The Synthesis of Hexahydrooxoepithiopyridinedicarboximides by the Reaction of Thioamides with *N*-substituted Maleimides

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The synthesis of hexahydrooxoepithiopyridinedicarboxyimide (**5**: X_2 = *N*-Ph) by the reaction of thioamides **1** with *N*-substituted maleimide (**2a**) was examined. The reaction of primary thioamides, such as thiobenzamide and *p*-toluthioamide with *N*-phenylmaleimide gives compounds **5** together with corresponding 4-hydroxy-1,3-thiazoles **4**. However, a similar reaction of secondary thioamides, such as *N*-methylthioacetamide, thiobenzanilide, with *N*-phenylmaleimide did not provide compounds **5** without addition of acid. The reaction pathway and the configuration of **5** were also investigated.

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Tricyclic compounds **5**, such as hexahydrooxoepithiopyridinemaleic acid anhydride and hexahydrooxoepithiopyridinecarboxyimide, are synthesized by the reaction of a mesoionic compound of anhydro-4-hydroxythiazolium hydroxide **3** with an electron-deficient olefin such as maleic acid anhydride or maleimide [1]. Compounds **5** have two stereoisomers of endo and exo conformations. Mesoionic compounds **3** are prepared from the reaction of α-bromoacylchloride, which is a 1,2-bielectrophile, with secondary thioamide as a 1,3-binucleophile [2], or the reaction of *gem*-dicyanoepoxide with a thioamide in the presence of triethylamine [3].

In a previous paper [4], we reported that the direct synthesis of hexahydrooxoepithiopyridinemaleic acid anhydride, one of the compounds **5**, by reaction of maleic acid anhydride with a thioamide. It is characteristic of this reaction that the reaction products are different depending upon the type of thioamide. Thus, the reaction of a primary thioamide with maleic acid anhydride gives only a hydroxythiazole **4**, and a compound **5** is obtained by the reaction of a secondary thioamide.

In this paper, we wish to report the results of an investigation on the reactions of maleimide instead of maleic acid anhydride with thioamides. The configuration of compounds **5** was determined by X-ray structural analysis, described herein.

Reaction of Primary Thioamide with *N*-substituted Maleimides.

The reaction of thiobenzamide (**1a**) with *N*-phenylmaleimide(**2a**: X = *N*-Ph) in dioxane at reflux temperature for 1 hour gave 4-hydroxy-2-phenyl-5-(*N*-phenylcarbamoylmethyl)-1,3-thiazole (**4a**: R^1 = H, R^2 = Ph, X^1 = *N*-Ph) in addition to 1,2,3,4,5,6-hexahydro-3-oxo-*N*,1-diphenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboximide (**5a**: R^1 = H, R^2 = Ph, $X^1 = X^2$ = *N*-Ph).

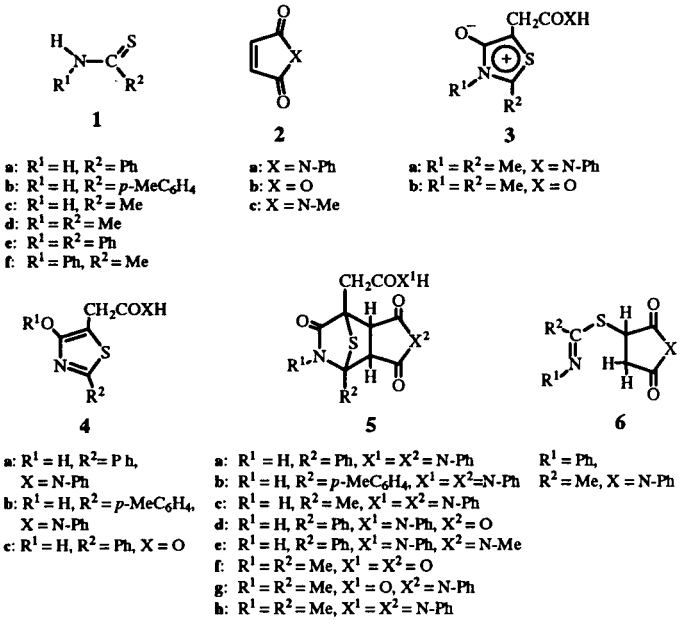


Figure 1

A similar reaction of *p*-toluthioamide (**1b**) with **2a** afforded 4-hydroxy-5-(*N*-phenylcarbamoylmethyl)-2-*p*-tolyl-1,3-thiazole (**4b**: R^1 = H, R^2 = *p*-$CH_3C_6H_4$-, X^1 = *N*-Ph) and 1,2,3,4,5,6-hexahydro-3-oxo-*N*-phenyl-4-(*N*-phenylcarbamoylmethyl)-1-*p*-tolyl-1,4-epithiopyridine-5,6-dicarboximide (**5b**: R^1 = H, R^2 = *p*-$CH_3C_6H_4$-, $X^1 = X^2$ = *N*- Ph).

On the other hand, the reaction of thioacetamide (**1c**) with **2a** gave only 1,2,3,4,5,6-hexahydro-1-methyl-3-oxo-*N*-phenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboximide (**5c**: R^1 = H, R^2 = Me, $X^1 = X^2$ = *N*-Ph), but not the compound of type **4**.

In the reactions of **1a** and **1b**, the yields of products **4** and **5** varied according to the molar ratio of starting materials.

The yield of **5** increases with an increasing molar ratio from **1** to **2**. In the case of the reaction of equimolar amount of **1a** with **2a** for 1 hour, the yields of **4a** and **5a** were 49% and 29%, respectively. In the reaction of two equimolar amount of **2a**, the yield of **5a** increased to 71% and the yield of **4a** decreased to only 5%.

The yield of **5** is also affected by the reaction time. The prolonged reaction time leads to an increase of **5a** with a decrease of **4a**. For an example, when the reaction time was extended to 3 hours, the yield of **4a** decreased to 39% and that of **5a** increased to 41%, while the yield of **4a** was 64% and that of **5a** was 17%, when the reaction time was shortened to half an hour. (Table 1)

Table 1

Reaction of Primary Thioamides with *N*-Phenylmareimide (**2a**) [a]

1	2	Molar ratio 1/2	Reaction time (hours)	Product (%) [b] 4	5
a	a	1/1	0.5	a 64	a 17
		1/1	1	49	29
		1/1	3	39	41
		1/2	1	5	71
		2/1	1	62	12
b	a	1/1	1	b 67	b 11
		1/2	1	56	23
c	a	1/1	1	–	c 47
		1/2	1	–	62

[a] Solvent: dioxane, reaction temperature: reflux temperature. [b] Yield based on **2**.

These results suggest that this reaction proceeds *via* a mesoionic intermediate (**3**) as shown in Scheme 1. It is considered that **3** is transformed into compound **4** by the intramolecular transfer of an amino proton onto a carbonyl oxygen, and compound **5** is formed by the cycloaddition of **3** with the electron-deficient olefin **2**.

dicarboxylic acid anhydride (**5d**: 9% yield) or 1,2,3,4,5,6-hexahydro-*N*-methyl-3-oxo-1-phenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboximide (**5e**: 15% yield), respectively.

These results suggest that compound **5** is formed not only by the cycloaddition of the mesoionic intermediate (**3a**: $R^1 = R^2 = Me$, X = *N*-Ph) with **2** but also the reaction of **4a** with **2**.

However, hydroxythiazole **4c**, which was obtained by the reaction of **1a** with **2b**, failed to react with **2a** and **2b**, and starting material **4c** was recovered quantitatively. It is also known that **3** reacts with **2a** and **2b** to form compounds **5** [1]. It is concluded from these results that the reaction of **4a** with **2** does not afford directly compound **5**, but an equilibrium reaction occurs between **4a** and the mesoionic intermediates **3**, which reacts with **2** to form **5**. These result suggests that the reverse reaction from **4c** to **3** dose not occur.

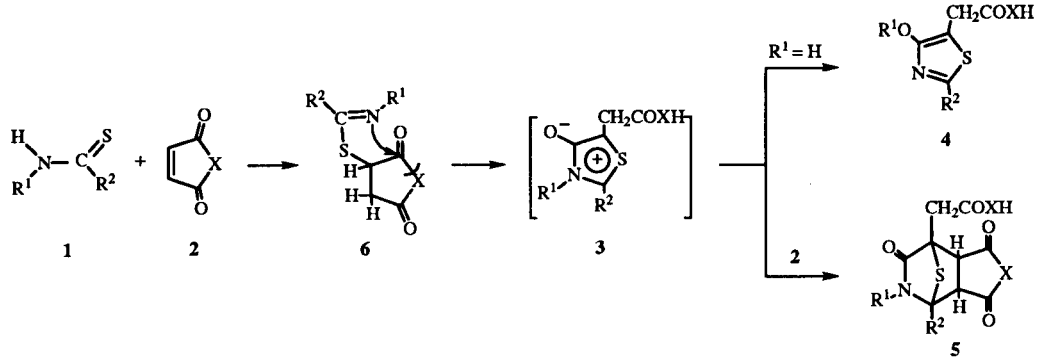
Reaction of Secondary Thioamides with *N*-substituted Maleimides.

The reaction of thioacetanilide (**1f**), a secondary thioamide, with **2a** yielded 3-(*N*-phenylacetimidoylthio)-*N*-phenylsuccinimide (**6**) in a yield of 40%. This reaction is supposed to proceed as shown in Scheme 1. The nucleophilic attack of sulfur atom of thioamide **1** with an olefinic carbon of **2** affords compound **6**, and then the intramolecular cyclization of an imine nitrogen with a carbonyl carbon of compounds **6** affords an imide ring, which cleaves to give the mesoionic intermediate **3**.

The compound **4** is formed by the intramolecular rearrangement of the amino proton to the oxygen atom of intermediate **3**, and product **5** is formed by the 1,3-dipolar cycloaddition of intermediate **3** with **2**.

The reaction of secondary thioamides **1d, 1e** with **2a** in dioxane at reflux temperature for 3 hours did not proceed, and the thioamides were recovered nearly quantitatively.

Scheme 1. Plausible Pathway for the Reaction of a Thioamide with an Electron-deficient Olefin



The equimolar reaction of hydroxythiazole **4a** with **2a**, maleic anhydride (**2b**) or *N*-methylmaleimide (**2c**) yielded **5a** (31% yield), 1,2,3,4,5,6-hexahydro-3-oxo-1-phenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-

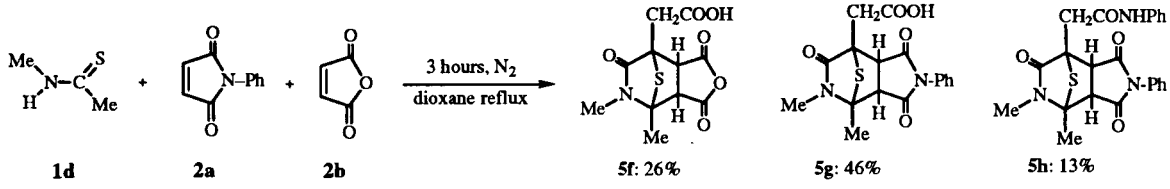
Even when the reaction time is extended from 3 hours to 8 hours, no reaction took place. On the other hand, the reaction of secondary thioamides **1d, 1e** with **2b** yielded compounds **5** quantitatively [4].

Interestingly, the reaction of **1d** with **2a** in the presence of **2b** proceeded to give 4-(carboxymethyl)-1,2,3,4,5,6-hexahydro-1,2-dimethyl-3-oxo-1,4-epithiopyrdine-5,6-dicarboxylic acid anhydride (**5f**) and 4-(carboxymethyl)-1,2,3,4,5,6-hexahydro-1,2-dimethyl-3-oxo-*N*-phenyl-1,4-epithiopyridine-5,6-dicarboximide (**5g**) together with an unexpected product, 1,2,3,4,5,6-hexahydro-1,2-dimethyl-3-oxo-*N*-phenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboximide (**5h**), which was not obtained by the reaction of **1d** with **2a** in the absence of **2b**; the yields of these products are 26%, 46% and 13%, respectively. (Scheme 2)

When an equimolar amount of succinic acid anhydride or furan instead of **2b** was added, the reaction did not take place and the starting materials were recovered quantitatively. On the other hand, an equimolar amount of benzoic acid, fumaric acid or maleic acid was added instead of **2b**, the reaction was promoted to afford **5h** in 10%, 51% or 86% yields. Furthermore, sulfuric acid is most effective; the addition of 0.1 *M* sulfuric acid gives **5h** in the yield of 57%. These results show clearly that the addition of an acid promotes the reaction of **1d** with **2a**.

Consequently, it is supposed that, in the competition reaction of **1d** with **2a** and **2b** mentioned above, preferential formation of mesoionic intermediate **3b, 5f** and **5g**, which have a carboxyl group, promote the reaction to give **5h**. Actually, the reaction of **1d** with **2a** with an added equimolar amount of **5f** gave **5h** in 12% yield.

Scheme 2. Competition Reaction of *N*-Methylthioacetamide with *N*-Phenylmaleimide and Maleic Acid Anhydride



1d **2a** **2b** **5f**: 26% **5g**: 46% **5h**: 13%

It is suggested that **5f** and **5g** are formed by the reactions of **2b** and **2a** with a mesoionic intermediate **3b** ($R^1 = R^2 =$ Me, X = O), which is formed by the reaction of **1d** with **2b**, respectively, and the reaction of **2a** with the mesoionic intermediate **3a** ($R^1 = R^2 =$ Me, X = *N*-Ph), which is obtained from the reaction of **1d** with **2a**, yielding compound **5h**.

The difference in the reactivity of **1d** with **2a** and **2b** was examined by comparison of the yields of the corresponding products of type **5**. The sum of yields of **5f** and **5g** exceeds the yield of **5h**, and this result shows that the reaction of **1d** with **2b** proceeds faster than that of **1d** with **2a** to form the mesoionic intermediate **3b**. On the other hand, the sum of yields of **5g** and **5h** exceeds the yield of **5f**, and compound **5i** ($R^1 = R^2 =$ Me, $X^1 =$ *N*-Ph, X^2 = O) is not formed; this result suggests that the cycloaddition of the mesoionic intermediate **3** proceeds more preferentially with **2a** over **2b** to form compounds **5**.

The formation of **5h** in the competition reaction mentioned above suggests that the addition of **2b** promotes the reaction of **1d** with **2a**. Then, the effect of additives other than **2b** on the reaction of **1d** with **2a** was examined.

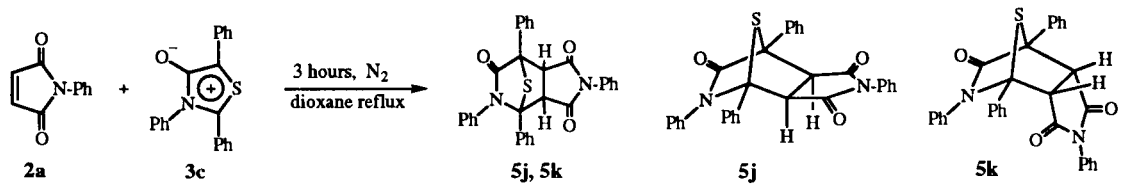
The reaction of the mesoionic compound **3**, which was prepared separately by a different method, with **2a** or **2b** yields compounds of type **5** in the absence of an added acid and consequently it is supposed that the addition of acid affects the formation step of the mesoionic intermediate **3** rather than the formation step of **5** by cycloaddition, although a detailed mechanism is not yet clear.

The difference in the reactivity of **1d** with **2a** and **2b** is presumed to be the difference in stability of the mesoionic intermediate **3**.

Compound **5** has two configurational isomers the endo and exo forms. The reaction of **2a** with the mesoionic compound **3c**, which was prepared by the reaction of **1e** with α-chlorophenylacetyl chloride [1], afforded products of type **5**, (**5j** and **5k**) in 94% yield (Scheme 3).

Products, **5j** and **5k**, possess the same molecular weight (M^+502) in the mass spectra, but the coupling constants of hydrogen atoms at the 5 and 6 position have different values,

Scheme 3. Products from the Reaction of *N*-Phenylmareimide(**2a**) with Mesoionic Compound **3c**



2a **3c** **5j, 5k** **5j** **5k**

6.6 Hz and 8.8 Hz, in ^{1}H-nmr spectra. The coupling constants of these two hydrogen atoms show good correlation with those of norbornane; that is, the coupling constants are 9-10 Hz for the endo proton and 6-7 Hz for the exo proton [5]. From these data, **5j** and **5k** are tentatively assigned as the endo and exo stereoisomers, respectively.

On the other hand, the type **5** compounds prepared by the present method show only the coupling constant of 6.6-6.9 Hz for 5- and 6-position hydrogen atoms in the nmr spectra. This shows that products **5** obtained by the present method have the exo configuration.

Table 2

Crystal and Refinement Data for **5c**

formula	$C_{22}H_{19}N_3O_4S\ C_3H_7NO$
formula weight	494.6
crystal system	monoclinic
space group	$P2_12_12_1$
a,Å	15.991(2)
b,Å	25.458(4)
c,Å	6.0858(8)
V,Å^3	2477.5(6)
Z	4
F(000)	1040
density (calc.), g/cm^3	1.33
crystal size, mm	0.6 x 0.1 x 0.1
μ, absorption coef., mm^{-1}	14.82
2Theta (max) deg.	128
index ranges	$0 \le h \le 18, 0 \le k \le 29, 0 \le l \le 7$
reflection collected	2486
independent reflections	2339
observed reflection	
[$I > 2.0\ \sigma(\pm)(I)$]	2279
parameters refined	403
S [a]	1.316
final *R* indices [b]	$R = 0.034$, $wR = 0.040$
larger diff. peak and hole, eA^{-3}	0.19 and -0.21

[a]: $S = [\Sigma(w(|F_o|-|F_c|)^2)/(\text{No. of reflections - No. of parameters})]^{1/2}$. [b]: $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR = [\Sigma(w(|F_o|-|F_c|)^2)/\Sigma(w|F_o|^2]^{1/2}$, where $w=1/[\sigma^2(F_o) + 0.0005*F_o**2]$.

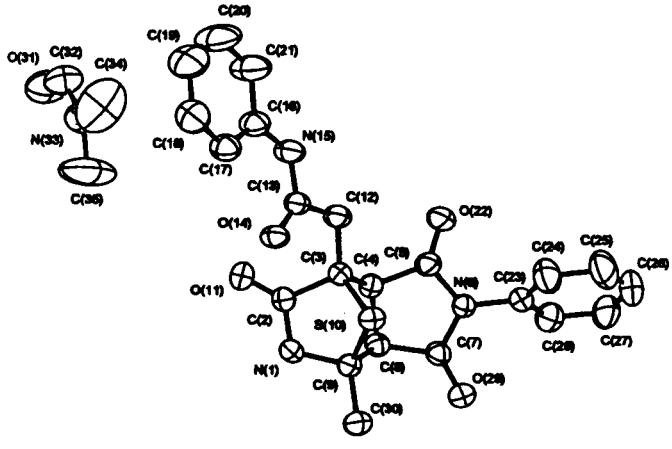


Figure 2. An ORTEP Diagram of **5c**.

In order to confirm this assignment, we tried to prepare a single crystal of compound **5c** and obtained a good crystal of **5c** from dimethylformamide. The X-ray crystal diffraction analysis of **5c** confirms that it has the exo configuration, as depicted in Figure 2 [6]. Details of the crystallographic data are shown in Tables 2, 3 and 4. Thus it is clearly evident that the reaction of thioamide **1** and *N*-phenyl maleimide **2a** selectively yields the exo isomer of type **5** compounds.

Table 3

Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters for **5c**

Atom	x	y	z	*U*(eq)
N(1)	0.19677(10)	0.50699(6)	0.08133(30)	0.0392(9)
C(2)	0.21603(11)	0.45510(7)	0.07923(31)	0.0349(9)
C(3)	0.13232(11)	0.42493(7)	0.08830(33)	0.0349(9)
C(4)	0.09576(12)	0.43603(7)	-0.14613(34)	0.036(1)
C(5)	0.01241(12)	0.40999(7)	-0.18785(34)	0.042(1)
N(6)	-0.04681(8)	0.44893(5)	-0.22016(29)	0.0377(8)
C(7)	-0.01456(11)	0.49937(7)	-0.19880(32)	0.039(1)
C(8)	0.07841(12)	0.49535(7)	-0.15403(33)	0.036(1)
C(9)	0.10650(12)	0.51656(7)	0.07336(34)	0.0369(9)
S(10)	0.06724(3)	0.46627(2)	0.26374(8)	0.0379(2)
O(11)	0.28413(8)	0.43513(5)	0.06150(25)	0.0444(7)
C(12)	0.14024(15)	0.36741(8)	0.14776(40)	0.043(1)
C(13)	0.19240(12)	0.35629(7)	0.34995(34)	0.038(1)
O(14)	0.21556(8)	0.39037(5)	0.47834(23)	0.0430(7)
N(15)	0.20969(12)	0.30471(6)	0.37280(32)	0.050(1)
C(16)	0.25817(14)	0.27939(8)	0.53543(40)	0.051(1)
C(17)	0.28974(14)	0.30360(9)	0.72132(41)	0.053(1)
C(18)	0.33597(18)	0.27490(11)	0.87032(50)	0.069(2)
C(19)	0.3514(2)	0.2225(1)	0.8389(6)	0.092(2)
C(20)	0.3193(3)	0.1987(1)	0.6536(7)	0.102(2)
C(21)	0.2734(2)	0.2262(1)	0.5042(6)	0.079(2)
O(22)	-0.00162(9)	0.36370(5)	-0.19714(33)	0.068(1)
C(23)	-0.13391(11)	0.43815(7)	-0.26158(43)	0.044(1)
C(24)	-0.17898(16)	0.41148(11)	-0.11057(55)	0.067(2)
C(25)	-0.26325(18)	0.40087(13)	-0.15319(72)	0.091(2)
C(26)	-0.29875(18)	0.41859(13)	-0.34167(73)	0.087(2)
C(27)	-0.25352(17)	0.44565(12)	-0.49322(60)	0.073(2)
C(28)	-0.16904(15)	0.45544(10)	-0.45632(47)	0.057(1)
O(29)	-0.05554(8)	0.53885(5)	-0.21857(32)	0.0576(9)
C(30)	0.08333(16)	0.57223(8)	0.13010(48)	0.051(1)
O(31)	0.62124(14)	0.26466(7)	-0.08307(38)	0.087(1)
C(32)	0.5865(2)	0.2559(1)	0.0917(5)	0.073(2)
N(33)	0.54466(14)	0.28958(8)	0.20950(41)	0.074(1)
C(34)	0.5068(3)	0.2750(3)	0.4168(7)	0.140(4)
C(35)	0.5340(3)	0.3430(1)	0.1272(11)	0.159(3)

*U*eq= (1/3)ΣiΣjUij ai*aj* ai. aj.

The results obtained by the present research are summarized as follows,

1. One step reactions of thioamide with electron-deficient olefins, such as maleic anhydride and maleimide, afford tetrahydrooxoepithiopyridinemaleic acid anhydrides and tetrahydrooxoepithiopyridinecarboxyimides, respectively.

Table 4

Bond lengths (Å) and Angles (°) for 5c

N(1)-C(2)	1.357(3)	N(1)-C(9)	1.465(3)
C(2)-C(3)	1.544(3)	C(2)-O(11)	1.207(3)
C(3)-C(4)	1.568(3)	C(3)-S(10)	1.825(2)
C(3)-C(12)	1.514(3)	C(4)-C(5)	1.510(3)
C(4)-C(8)	1.536(3)	C(5)-C(6)	1.385(3)
C(5)-O(22)	1.201(3)	N(6)-C(7)	1.390(3)
N(6)-C(23)	1.442(3)	C(7)-C(8)	1.515(3)
C(7)-O(29)	1.206(3)	C(8)-C(9)	1.552(3)
C(9)-S(10)	1.837(2)	C(9)-C(30)	1.505(3)
C(12)-C(13)	1.513(4)	C(13)-O(14)	1.225(3)
C(13)-N(15)	1.349(3)	N(15)-C(16)	1.413(3)
C(16)-C(17)	1.384(4)	C(16)-C(21)	1.389(4)
C(17)-C(18)	1.379(4)	C(18)-C(19)	1.369(5)
C(19)-C(20)	1.380(6)	C(20)-C(21)	1.361(6)
C(23)-C(24)	1.351(4)	C(23)-C(28)	1.383(4)
C(24)-C(25)	1.399(4)	C(25)-C(26)	1.357(6)
C(26)-C(27)	1.360(5)	C(27)-C(28)	1.392(4)
O(31)-C(32)	1.220(4)	C(32)-N(33)	1.302(4)
N(33)-C(34)	1.448(6)	N(33)-C(35)	1.460(5)
C(2)-N(1)-C(9)	112.7(2)	N(1)-C(2)-C(3)	106.7(2)
N(1)-C(2)-O(11)	128.0(2)	C(3)-C(2)-O(11)	125.2(2)
C(2)-C(3)-C(4)	101.6(2)	C(2)-C(3)-S(10)	103.2(2)
C(2)-C(3)-C(12)	114.7(2)	C(4)-C(3)-S(10)	102.5(2)
C(4)-C(3)-C(12)	115.0(2)	S(10)-C(3)-C(12)	117.8(2)
C(3)-C(4)-C(5)	113.8(2)	C(3)-C(4)-C(8)	105.8(2)
C(5)-C(4)-C(8)	105.5(2)	C(4)-C(5)-N(6)	108.2(2)
C(4)-C(5)-O(22)	127.1(2)	N(6)-C(5)-O(22)	124.6(2)
C(5)-N(6)-C(7)	113.2(2)	C(5)-N(6)-C(23)	123.3(2)
C(7)-N(6)-C(23)	123.4(2)	N(6)-C(7)-C(8)	108.6(2)
N(6)-C(7)-O(29)	124.0(2)	C(8)-C(7)-O(29)	127.4(2)
C(4)-C(8)-C(7)	104.4(2)	C(4)-C(8)-C(9)	105.2(2)
C(7)-C(8)-C(9)	114.9(2)	N(1)-C(9)-C(8)	104.9(2)
N(1)-C(9)-S(10)	101.5(2)	N(1)-C(9)-C(30)	113.1(2)
C(8)-C(9)-S(10)	102.8(2)	C(8)-C(9)-C(30)	117.5(2)
S(10)-C(9)-C(30)	115.3(2)	C(3)-S(10)-C(9)	80.7(1)
C(3)-C(12)-C(13)	114.9(2)	C(12)-C(13)-O(14)	123.6(2)
C(12)-C(13)-N(15)	112.3(2)	O(14)-C(13)-N(15)	124.2(2)
C(13)-N(15)-C(16)	129.0(2)	N(15)-C(16)-C(17)	124.7(2)
N(15)-C(16)-C(21)	116.4(3)	C(17)-C(16)-C(21)	118.8(3)
C(16)-C(17)-C(18)	119.8(3)	C(17)-C(18)-C(19)	121.4(3)
C(18)-C(19)-C(20)	118.4(4)	C(19)-C(20)-C(21)	121.3(3)
C(16)-C(21)-C(20)	120.3(3)	N(6)-C(23)-C(24)	119.5(3)
N(6)-C(23)-C(28)	118.8(2)	C(24)-C(23)-C(28)	121.7(3)
C(23)-C(24)-C(25)	119.0(3)	C(24)-C(25)-C(26)	119.7(4)
C(25)-C(26)-C(27)	121.3(3)	C(26)-C(27)-C(28)	119.8(4)
C(23)-C(28)-C(27)	118.4(3)	O(31)-C(32)-N(33)	126.5(3)
C(32)-N(33)-C(34)	121.8(4)	C(32)-N(33)-C(35)	118.9(4)
C(34)-N(33)-C(35)	119.3(4)		

2. The reaction of secondary thioamides with *N*-substituted maleimide is promoted by the addition of acid, which affects the mesoionic intermediate formation step.

3. The products possess the exo configuration.

EXPERIMENTAL

Melting points were determined using a Yanagimoto melting apparatus and are uncorrected. The ^{1}H-nmr and ^{13}C-nmr spectra were measured with a JEOL JNM-GX400 spectrometer in the solvents indicated. Chemical shifts and coupling constants were expressed in ppm (δ) and J (Hz) with respect to tetramethylsilane. The mass spectra were obtained on a Hitachi M-80B spectrometer. Elemental analyses were carried out using a Perkin-Elmer 240C elemental analyzer. X-ray structure determination was confirmed using a Mac Science MXC18 diffractometer.

Reaction of Primary Thioamides with *N*-Phenylmaleimides. General Procedures.

N-Phenylmaleimide (**2a**, 50 mmoles) and primary thioamide (**1**, 50 mmoles) were refluxed in dioxane (50 ml) for 1hour under a nitrogen atmosphere. After evaporation of the solvent under reduced pressure the viscous residue was washed with acetone to separate compound **4**, which is almost insoluble in acetone. The filtrate was then chromatographed on silica gel with benzene/acetone (2:1) as the eluent. Products **4, 5** and a mixture of unreacted **2a**, and **1** together with a small amount of unknown product were eluted from the column.

The products from the reaction of **2a** with thiobenzamide (**1a**) are recorded below:

1,2,3,4,5,6-Hexahydro-3-oxo-*N*,1-diphenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboximide (**5a**).

This compound was obtained as white crystals, mp 240-244°(1.21 g, 10% yield); ms: m/z [M$^+$] Found: 483.1242; Calcd. for $C_{27}H_{21}O_4N_3S$: 483.1251; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 3.36 (s, 2H, CH_2), 3.83 (d, 1H, J = 6.6 Hz, CH), 4.22 (d, 1H, J = 6.6 Hz, CH), 7.02-7.57 (m, 15H, arom), 9.56 (s, 1H, NH), 10.17 (s, 1H, NH); ^{13}C-nmr (dimethyl-d_6 sulfoxide): δ 33.3 (CH_2), 50.4, 58.7 (CH), 62.3, 78.7 (C), 119.1, 123.1, 126.7, 127.7, 128.2, 128.6, 128.9, 129.1 (=CH, arom), 132.0, 132.8, 139.0 (=C-, arom), 167.2, 171.9, 173.5, 175.7 (C=O).

Anal. Calcd. for $C_{27}H_{21}O_4N_3S$: C, 67.08; H, 4.35; N, 8.69; S, 6.63. Found: C, 66.86; H, 4.45; N, 8.83; S, 6.59.

4-Hydroxy-2-phenyl-5-(*N*-phenylcarbamoylmethyl)-1,3-thiazole (**4a**).

This compound was obtained as white crystals, mp 198-200° (49% yield); ms: m/z [M$^+$] Found: 310.0754; Calcd. for $C_{17}H_{14}O_2N_2S$: 310.0775; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 3.78 (s, 2H, CH_2), 7.29-7.85 (m, 10H, arom), 10.21 (s, 1H, NH), 10.63 (s, 1H, OH); ^{13}C-nmr (dimethyl-d_6 sulfoxide): δ 32.0 (CH_2), 100.9, 159.1, 160.4 (=C-), 119.1, 123.3, 124.8, 128.6, 129.0, 129.5 (=CH, arom), 133.3, 138.8 (=C-, arom), 167.9 (C=O).

Anal. Calcd. for $C_{17}H_{14}O_2N_2S$: C, 65.81; H, 4.52; N, 9.03; S, 10.32. Found: C, 66.17; H, 4.48; N, 8.73; S, 10.52.

The products from the reaction of **2a** with *p*-toluthioamide (**1b**) are recorded below:

1,2,3,4,5,6-Hexahydro-3-oxo-*N*-phenyl-4-(*N*-phenylcarbamoylmethyl)-1-*p*-tolyl-1,4-epithiopyridine-5,6-dicarboximide (**5b**).

This compound was obtained as white crystals, mp 258-262° (1.37 g, 11% yield); ms: m/z [M$^+$] Found: 497.1423; Calcd. for $C_{28}H_{23}O_4N_3S$: 497.1408; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 2.34 (s, 3H, CH_3), 3.38 (s, 2H, CH_2), 3.82 (d, 1H, J = 6.6 Hz, CH), 4.18 (d, 1H, J = 6.6 Hz, CH), 7.05-7.59 (m, 14H, arom), 9.50 (s, 1H, NH), 10.15 (s, 1H, NH); ^{13}C-nmr (dimethyl-d_6 sulfoxide): δ 21.1 (CH_3), 33.6 (CH_2), 50.8,59.0 (CH), 62.6,78.9 (C), 119.5, 123.8, 127.1, 127.9, 129.1, 129.3, 129.4 (=CH, arom), 129.4, 132.0, 132.8, 139.0 (=C-, arom), 167.6, 172.2, 173.8, 176.1 (C=O).

Anal. Calcd. for $C_{28}H_{23}O_4N_3S$: C, 67.60; H, 4.63; N, 8.45; S, 6.44. Found: C, 67.63; H, 4.65; N, 8.58; S, 6.44.

4-Hydroxy-5-(*N*-phenylcarbamoylmethyl)-2-*p*-tolyl-1,3-thiazole (**4b**).

This compound was obtained as pale yellow crystals, mp 223-225° (10.8 g, 67% yield); ms: m/z [M+] Found: 324.0909; Calcd. for $C_{18}H_{16}O_2N_2S$: 324.0931; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 2.34 (s, 3H, CH_3), 3.76 (s, 2H, CH_2), 7.03-7.73 (m, 9H, arom), 10.19 (s, 1H, NH), 10.56 (s, 1H, OH); ^{13}C-nmr (dimethyl-d_6 sulfoxide): δ 20.9 (CH_3), 32.0 (CH_2), 100.3, 159.1, 160.4 (=C-), 119.2, 123.3, 124.8, 128.7, 129.7 (=CH, arom), 130.9, 139.0, 139.4 (=C-, arom), 167.9 (C=O).

Anal. Calcd. for $C_{18}H_{16}O_2N_2S$: C, 66.67; H, 4.94; N, 8.64; S, 9.88. Found: C, 66.88; H, 4.97; N, 8.68; S, 10.02.

The products from the reaction of **2a** with thioacetamide (**1c**) stand below:

1,2,3,4,5,6-Hexahydro-1-methyl-3-oxo-*N*-phenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboximide (**5c**).

This compound was obtained as white crystals, mp 247-250° (4.94 g, 47% yield); ms: m/z [M+] Found: 421.1107; Calcd. for $C_{22}H_{19}O_4N_3S$: 421.1095; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 1.85 (s, 3H, CH_3), 3.22 (d, 1H, J_{gem} = 16.0 Hz, *H*CH), 3.27 (d, 1H, J_{gem} = 16.0 Hz, HC*H*), 3.59 (d,1H, J = 6.6 Hz, CH), 3.72 (d, 1H, J = 6.6 Hz, CH), 7.00-7.57 (m,10H, arom), 9.15 (s,1H, NH), 10.07 (s, 1H, NH); ^{13}C-nmr (dimethyl-d_6 sulfoxide): δ 17.0 (CH_3), 36.9 (CH_2), 50.2, 58.4 (CH), 63.2, 72.4 (C), 118.9, 122.9, 126.6, 128.4, 128.9 (=CH, arom), 131.9, 139.0 (=C-, arom), 167.0, 173.0, 173.4,175.7 (C=O).

Anal. Calcd. for $C_{22}H_{19}O_4N_3S$: C, 62.71; H, 4.51; N, 9.98; S, 7.60. Found: C, 62.99; H, 4.56; N, 9.84; S, 7.79.

The Reaction of **4a** with Maleic Anhydride (**2b**), *N*-Phenylmaleimide (**2a**) and *N*-Methylmaleimide (**2c**).

Compound **4a** (1.06 g, 3.4 mmoles) and maleic anhydride (**2b**, 0.33 g, 3.4 mmoles) are refluxed in dioxane (50 ml) for 3 hours under a nitrogen atmosphere. After evaporation of the solvent under reduced pressure, to the residue was added a small amount of acetone to separate **4a** (0.63 g, 59% yield) as white crystals.

The acetone soluble portion was evaporated and methanol added to give 1,2,3,4,5,6-hexahydro-3-oxo-1-phenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboxylic acid anhydride (**5d**, 0.12 g, 9% yield) as white crystals, mp 215-218°; ms: m/z [M+] Found: 408.0768; Calcd. for $C_{21}H_{16}O_5N_2S$: 408.0778; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 3.28, (s, 2H, CH_2), 4.20 (d, 1H, J = 6.6 Hz, CH), 4.49 (d, 1H, J = 6.6 Hz, CH), 7.03-7.59 (m, 10H, arom), 9.65 (s, 1H, NH), 10.20 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{16}O_5N_2S$: C, 61.76; H, 3.92; N, 6.86; S, 7.84. Found: C, 62.74; H, 3.96; N, 6.98; S, 7.82.

In a similar reaction of **4a** (1.35 g, 4.3 mmoles) with *N*-phenylmaleimide (**2a**, 0.75 g, 4.3 mmoles) gave **5a** (0.65 g, 31% yield); **4a** (0.57 g, 42% yield) was recovered.

Furthermore, the reaction of *N*-methylmaleimide (**2c**, 0.38 g, 3.4 mmoles) with **4a** (1.06 g, 3.4 mmoles), **4a** (0.84 g, 79% yield) was recovered and 1,2,3,4,5,6-hexahydro-*N*-methyl-3-oxo-1-phenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboximide (**5e**, 0.21g, 15% yield) was obtained as white crystals, mp 146-150°; ms: m/z [M+] Found: 421.1117; Calcd. for $C_{22}H_{19}O_4N_3S$: 421.1095; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 2.80 (s, 3H, CH_3), 3.33 (s, 2H, CH_2), 3.71 (d, 1H, J = 6.6 Hz, CH), 4.05 (d, 1H, J = 6.6 Hz, CH), 7.02-7.59 (m, 10H, arom), 9.47 (s, 1H, NH), 10.14 (s, 1H, NH).

Anal. Calcd. for $C_{22}H_{19}O_4N_3S$: C, 62.71; H, 4.51; N, 9.98 S,7.60. Found: C, 63.05; H, 4.61 N, 10.09 S, 7.82.

Reaction of Secondary Thioamides with *N*-Phenylmaleimides. General Procedures.

N-Phenylmaleimide (**2a**, 10 mmoles) and secondary thioamide, *N*-methylthioacetamide (**1d**), thiobenzanilide (**1e**) or thioacetanilide (**1f**), (10 mmoles) were refluxed in dioxane (50 ml) for 1 hour or 5 hours under a nitrogen atmosphere.

The above reactions did not proceed except for the reaction of **2a** with thioaceteanilide (**1f**).

The reaction of **2a** (1.73 g, 10 mmoles) with thioacetanilide (**1f**, 1.51 g, 10 mmoles) were refluxed in dioxane for 5 hours under nitrogen atmosphere. After evaporation of solvent under reduced pressure the viscous residue was extracted by diethyl ether. The extract was dried over sodium sulfate and evaporated to give 3-(*N*-phenylacetimidoylthio)-*N*-phenylsuccinimide (**6**, 1.29 g, 40% yield) as white crystals. mp 148-151°; ms: m/z [M+] Found: 324.0958; Calcd. for $C_{18}H_{16}O_2N_2S$: 324.0932; ^{1}H-nmr (deuteriochloroform): δ 2.06 (s, 3H, CH_3), 3.26 (dd, 1H, J_{gem} = 18.1 Hz, J_{vic} = 5.8 Hz, *H*CH), 3.39 (dd, 1H, J_{gem} = 18.1 Hz, J_{vic} = 9.3 Hz, HC*H*), 4.14 (dd, 1H, J = 5.8, 9.3 Hz, CH), 6.67-7.38 (m, 10H, arom). ^{13}C-nmr (deuteriochloroform): δ 20.5 (CH_3), 36.5 (CH_2), 41.3 (CH), 120.1, 124.1, 126.8, 128.6, 129.0, 129.1 (=CH, arom), 132.3, 148.8 (=C-, arom), 163.6 (-C =), 174.0, 174.2 (C=O).

Anal. Calcd. for $C_{18}H_{16}O_2N_2S$: C, 66.67; H, 4.94; N, 8.64 S, 9.88. Found: C, 66.74; H, 4.99; N, 8.79 S, 10.04.

Competition Reactions of *N*-Methylthioacetamide (**1d**) with *N*-Phenylmaleimide (**2a**) and Maleic Anhydride (**2b**).

A mixture of *N*-methylthioacetamide (**1d**, 0.89g, 10 mmoles), *N*-phenylmaleimide (**2a**, 1.73 g, 10 mmoles) and maleic anhydride (**2b**, 0.98 g, 10 mmoles) was refluxed in dioxane (50 ml) for 3 hours under a nitrogen atmosphere. After evaporation of solvent under reduced pressure the viscous residue was added with acetone to separate 1,2,3,4,5,6-hexahydro-1,2-dimethyl-3-oxo-*N*-phenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboximide (**5h**), which is sparingly soluble in acetone. Then, to the filtrate is added a very small amount of acetone to separate 4-(carboxymethyl)-1,2,3,4,5,6-hexahydro-1,2-dimethyl-3-oxo-*N*-phenyl-1,4-epithiopyridine-5,6-dicarboximide (**5g**), and the presence of 4-(carboxymethyl)-1,2,3,4,5,6-hexahydro-1,2-dimethyl-3-oxo-1,4-epithiopyridine-5,6-dicarboxylic acid anhydride (**5f**) in the filtrate was identified and determined by comparison of gc-ms fragment analysis of **5f**, which was obtained from the reaction of **1d** with **2b**. The yields of **5f** and **5g** are determined on gas chromatography using internal standard (column: OV-17, 2m, internal standard: 2,2,3-trimethylindorenine).

4-(Carboxymethyl)-1,2,3,4,5,6-hexahydro-1,2-dimethyl-3-oxo-1,4-epithiopyridine-5,6-dicarboxylic Acid Anhydride (**5f**).

This compound was obtained as white crystals, mp 202-205° (67% yield by glc); ms: m/z [M+] Found: 285.0337; Calcd. for $C_{11}H_{11}O_6NS$: 285.0306; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 1.90 (s, 3H, CH_3), 2.77 (s, 3H, *N*-CH_3), 3.05 (d, 1H, J_{gem} = 17.0 Hz, *H*CH), 3.15 (d, 1H, J_{gem} = 17.0 Hz, HC*H*), 3.98 (d, 1H, J = 7.2 Hz, CH), 4.02 (d, 1H, J = 7.2 Hz, CH), 12.52 (br, 1H, OH); ^{13}C-nmr (dimethyl-d_6 sulfoxide): δ 15.5 (CH_3), 26.1 (*N*-CH_3,), 31.4 (CH_2), 52.5, 57.0 (CH), 61.6, 76.2 (C), 168.2, 169.0, 170.1, 172.8 (C=O).

Anal. Calcd. for $C_{11}H_{11}O_6NS$: C, 46.32; H, 3.86; N, 4.91; S, 11.23. Found: C, 46.58; H, 3.89; N, 4.72; S, 11.39.

4-(Carboxymethyl)-1,2,3,4,5,6-hexahydro-1,2-dimethyl-3-oxo-*N*-phenyl-1,4-epithiopyridine-5,6-dicarboximide (**5g**).

This compound was obtained as white crystals, mp 206-209° (46% yield by glc); ms: m/z [M+] Found: 360.0763; Calcd. for $C_{17}H_{16}O_5N_2S$: 360.0778; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 1.91 (s, 3H, CH_3), 2.80 (s, 3H, *N*-CH_3), 3.11 (d, 1H, J_{gem} = 17.6 Hz, *H*CH), 3.17 (d, 1H, J_{gem} = 17.6 Hz, HC*H*), 3.65 (d, 1H, J = 7.2 Hz, CH), 3.73 (d, 1H, J = 7.2 Hz, CH), 7.23-7.53 (m, 5H, arom), 12.42 (br, 1H, OH); ^{13}C-nmr (dimethyl-d_6 sulfoxide): δ 15.8 (CH_3), 26.0 (*N*-CH_3), 31.6 (CH_2), 50.4, 55.1 (CH), 61.7, 76.3 (C), 126.8, 128.6, 128.9 (=CH, arom), 131.9 (=C-, arom), 170.4, 173.0, 173.4, 173.7 (C=O).

Anal. Calcd. for $C_{17}H_{16}O_5N_2S$: C, 56.67; H, 4.44; N, 7.78; S, 8.89. Found: C, 56.61; H, 4.39; N, 7.61; S, 9.05.

1,2,3,4,5,6-Hexahydro-1,2-dimethyl-3-oxo-*N*-phenyl-4-(*N*-phenylcarbamoylmethyl)-1,4-epithiopyridine-5,6-dicarboximide (**5h**).

This compound was obtained as white crystals, mp 302-304° (0.57 g, 13% yield); ms: m/z [M+] Found: 435.1215; Calcd. for $C_{23}H_{21}O_4N_3S$: 435.1251; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 1.91 (s, 3H, CH_3), 2.80 (s, 3H, *N*-CH_3), 3.27 (d, 1H, J_{gem} = 17.6 Hz, *H*CH), 3.37 (d, 1H, J_{gem} = 17.6 Hz, HC*H*), 3.56 (d, 1H, J = 6.6 Hz, CH), 3.73 (d, 1H, J = 6.6 Hz, CH), 7.00-7.56 (m, 10H, arom), 10.11 (br, 1H, NH); ^{13}C-nmr (dimethyl-d_6 sulfoxide): δ 15.8 (CH_3), 26.0 (*N*-CH_3), 33.6 (CH_2), 51.0, 55.1 (CH), 62.3, 76.0 (C), 119.0, 123.1, 126.8, 128.5, 128.6, 128.9 (=CH, arom), 132.0, 139.0 (=C-, arom), 167.0, 173.0, 173.3, 174.1 (C=O).

Anal. Calcd. for $C_{23}H_{21}O_4N_3S$: C, 63.45; H, 4.83; N, 9.65; S, 7.35. Found: C, 63.52; H, 4.89; N, 9.19; S, 7.36.

Reaction of *N*-Phenylmaleimide (**2a**) with Mesoionic Compound (**3c**). General Procedure.

Compound **2a** (0.86 g, 5 mmoles) and anhydro-2,3,5-triphenyl-4-hydroxythiazolium hydroxide (**3c**, 1.64 g, 5 mmoles) were refluxed in dioxane (50 ml) for 3 hours under a nitrogen atmosphere. After evaporation of the solvent under reduced pressure diethyl ether was added to the residue to separate white crystals (2.35 g, 94% yield) which included **5j** and **5k** in a ratio of 18:1 by ^{1}H-nmr.

Then a small amount of acetone was added to the white crystals and the acetone soluble portion was evaporated to give compound **5j** as the main product. The acetone insoluble portion afforded compound **5k**.

1,2,3,4,5,6-Hexahydro-3-oxo-*N*-phenyl-1,2,4-triphenyl-1,4-epithiopyridine-5,6-dicarboximides (**5j**, and **5k**).

Compound **5j** was obtained as white crystals, mp 230-234°; ms: m/z [M+] Found: 502.1356; Calcd. for $C_{31}H_{22}O_3N_2S$: 502.1348; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 4.49 (d, 1H, J = 6.6 Hz, CH), 4.83 (d, 1H, J = 6.6 Hz, CH), 6.81-7.96 (m, 20H, arom).

Compound **5k** was also obtained as white crystals, mp 326-329°; ms: m/z [M+] Found: 502.1356; Calcd. for $C_{31}H_{22}O_3N_2S$: 502.1348; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 5.00 (d, 1H, J = 8.8 Hz, CH), 5.16 (d, 1H, J = 8.8 Hz, CH), 6.92-8.17 (m, 20H, arom).

Crystallographic Structure Determination of **5c**.

A colorless crystal of **5c** grown by slow evaporation of a dimethylformamide solution, belongs to the monoclinic space group $P2_12_12_1$: a = 15.991 (2)Å, b = 25.458 (4)Å, c = 6.0858 (8)Å, V = 2477.5 (6) Å^3, Z = 4, D (calcd.) = 1.33 g/cm^3, and μ = 14.82 mm^{-1}. Of 2486 reflections collected at 25 (Cu-Kα, 3.0 ≤ 2Θ ≤ 128.0), 2279 unique reflections with $I > 2\ \sigma(I)$ were used in the solution and refinement of the structure. All non-hydrogen atoms were located by direct methods and subsequent difference Fourier syntheses. Hydrogen atoms except the attached to the methyl groups of dimethylformamide were found in difference maps and refined. Six hydrogen atoms connected to the methyl groups of dimethylformamide were added at calculated positions but parameters were not refined. Refinement of all non-hydrogen atoms with anisotropic temperature factors (hydrogen atoms isotropic) led to convergence at R = 0.034, wR = 0.040, S = 1.316, with the highest peak on the final difference map of 0.19 e A^{-3}. All calculations were performed using *CRYSTAN* version 6.3.3 (Mac Science, Japan).

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[6] In a previous paper [4], we assumed tentatively that the compound of type **5** which was obtained by the reaction of **1** (R^1 = CH_3, R^2 = H) with maleic anhydride (**2b**) is in the endo configuration. The present results from the X-ray analysis suggest that this assumption is incorrect and it is supported by analysis of nmr coupling constants that the compound is also in the exo configuration.