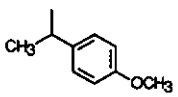
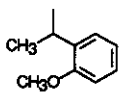
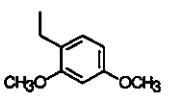
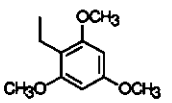
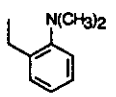
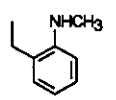
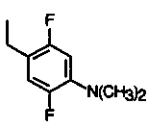
Our efforts were directed toward the preparation of nicotinamides (**17a-l**) bearing various leaving groups and the following conversion into the corresponding isothiazolopyridines (**1**) and (**18**). The requisite nicotinamides (**17a-l**) were synthesized by the route shown in Scheme 2. The nicotinic acids (**7-15**) were prepared by condensation of 2-mercaptonicotinic acid (**6**) with the corresponding benzyl chlorides (procedure A) or with the corresponding benzyl alcohols under acidic conditions (procedure B). The nicotinic acids (**7-15**) obtained were allowed to condense with isobutylamine or 4-aminopyridine by the use of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (procedure C), or oxalyl chloride (procedure D), giving the nicotinamides (**16a-l**). The desired compounds (**17a-l**) were synthesized by oxidation of **16a-l** with *m*-chloroperbenzoic acid (*m*CPBA). It was then examined whether or not the compounds (**17a-c**) could be converted into the isothiazolopyridines in a hydrochloric acid-methanol solution and the other compounds (**17d-l**) were sequently examined.

As shown in Table 1, **17a-c** were not readily converted into the respective isothiazolopyridines at room temperature, but the conversion of **17a** and **17b** with an isobutyl group for R was performed at reflux temperature in high yields. Moreover, it took somewhat more time to convert **17b** as compared with

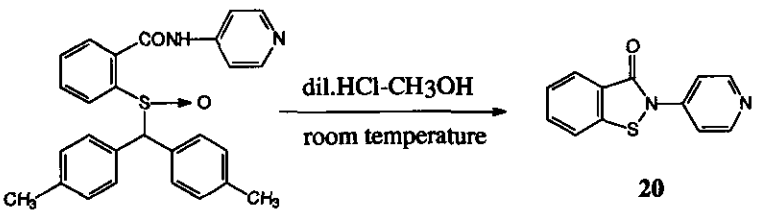
Table 1. Conversion of the Nicotinamides (**17a-l**) in a Diluted Hydrochloric Acid-Methanol Solution.



17a-l **1** **18**

Compd	R^1	R	Temperature	Yield (%)
17a		isobutyl	reflux	89
17b	isopropyl	isobutyl	reflux	81
17c			reflux	trace
17d			room temperature	91
17e			room temperature	85
17f			room temperature	82
17g			room temperature	69
17h			room temperature	84
17i			room temperature	86
17j			room temperature	79
17k			room temperature	88
17l			room temperature	75

17a. These findings suggested that the nucleophilicity of the nitrogen atom on the carbamoyl moiety[10] and the stability of the carbonium ions of the leaving group R^1 probably influenced the conversion. Hence we anticipated that when nicotinamides possessed a leaving group R^1 having a more stable carbonium ion, not only nicotinamides bearing an electron-donating isobutyl group for R but also nicotinamides bearing an electron-withdrawing 4-pyridyl group might be converted into the isothiazolopyridines in a diluted hydrochloric acid-methanol solution at room temperature. As anticipated, *N*-(4-pyridyl)nicotinamides having a benzyl group substituted with electron-donating groups such as an alkoxy and an alkylamino group at the *ortho* and/or *para* position(s), 1-(2- or 4-methoxyphenyl)ethyl group, or benzhydryl group, were readily converted into **18** at room temperature in high yields. Besides, *N*-(4-pyridyl)-1,2-benzisothiazol-3(2*H*)-one (**20**) was also prepared readily starting from 4,4'-dimethylbenzhydryl *o*-[*N*-(4-pyridyl)carbamoyl]phenyl sulfoxide (**19**) in the same reaction conditions in 94% yield as shown in Scheme 3. Introduction of the leaving group, 4,4'-dimethylbenzhydryl group, having a much stable carbonium ion made a success of the preparation of the benzisothiazolone (**20**) in a hydrochloric acid-methanol solution.

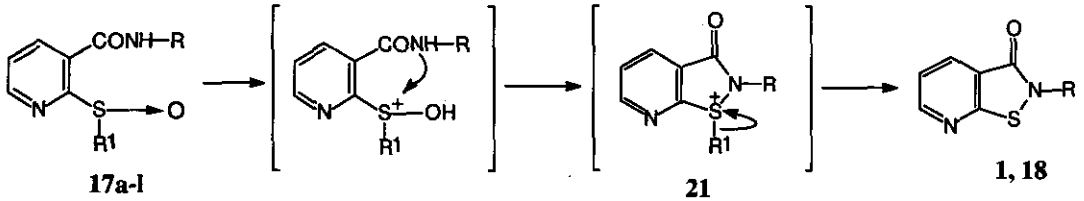


19 **20**

Scheme 3

On the basis of the results described above, these conversions may proceed in a manner similar to that of the conversion of **3** to **5** reported by Uchida *et al.*[8] to afford sulfonium salts (**21**) as intermediates, followed by elimination of leaving groups R^1 to give **1** and **18** as shown in Scheme 4, and the the conversion rate may depend on the stability of the carbonium ions of the leaving group R^1 as well as the nucleophilicity of the nitrogen atom on the carbamoyl moiety.

In conclusion, we developed a novel and convenient synthetic method of preparing the 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridines in a hydrochloric acid-methanol solution.



Scheme 4

EXPERIMENTAL SECTION

All melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. Ir spectra were recorded on a Shimazu FTIR-8200PC spectrophotometer. ^{1}H-Nmr spectra were taken at 200 MHz with a Varian Gemini-200 spectrometer in $(CH_3)_2SO$-d_6. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as the internal standard. Electron ionization and liquid secondary ion mass spectra were obtained on a JOEL JMS D-300 and a Hitachi M-80-B spectrometer. Organic extracts were dried over anhydrous $MgSO_4$.

The following intermediates were prepared according to the cited literature: 4,4'-dimethylbenzhydryl chloride,[11] 2-methylaminobenzyl chloride,[12] 2-benzylthionicotinic acid,[13] and 2-(isopropylthio)-nicotinic acid.[14] 2,4,5-Trifluorobenzoic acid, benzhydryl chloride, 1-(2- or 4-methoxyphenyl)ethyl alcohol, 2,4-dimethoxybenzyl alcohol, 2,4,6-trimethoxybenzyl alcohol, and 2-dimethylaminobenzyl chloride were commercially available.

4-Dimethylamino-2,5-difluorobenzyl Chloride Hydrochloride. To a stirred solution of 2,4,5-trifluorobenzoic acid (100 g, 568 mmol) in dioxane (600 ml) was added oxalyl chloride (100 ml, 1.14 mol) at room temperature. The resulting mixture was stirred at room temperature for 30 min and concentrated to dryness *in vacuo*. The residue was dissolved in 300 ml of THF and CH_3OH (100 ml) were added at 0°C. The reaction mixture was stirred at room temperature for 30 min and concentrated

in vacuo. The residue was taken up in 200 ml of water, and the aqueous mixture was extracted with two 500-ml portions of ether. The combined extracts were dried and concentrated to dryness *in vacuo* to give crude methyl 2, 4, 5-trifluorobenzoate (77 g, 71%).

A mixture of the crude benzoate (41 g, 191 mmol), dimethylamine (50% in water) (500 ml, 4.77 mol), and C_2H_5OH (500 ml) was stirred at reflux temperature for 3 h and concentrated *in vacuo*. The residue was taken up in 100 ml of water, and the aqueous mixture was extracted with two 500-ml portions of ethyl acetate. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel and eluted with $CHCl_3$-hexane (4:1) to give 43 g (93%) of methyl 4-dimethylamino-2,5-difluorobenzoate.

A stirred solution of sodium bis(2-methoxyethoxy)aluminium hydride (Vitride®) (70% solution in toluene) (53.0 g, 184 mmol) in toluene (100 ml) was added dropwise to a solution of methyl 4-dimethylamino-2,5-difluorobenzoate (20.0 g, 93 mmol) in toluene (300 ml) at 5℃. The mixture was stirred at the same temperature for 30 min and then at room temperature for 3 h. The remaining sodium bis(2-methoxyethoxy)aluminium hydride was allowed to decompose by addition of 200 ml of water at 5℃. The organic layer was separated, and the aqueous layer was extracted with toluene (500 ml). The combined extracts were dried and concentrated to about 200 ml. To the solution was added dropwise thionyl chloride (22.8 g, 192 mmol) at 0℃. The resulting mixture was stirred at room temperature for 30 min and concentrated to dryness *in vacuo* to give crude 4-dimethylamino-2,5-difluorobenzyl chloride hydrochloride (21.4 g, 95%). The crude product, without further purification, was used for the preparation of 2-[(2,5-difluoro-4-dimethylanimobenzyl)thio]nicotinic acid (**15**).

Nicotinic Acids (7-15). Procedure A. 2-[(2-Dimethylanimobenzyl)thio]nicotinic Acid (13). To a stirred solution of 2-dimethylaminobenzyl chloride hydrochloride (9.0 g, 44 mmol) in dimethylformamide (300 ml) were added slowly 6.2 g (40 mmol) of 2-mercaptonicotinic acid, and then 16.1 g (159 mmol) of triethylamine. The resulting mixture was stirred at room temperature for 2 h and concentrated to dryness *in vacuo*. The residue was taken up in 100 ml of water, and the aqueous

mixture was extracted with two 300-ml portions of $CHCl_3$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was crystallized from CH_3CN to give **13** (7.8 g, 68%). Compounds (**7, 8, 14,** and **15**) were prepared in a manner similar to that described above. Physical and spectral data for the compounds are summarized in Tables 2 and 3.

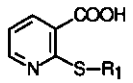
Procedure B. 2-[(2,4-Dimethoxybenzyl)thio]nicotinic Acid (11). To a stirred mixture of 2-mercaptonicotonic acid (90.5 g, 583 mmol), 2,4-dimethoxybenzyl alcohol (100.0 g, 595 mmol) and acetone (1 l) was added concentrated HCl (50 ml) in a small portion. The mixture was stirred at room temperature for 3 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$, concentrated to about 400 ml, and cooled to 0℃. The mixture was acidified with concentrated HCl and the resulting precipitates were collected by filtration, washed with CH_3OH, and dried to give **11** (170.9 g, 96%). Compound (**11**) recrystallized from CH_3OH was subjected to elemental analysis.

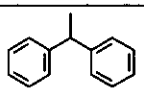
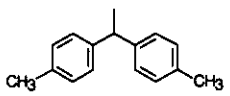
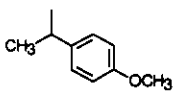
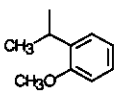
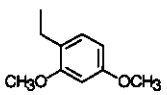
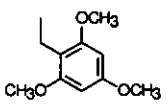
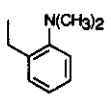
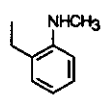
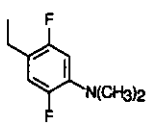
Compounds (**9, 10,** and **12**) were prepared in a manner similar to that described above. Physical and spectral data for the compounds are summarized in Tables 2 and 3.

Nicotinamides 16a-l. Procedure C. 2-[(2-Dimethylanimobenzyl)thio]-(4-pyridyl)nicotinamide (16j). A mixture of **13** (6.0 g, 21 mmol), 4-aminopyridine (2.4 g, 32 mmol, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.8 g, 25 mmol), and CH_2Cl_2 (300 ml) was stirred at room temperature for 3 h, washed with 200 ml of water, and dried. The solvent was removed by distillation *in vacuo*. The residue was chromatographed on silica gel and eluted with $CHCl_3$-CH_3OH (50:1) to give **16j** (7.5 g, 99%) as an oily product. The product was used in the next step without further purification. Compounds (**16f-i, 16k,** and **16l**) were prepared in a manner similar to that described above. Physical and spectral data for the compounds are summarized Tables 4 and 5.

Procedure D. 2-(Benzhydryl)thio-*N*-(4-pyridyl)nicotinamide (16d). Oxalyl chloride (5.0 g, 39 mmol) was added to a stirred suspension of **7** (5.0 g, 16 mmol) in dioxane (400 ml) at room temperature. The resulting mixture was heated at 80℃ for 30 min with stirring. The mixture was concentrated to

Table 2. Ir and ^{1}H-Nmr Spectral Data for the Nicotinic Acids (**7-15**).



Compd	R1	Ir (cm^{-1})	^{1}H-Nmr δ (ppm)
7		1687	6.56 (1H, s), 7.04 (1H, dd, *J* = 4.9, 8.1 Hz), 7.20-7.51 (10H, m), 8.27 (1H, dd, *J* = 2.2, 8.1 Hz), 8.49 (1H, dd, *J* = 2.2, 4.9 Hz).
8		1691	2.23 (6H, s), 6.29 (1H, s), 7.05-7.10 (4H, m), 7.27-7.32 (4H, m), 8.10 (1H, dd, *J* = 2, 7 Hz), 8.39 (1H, dd, *J* = 2, 5 Hz).
9		1680	1.64 (3H, d, *J* = 6.9 Hz), 3.73 (3H, s), 5.12 (1H, q, *J* = 6.9 Hz), 6.84-6.92 (2H, m), 7.22 (1H, dd, *J* = 4.9, 8.2 Hz), 7.34-7.41 (2H, m), 8.18 (1H, dd, *J* = 1.8, 8.2 Hz), 8.64 (1H, dd, *J* = 1.8, 4.9 Hz).
10		1684	1.63 (3H, d, *J* = 6.8 Hz), 3.79 (3H, s), 5.54 (1H, q, *J* = 6.8 Hz), 8.19 (1H, dd, *J* = 1.8, 7.8 Hz), 8.66 (1H, dd, *J* = 1.8, 5.8 Hz)
11		1682	3.75 (3H, s), 3.81 (3H, s), 4.27 (2H, s), 6.46 (1H, dd, *J* = 2.1, 8.2 Hz), 6.57 (1H, d, *J* = 2.1 Hz), 7.23 (1H, dd, *J* = 4.9, 7.9 Hz), 7.27 (1H, d, *J* = 8.2 Hz), 8.20 (1H, dd, *J* = 2.1, 7.9 Hz), 8.66 (1H, dd, *J* = 2.1, 4.9 Hz)
12		1682	3.76 (6H, s), 3.79 (3H, s), 4.22 (2H, s), 6.26 (2H, s), 7.21 (1H, dd, *J* = 4.8, 7.9 Hz), 8.19 (1H, dd, *J* = 1.8, 7.9 Hz), 8.65 (1H, dd, *J* = 1.8, 4.8 Hz)
13		1687	2.67 (6H, s), 4.42 (2H, s), 8.82 (1H, dd, *J* = 3, 8 Hz), 8.67 (1H, dd, *J* = 3, 5 Hz), 13.40 (1H, s).
14		1703	2.72 (3H, s), 4.29 (2H, s), 8.21 (1H, dd, *J* = 2, 7 Hz), 8.69 (1H, dd, *J* = 2, 5 Hz)
15		1687	2.79 (6H, d, 1.0 Hz), 4.29 (2H, s), 6.74 (1H, dd, *J* = 8, 12 Hz), 8.25 (1H, dd, *J* = 2, 7 Hz), 8.69 (1H, dd, *J* = 2, 5 Hz)

dryness *in vacuo*. The residue was dissolved in 300 ml of THF, and then a solution of 4-aminopyridine (1.6 g, 17 mmol) and triethylamine (2.4 g, 24 mmol) in THF (100 ml) was added. The reaction mixturewas stirred at room temperature for 30 min, then ethyl acetate (300 ml) and saturated aqueous $NaHCO_3$ (100 ml) were added. The organic layer was separated, washed with 150 ml of water, and dried. The solvent was removed by distillation *in vacuo*. The residue was chromatographed on silica gel and eluted with $CHCl_3$-CH_3OH (50:1) to give an oily product, which was crystallized from CH_3CN

Table 3. Procedure and Physico-chemical Data for the Nicotinic Acids (**7-15**).

Compd	Procedure	mp (℃) (Recryst. Solvent[a])	Yield (%)	Formula	Ms m/z	Analysis (%) Calcd (Found) C	H	N	S	F
7	A	209−211 (A)	60	$C_{19}H_{15}NO_2S$	321 (M^+)	71.00 (70.82	4.70 4.78	4.36 4.47	9.98 9.83)	
8	A	211−214 (A)	92	$C_{21}H_{19}NO_2S$	350 (MH^+)	72.18 (72.15	5.48 5.40	4.01 4.17	9.18 8.90)	
9	B	167−169 (B)	89	$C_{15}H_{15}NO_3S$	290 (MH^+)	62.26 (62.46	5.23 5.18	4.84 4.77	11.08 10.86)	
10	B	168−170 (C)	97	$C_{15}H_{15}NO_3S \cdot 1/10H_2O$	289 (M^+)	61.88 (61.88	5.26 5.21	4.81 4.73	11.01 10.82)	
11	B	189−192 (C)	96	$C_{15}H_{15}NO_4S$		59.00 (58.79	4.95 5.05	4.59 4.46	10.50 10.20)	
12	B	189−192 (B)	99	$C_{16}H_{17}NO_5S$		57.30 (57.42	5.11 5.18	4.18 4.03	9.56 9.41)	
13	A	141−143 (A)	68	$C_{15}H_{16}N_2O_2S$	268 (M^+)	62.48 (62.20	5.59 5.59	9.71 9.65	11.12 11.04)	
14	A	oil	45	$C_{14}H_{14}N_2O_2S$	274 (M^+)					
15	A	177−178 (A)	78	$C_{15}H_{14}N_2O_2F_2S$	325 (MH^+)	55.55 (55.45	4.35 4.22	8.64 8.65	9.89 9.89	11.71 11.67)

a) Abbreviations for the solvent used as follows: A, CH_3CN; B, CH_3OH-H_2O; C, CH_3OH; D, isopropyl ether; E, toluene; F, Acetone; G, CH_3CN-Acetone; H, $(C_2H_5)_2O$.

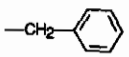
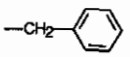
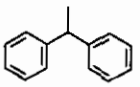
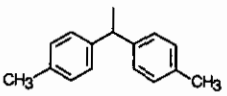
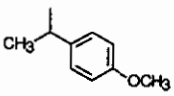
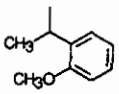
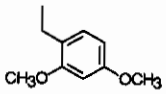
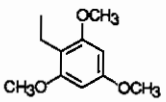
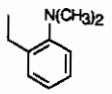
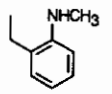
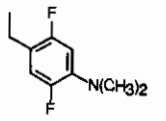
to give **16d** (5.6 g, 42%). Compounds (**16a-c**) and (**16e**) were prepared in a manner similar to that described above. Physical and spectral data for the compounds are summarized in Tables 4 and 5.

2-[(2,4-Dimethoxybenzyl)sulfinyl]-*N*-(4-pyridyl)nicotinamide (17h). To a stirred solution of **16h** (6.4 g, 16.8 mmol) in CH_2Cl_2 (200 ml) was added dropwise 80% *m*CPBA (4.1 g, 19.0 mmol) in CH_2Cl_2 (50 ml) at 0℃. The resulting mixture was stirred at same temperature for 3 min, washed with saturated aqueous $NaHCO_3$ (20 ml), and dried. The solvent was removed by distillation *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$-CH_3OH (30:1) as the eluent, and recrystallized from CH_3CN to give **17h** (4.5 g, 68%).

Compounds (**17a-g**) and (**17i-l**) were obtained by a procedure similar to that described for **17h**. Physical and spectral data for the compounds are summarized in Tables 6 and 7.

2-[(4,4'-Dimethylbenzhydryl)thio]benzoic Acid. This compound was prepared from thiosalicylic

Table 4. Ir and ^{1}H-Nmr Spectral Data for the Nicotinamides (**16a-l**).

Compd	R1	R	Ir (cm^{-1})	^{1}H-Nmr δ (ppm)
16a		isobutyl	1687	0.89 (6H, d, *J* = 6.9 Hz), 1.68-1.89 (1H, m), 3.02 (2H, dd, *J* = 5.2, 6.9 Hz), 7.75 (1H, dd, *J* = 2.0, 8.0 Hz), 8.47 (1H, t, *J* = 5.2 Hz), 8.53 (1H, *J* = 2.0, 4.8 Hz)
16b	isopropyl	isobutyl	1687	1.01 (6H, d, *J* = 6.5 Hz), 1.40 (6H, d, *J* = 6.9 Hz), 1.83-2.04 (1H, m), 3.30 (2H, dd, *J* = 6.0, 7.0 Hz), 4.05-4.26 (1H, m), 7.05 (1H, dd, *J* = 5.0, 7.0 Hz), 7.87 (1H, *J* = 2.0, 7.0 Hz)
16c			1655	7.21-7.42 (5H, m), 7.63 (2H, m), 7.95 (1H, dd, *J* = 2.0, 8.1 Hz), 8.40 (2H, m), 8.64 (1H, dd, *J* = 2.0, 4.5 Hz)
16d			1635	6.41 (1H, s), 7.20-7.47 (10H, m), 7.69 (2H, m), 7.89 (1H, dd, *J* = 2.2, 7.9 Hz)
16e			1687	2.30 (6H, s), 6.52 (1H, s), 7.30-7.35 (4H, m), 7.59 (2H, m), 7.92 (1H, dd, *J* = 2.0, 7.9 Hz)
16f			1684	1.64 (3H, d, *J* = 6.2 Hz), 3.71 (3H, s), 5.14 (1H, q, *J* = 6.2 Hz), 6.86 (2H, m), 7.27 (1H, dd, *J* = 5.0, 7.8 Hz), 7.35 (2H, m), 7.65 (2H, m), 7.93 (1H, dd, *J* = 1.9, 7.8 Hz), 8.47 (2H, m), 8.62 (1H, dd, *J* = 1.9, 5.0 Hz), 10.79 (1H, s).
16g			1684	1.63 (3H, d, *J* = 6.7 Hz), 3.79 (3H, s), 5.56 (1H, q, *J* = 6.7 Hz), 6.88-7.02 (2H, m), 7.27 (1H, dd, *J* = 5.2, 7.5 Hz), 7.66 (2H, m), 7.94 (1H, dd, *J* = 1.9, 7.5 Hz), 8.47 (2H, m), 8.64 (1H, dd, *J* = 1.9, 5.2 Hz), 10.81 (1H, s).
16h			1665	3.72 (3H, s), 3.77 (3H, s), 4.32 (2H, s), 6.46 (1H, dd, *J* = 2.6, 8.4 Hz), 6.54 (1H, d, *J* = 2.6 Hz,), 7.25 (1H, d, *J* = 8.4 Hz), 7.28 (1H, dd, *J* = 4.9, 7.7 Hz), 7.66 (2H, m), 7.96 (1H, dd, *J* = 1.9, 7.7 Hz), 8.47 (2H, m), 8.64 (1H, dd, *J* = 1.9, 4.9 Hz), 10.79 (1H, s).
16i			1682	3.75 (6H, s), 3.78 (3H, s), 4.32 (2H, s), 6.23 (2H, s), 7.26 (1H, dd, *J* = 4.8, 7.8 Hz), 7.64 (2H, m), 7.94 (1H, dd, *J* = 1.8, 7.8 Hz), 8.46 (2H, m), 8.63 (1H, dd, *J* = 1.8, 4.8 Hz), 10.79 (1H, s).
16j			1683	2.64 (6H, s), 4.53 (2H, s), 7.31 (1H, dd, *J* = 4.5, 7.5 Hz), 7.69 (2H, m), 8.01 (1H, dd, *J* = 2.0, 7.5 Hz), 8.45 (2H, m), 8.66 (1H, dd, *J* = 2.0, 4.5 Hz), 11.28 (1H, s)
16k			1681	2.74 (3H, d, *J* = 5.0 Hz), 4.38 (2H, s), 5.48 (1H, q, *J* = 5.0), 7.30 (1H, dd, *J* = 5.1, 7.0 Hz), 7.65 (2H, m), 7.97 (1H, dd, *J* = 2.5, 7.0 Hz), 8.47 (2H, m), 8.67 (1H, dd, *J* = 2.5, 5.1 Hz), 10.81 (1H, s)
16l			1686	2.77 (6H, d, 1.2 Hz), 4.35 (2H, s), 6.72 (1H, dd, *J* = 8.0, 12.0 Hz), 7.21 (1H, dd, *J* = 8.0, 13.0 Hz), 7.32 (1H, dd, *J* = 5.0, 7.0 Hz), 7.65 (2H, m), 8.02 (1H, dd, *J* = 2.0, 7.0 Hz), 8.50 (1H, dd, *J* = 2.0, 5.0 Hz), 10.90 (1H, s)

acid by procedure A. Yield: 81%. mp 211−212℃ (CH_3CN). ^{1}H-Nmr δ: 2.25 (6H, s), 5.89 (1H, s), 7.12 (4H, m), 7.81-7.86 (1H, m), 13.07 (1H, s). Ir (KBr): 1680 cm^{-1} (C=O). Ms m/z: 349

Table 5. Physico-chemical Data for the Nicotinamides (**16a-l**).

Compd	Procedure	mp (℃) (Recryst. Solvent[a])	Yield (%)	Formula	Ms m/z	Analysis (%) Calcd (Found)				
						C	H	N	S	F
16a	D	102−103 (D)	66	$C_{17}H_{20}N_2OS$	301 (MH^+)	67.97 (67.85	6.71 6.69	9.32 9.28	10.67 10.58)	
16b	D	oil	82	$C_{13}H_{20}N_2OS$	253 (M^+)					
16c	D	124−125 (A)	85	$C_{18}H_{15}N_3OS \cdot 1/4H_2O$	322 (MH^+)	66.34 (66.43	4.79 4.69	12.89 13.02	9.84 9.76)	
16d	D	175−178 (A)	42	$C_{24}H_{19}N_3O_2S \cdot 1/4H_2O$	401 (MH^+)	68.96 (69.20	4.70 4.63	10.05 10.03	7.67 7.86)	
16e	D	206−209 (A)	48	$C_{26}H_{23}N_3OS$	426 (MH^+)	73.38 (73.22	5.45 5.36	9.87 9.89	7.54 7.38)	
16f	C	61−63 (E)	60	$C_{20}H_{19}N_3O_2S$	366 (MH^+)	65.73 (65.95	5.24 5.29	11.50 11.14	8.77 8.39)	
16g	C	oil	76	$C_{20}H_{19}N_3O_2S$	366 (MH^+)					
16h	C	166−167 (C)	52	$C_{20}H_{19}N_3O_3S$	382 (MH^+)	59.00 (58.79	4.95 5.05	4.59 4.46	10.50 10.20)	
16i	C	210−212 (G)	64	$C_{21}H_{21}N_3O_4S$	412 (MH^+)	61.30 (61.35	5.14 5.08	10.21 10.34	7.79 7.54)	
16j	C	oil	99	$C_{20}H_{20}N_4OS$	364 (M^+)					
16k	C	oil	50	$C_{19}H_{18}N_4OS$	351 (MH^+)					
16l	C	170−171 (A)	72	$C_{20}H_{18}N_4OF_2S$	401 (MH^+)	59.99 (59.94	4.53 4.55	13.99 14.11	8.01 7.72	9.12 9.08)

a) See footnote a) in Table 3.

(MH^+). *Anal.* Calcd for $C_{22}H_{20}O_2S$: C, 75.83; H,5.79; S, 9.20. Found: C, 75.85; H, 5.77; S; 9.05.

4,4'-Dimethylbenzhydryl *o*-[*N*-(4-Pyridyl)carbamoyl]phenyl Sulfide. This compound was prepared starting from 2-[(4,4'-dimethylbenzhydryl)thio]benzoic acid by procedure D. Yield: 57%. mp: 227−229℃ (acetone). ^{1}H-Nmr δ: 2.22 (6H, s), 5.88 (1H, s), 7.08 (4H, d, J = 7.9 Hz), 7.30 (4H, d, J = 7.9 Hz), 7.71 (2H, m), 8.48 (2H, m), 10.76 (1H, s). Ir (KBr): 1688 cm^{-1} (C=O). Ms m/z: 425(MH^+). *Anal.* Calcd for $C_{27}H_{24}N_2OS$: C, 76.38; H, 5.70; N, 6.60; S, 7.55. Found: C, 76.34; H, 5.66; N; 6.62, S; 7.44.

Table 6. Ir and ^{1}H-Nmr Spectral Data for the Nicotinamides (**17a-l**).

Compd	Ir (cm^{-1})	^{1}H-Nmr δ (ppm)
17a	1689 1047	0.98 (6H, d, *J* = 6.7 Hz), 1.75-1.95 (1H, m), 3.11 (2H, m), 4.02 (1H, d , *J* = 13.0 Hz), 4.44 (1H, d, *J* = 13.0 Hz), 7.26-7.38 (5H, m), 7.67 (1H, dd, *J* = 5.0, 7.0 Hz), 8.13 (1H, dd, *J* = 2.1, 7.0 Hz), 8.84 (1H, dd, *J* = 2.1, 5.0 Hz)
17b	1641 1045	1.00 (6H, d, *J* = 7.0 Hz), 1.29 (6H, d, *J* = 7.0 Hz), 1.83-2.05 (1H, m), 3.28 (2H, dd, *J* = 6.0, 7.0 Hz), 3.49-3.63 (1H, m), 7.48 (1H, dd, *J* = 4.9, 8.2 Hz), 7.90 (1H, br, t), 8.21 (1H, dd, *J* = 2.2, 8.2 Hz), 8.75 (1H, dd, *J* = 2.2, 4.9 Hz)
17c	1672 1035	4.20 (1H, d, *J* = 12.9 Hz), 4.48 (1H, d, *J* = 12.9 Hz), 7.26-7.37 (5H, m), 7.70 (2H, m), 7.76 (1H, dd, *J* = 4.9, 8.5 Hz). 8.31 (1H, dd, *J* = 2.2, 8.5 Hz), 8.53 (2H, m), 8.90 (1H, dd, *J* = 2.2, 4.9 Hz), 11.02 (1H, s)
17d	1665 1041	6.41 (1H, s), 7.22-7.44 (10H, m), 7.62 (1H, dd, *J* = 5.1, 8.0 Hz), 7.64 (2H, m), 8.12 (1H, dd, *J* = 2.0, 8.0 Hz), 8.52 (2H, m), 8.69 (1H, dd, *J* = 2.0, 5.1 Hz)
17e	1680 1045	2.20 (3H, s), 2.26 (3H, s), 5.71 (1H, s), 6.29-6.99 (8H, m), 8.11 (1H, dd, *J* = 1.9, 7.9 Hz), 8.52 (2H, m), 8.72 (1H, dd, *J* = 1.9, 4.9 Hz)
17f	1682 1020	1.40 (3H, d, *J* = 7.1), 3.72 (3H, s), 4.54 (1H, q, *J* = 7.1 Hz), 6.82-6.90 (2H, m), 7.16-7.21 (2H, m), 7.64 (2H, m), 7.70 (1H, dd, *J* = 4.6, 7.7 Hz), 8.20 (1H, dd, *J* = 1.8, 7.7 Hz), 8.50 (2H, m), 8.86 (1H, dd, *J* = 1.8, 4.6 Hz), 10.86 (1H, s)
17g	1674 1040	1.36 (3H, d, *J* = 7.2), 3.63 (3H, s), 4.95 (1H, q, *J* = 7.2 Hz), 6.84-6.97 (2H, m), 7.20-7.31 (2H, m), 7.61 (2H, m), 7.67 (1H, dd, *J* = 4.7, 7.5 Hz), 8.11 (1H, dd, *J* = 1.9, 7.5 Hz), 8.48 (2H, m), 8.83 (1H, dd, *J* = 1.9, 4.7 Hz), 10.79 (1H, s)
17h	1684 1040	3.60 (3H, s), 3.73 (3H,s), 4.18 (1H, d, *J* = 12.4 Hz), 4.38 (1H, d, *J* = 12.4 Hz), 6.44 (1H, dd, J = 2.3, 8.2 Hz), 6.50 (1H, d, *J* = 2.3 Hz), 6.99 (1H, d, *J* = 8.2 Hz), 7.66 (2H, m), 7.71 (1H, dd, *J* = 4.5, 7.8 Hz), 8.22 (1H, dd, *J* = 1.8, 7.8 Hz), 8.51 (2H, m), 8.85 (1H, dd, *J* = 1.8, 4.5 Hz), 10.94 (1H, s)
17i	1690 1032	3.49 (6H, s), 3.72 (3H, s), 4.18 (1H, d, *J* = 11.8 Hz), 4.38 (1H, d, *J* = 11.8 Hz), 6.09 (2H, s), 7.60 (2H, m), 7.67 (1H, dd, *J* = 4.9, 7.9 Hz), 8.13 (1H, dd, *J* = 1.8, 7.9 Hz), 8.49 (2H, m), 8.82 (1H, dd, *J* = 1.8, 4.9 Hz), 10.78 (1H, s)
17j	1676 1036	2.57 (3H, s), 2.60 (3H, s), 4.37 (1H, d, *J* = 12.5 Hz), 4.54 (1H, d, *J* = 12.5 Hz), 7.00-7.33 (4H, m), 8.29 (1H, dd, *J* = 2.0, 7.0 Hz), 8.55 (2H, m), 8.90 (1H, dd, *J* = 2.0, 5.0 Hz)
17k	1676 1030	2.76 (3H, d, *J* = 4.9 Hz), 4.18 (1H, d, *J* =13.0 Hz), 4.36 (1H, d, *J* = 13.0 Hz), 5.59 (1H, q, *J* = 4.9 Hz), 7.71 (2H, m), 7.77 (1H, dd, *J* = 4.9, 7.9 Hz), 8.35 (1H, *J* = 1.8, 7.9 Hz), 8.61 (2H, m), 8.92 (1H, dd, *J* =1.8, 4.9 Hz)
17l	1672 1036	2.79 (6H, d, 1.3 Hz), 4.23 (1H, d, *J* = 13.0 Hz), 4.41 (1H, d, *J* = 13.0 Hz), 6.68 (H, dd, *J* = 8.0, 12.0 Hz), 6.96 (1H, dd, *J* = 7.0, 13.0 Hz). 7.67 (2H, m), 7.75 (1H, dd, *J* = 5.0, 8.0 Hz), 8.31 (1H, dd, *J* = 2.0, 8.0 Hz), 8.52 (2H, m), 8.86 (1H, dd, *J* = 2.0, 5.0 Hz)

4,4'-Dimethylbenzhydryl *o*-[*N*-(4-Pyridyl)carbamoyl]phenyl Sulfoxide (19). This compound was prepared in a manner similar to that described for **17h**. Yield: 58%. mp 162−164℃ (CH_3CN). ^{1}H-Nmr δ: 2.25 (3H, s), 2.30 (3H, s), 5.51 (1H, s), 6.86 (2H, d, *J* = 8.1 Hz), 7.01 (2H, d, *J* = 8.1 Hz), 7.09 (1H, dd, *J* = 1.4, 7.6 Hz), 7.22 (2H, d, *J* = 7.9 Hz), 7.63 (1H, ddd, *J* = 1.4, 7.3, 7.3 Hz), 7.76 (2H, m), 8.01 (1H, dd, *J* = 1.3, 7.3 Hz), 8.52 (2H, m), 10.93 (1H, s). Ir (KBr): 1685 cm^{-1} (C=O). Ms m/z: 425 (MH^+). *Anal.* Calcd for $C_{27}H_{24}N_2O_2S \cdot 1/10H_2O$: C, 73.31; H, 5.51; N, 6.33; S, 7.25. Found: C, 73.20; H, 5.47; N; 6.33, S; 7.16.

Table 7. Physico-chemical Data for the Nicotinamides (**17a-l**).

Compd	mp (℃) (Recryst. Solvent[a])	Yield (%)	Formula	Ms m/z	Analysis (%) Calcd (Found) C	H	N	S	F
17a	158−161 (A)	51	$C_{17}H_{20}N_2O_2S$	317 (MH^+)	64.53 (64.54	6.37 6.36	8.85 8.84	11.65 10.16)	
17b	129−131 (D)	91	$C_{13}H_{20}N_2O_2S$	269 (MH^+)	58.18 (58.09	7.63 7.63	10.44 10.40	11.95 12.11)	
17c	217−219 (A)	46	$C_{18}H_{15}N_3O_2S$	338 (MH^+)	64.08 (63.89	4.48 4.46	12.45 12.41	9.50 9.51)	
17d	175−178 (C)	54	$C_{24}H_{19}N_3O_2S \cdot 1/4H_2O$	413 (MH^+)	68.96 (69.20	4.70 4.63	10.05 10.03	7.67 7.86)	
17e	159−163 (A)	48	$C_{26}H_{23}N_3O_2S$	442 (MH^+)	70.72 (70.54	5.25 5.23	9.52 9.45	7.26 7.04)	
17f b)	240−243 (H)	28	$C_{20}H_{19}N_3O_3S$	382 (MH^+)	62.97 (62.66	5.02 5.12	11.02 10.62	8.41 8.20)	
17g c)	219−221 (A)	17	$C_{20}H_{19}N_3O_3S$	382 (MH^+)	62.97 (62.70	5.02 5.04	11.02 11.28	8.41 8.11)	
17h	190−192 (A)	73	$C_{20}H_{19}N_3O_4S$	398 (MH^+)	60.44 (60.29	4.82 4.74	10.57 10.83	8.07 7.90)	
17i	182−185 (A)	48	$C_{21}H_{21}N_3O_5S$	428 (MH^+)	59.00 (58.88	4.95 4.89	9.83 10.03	7.50 7.45)	
17j	162−166 (A)	42	$C_{20}H_{20}N_4O_2S \cdot 1/4H_2O$	381 (MH^+)	62.40 (62.24	5.37 5.11	14.55 14.29	8.33 8.03)	
17k	154−156 (A)	17	$C_{19}H_{17}N_4O_2S \cdot 1/4H_2O$	367 (MH^+)	61.69 (61.55	4.77 4.91	15.15 15.00	8.67 8.88)	
17l	176−178 (A)	18	$C_{20}H_{18}N_4O_2F_2S$	417 (MH^+)	57.68 (57.72	4.36 4.35	13.45 13.29	7.70 7.54	9.12 9.08)

a) See footnote a) in Table 3. b) The more polar isomer of the diastereomeric mixture. c) The less polar isomer of the diastereomeric mixture.

General Procedure to Prepare the Isothiazolones (1, 18, and 20) in Acidic Conditions. *N*-(4-Pyridyl)-2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridine (18). To a stirred solution of **17e** (500 mg, 1.13 mmol) in CH_3OH (190 ml) was added 10 ml of 2N HCl at room temperature. The resulting mixture was stirred at room temperature for 5 min, then $CHCl_3$ (400 ml) and saturated aqueous $NaHCO_3$ (100 ml) were added. The organic layer was separated, washed with 100 ml of water, and dried. The solvent was removed by distillation *in vacuo*. The residue was chromatographed on silica gel and eluted with $CHCl_3$-CH_3OH (50:1) to give **18** (229 mg, 85%). Compound (**18**) recrystallized from $CHCl_3$- CH_3OH was subjected to elemental analysis. mp 238-240℃. ^{1}H-Nmr δ: 7.63 (1H, dd, J = 5, 7 Hz), 8.06 (2H, m), 8.45 (1H, dd, J = 2, 7 Hz), 8.74 (2H, m), 8.97 (1H, dd, J = 2, 5 Hz). Ms

m/z: 230 (MH^+). Ir (KBr): 1680 cm^{-1} (C=O). *Anal.* Calcd for $C_{11}H_7N_3OS$: C, 57.63; H, 3.08; N, 18.33; S, 13.99. Found: C, 57.63; H, 2.91; N, 18.30; S; 14.06.

Compounds (**1** and **20**) were prepared from **17a,b** and **19,** respectively, in a manner similar to that described for **18**. The yields are given in Table 1. Compounds (**1** and **20**) recrystallized from hexane and acetonitrile, respectively, were subjected to elemental analyses.

***N*-Isobutyl-2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridines (1).** mp: 79−81℃. ^{1}H-Nmr δ: 1.01 (6H, d, J = 7 Hz), 2.16 (1H, m), 3.75 (2H, d, J = 7 Hz), 7.40 (1H, dd, J = 5, 7 Hz), 8.30 (1H, dd, J = 2, 7 Hz), 8.78 (1H, dd, J = 2, 5 Hz). Ms m/z: 208(M^+). Ir (KBr): 1679 cm^{-1} (C=O). *Anal.* Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45; S, 15.39. Found: C, 57.64; H, 5.63; N, 13.42; S; 15.50.

2-(4-Pyridyl)-1,2-benzisothiazol-3(2*H*)-one (20). Yield: 94%. mp: 179−180℃ (lit.,[15] 181−182℃).

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