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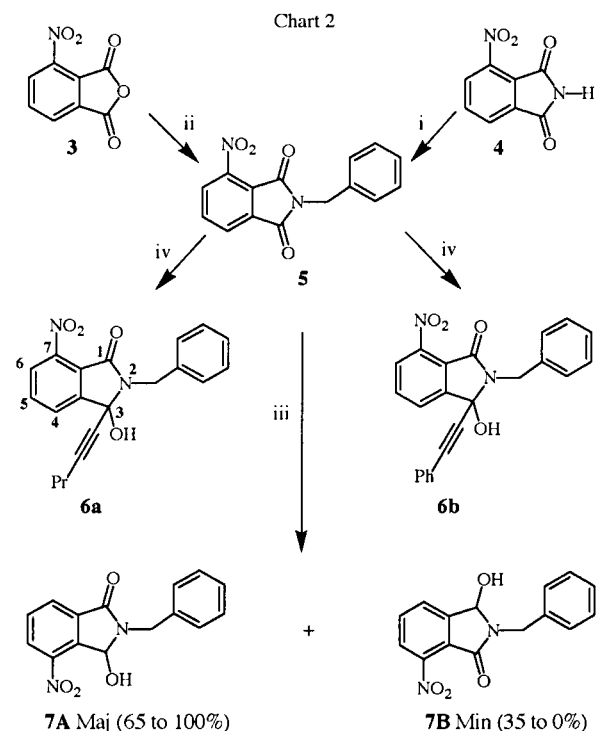
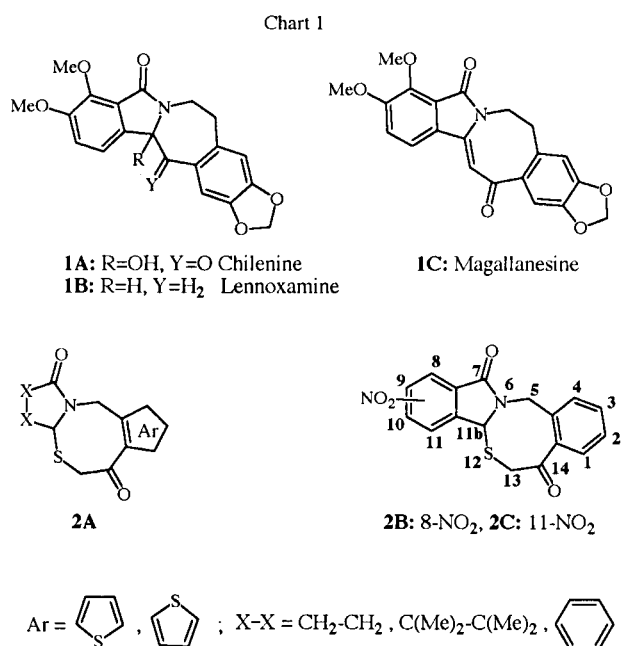
A functionalized isoindolo[1,2-*d*][3,5]benzothiazocine **2B** has been synthesized in three steps from the nitro-imide derivative **5**. The key step of this sequence was the cyclization of the thioglycolic acid derivative **9** under acidic conditions. An evaluation of the reactivity of the imide **5** and the corresponding *N*-acyliminium ion toward borohydride reduction, organometallic addition, Meyer-Schuster rearrangement and intermolecular alkoxylation and thioalkoxylation reactions was reported.

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Mono(or poly)hydroxylated and methoxylated dihydroisoindolones units are present in a large number of interesting classes of benzazepine and benzazocine alkaloids. These structures are exemplified by chilénine **1A** [1,2,3], lennoxamine **1B** [1,4] and magallanesine **1C** [5] extracted from the Chilean Berberidaceae, *Berberis darwinii* Hook (Chart 1). In the course of our continuing efforts towards the synthesis of new fused 5-8-5 and 5-8-6 tricyclic thioanalogue systems including thieno[1,3]thiazocines annelated to isoindolone **2A** (X-X=benzene) [6,7] or pyrrolidone **2A** (X-X=CH₂-CH₂, CMe₂-CMe₂) [8], we wish to report herein the synthesis of new isoindolo[1,2-*d*][3,5]benzothiazocine **2B**. This structure constitutes, in our knowledge, the first example in which the nitro group is incorporating at the isoindolone moiety.

As depicted in Chart 2, the commercially available

3-nitrophthalimide (**4**) was *N*-alkylated with benzyl chloride under solid-liquid phase transport catalysis using anhydrous potassium carbonate as base and a mixture of potassium iodide and crown ether 18-C-6 as catalysts [9]. Compound **5** was isolated after refluxing in toluene for 24 hours as a crystalline solid in 74% yield. Compound **5** was also obtained in a more attractive way from 3-nitrophthalic anhydride (**3**) and benzylamine by warming in azeotropic conditions with a catalytic amount of triethylamine. Under these conditions, the expected *N*-benzylated product **5** was isolated in 87% yield. This imide was then submitted to reduction and carbophilic



i) K₂CO₃, KI, 18-C-6, C₆H₅CH₂Cl, toluene, reflux, 24 h; ii) C₆H₅CH₂NH₂, toluene, NEt₃, Dean Stark; iii) NaBH₄, MeOH, -5.0°, 20 minutes to 1 h; iv) BuLi, R-C≡CH, CH₂Cl₂, r. t, 3 h. (with R = Propyl and Phenyl).

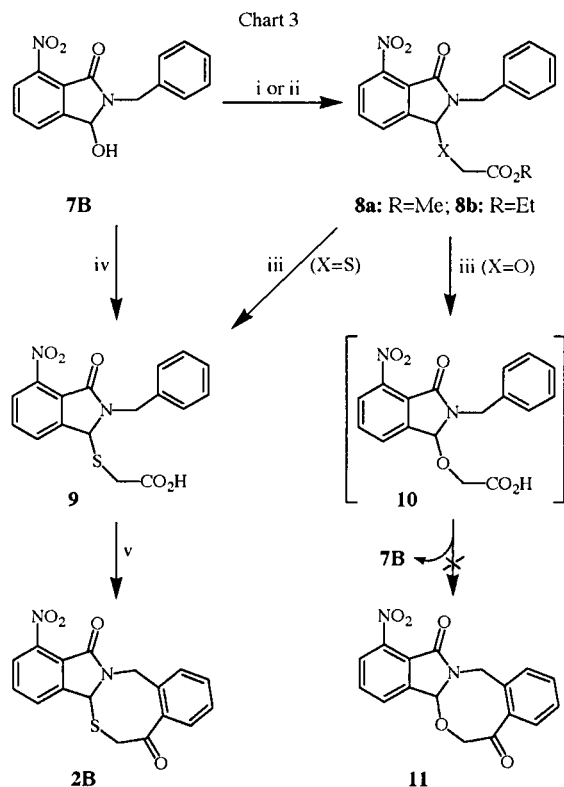
addition reactions in order to study the steric and electronic effects on both the reduction and addition process.

Thus, reduction reaction was carried out with a large excess of sodium borohydride in methanol with regular addition of an ethanolic hydrochloric acid solution to avoid the formation of the opened amide-alcohol [10,11]. The resulting ω -carbinol lactam **7** was isolated in 94% yield as a mixture of positional isomers **7A** and **7B** (65/35) after 20 minutes to 1 hour period of the reaction at $-5-0^\circ$. These α -hydroxylactams were separated by preparative tlc. Likewise when a similar reaction was carried out at -15 to -10° , the reduction occurred regioselectively to give the isomer **7A** in 84% yield. On the other hand, treatment of the imide **5** with pentynyllithium or phenylethynyllithium in dry dichloromethane, led to ω -alkynyl- ω -carbinol lactams **6a** and **6b** in good yields of 87 and 90% respectively. The structures of compounds **6a** and **6b** were deduced from their spectroscopic analyses. Especially, the ^1H nmr spectra of **6a** and **6b** showed that the chemical shifts are comparable with respect to those observed for the α -hydroxylactam **7B**.

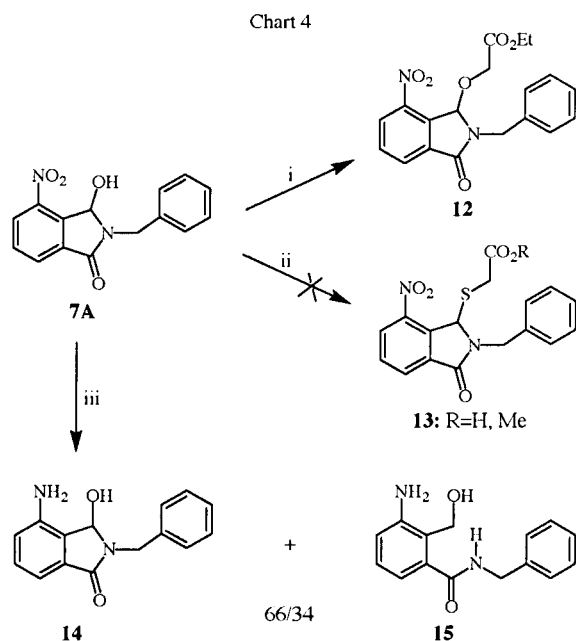
At this stage, the hydride ion and the carbon of the lithiated reagents used as the nucleophile did not affect the yields of both reactions but the steric hindrance of propyl and phenyl groups induced a regiofacial discrimination during approach of the incoming organometallic. In this case, only ω -carbinol lactams **6a** and **6b**, which bear the hydroxy function on the side opposite to the nitro substituent, were formed.

Since it has been demonstrated [12] that ω -carbinol lactams with various nucleophiles underwent an acid-catalyzed substitution reaction involving *N*-acyliminium species, we attempted to synthesize acid derivatives **9** and **10** as precursors for Friedel-Crafts cyclodehydration (Chart 3). In fact, treatment of hydroxylactams **7**, as a mixture of **7A** and **7B**, with an excess of methyl thioglycolate (i) or thioglycolic acid (iv) and a catalytic amount of *p*-toluenesulfonic acid afforded **8a** ($X=\text{S}$) (78%) and **9** (80%) respectively based on **7B**. In both cases, separation of products was easy and the starting unreacted ω -carbinol lactam **7A** was recovered. Saponification of the ester **8a** ($X=\text{S}$) also gave **9** in 76% yield. Because glycolic acid and its corresponding ethyl ester did not react with **7B** under the outlined conditions i or iv [13], the *O*-alkylation of the α -hydroxylactam **7B** leading to **8b** ($X=\text{O}$) was accomplished in an alkaline medium in the presence of ethyl bromoacetate. Under these conditions using sodium hydride as a base, the ether **8b** ($X=\text{O}$) was isolated in 82% yield. In comparison to **9**, we have never isolated the acid **10** whatever the experimental conditions used. In all cases, only the hydroxylactam **7B** was recovered. This result is a consequence of the generation of the *N*-acyliminium ion formed from the α -alkoxylactam derivatives **8b** ($X=\text{O}$) or **10** in acidic medium [12].

The above acid derivative **9** was then treated with thionyl chloride under reflux of dichloromethane for 2 hours and the resulting acid chloride in the presence of aluminium trichloride as catalyst at $-5-0^\circ$ gave the cyclic ketone **2B** in 56% yield. It is worth mentioning that the ketone **2B** was also obtained in 62% yield when refluxing in dichloromethane was extended to 5 hours without addition of aluminium trichloride as catalyst.

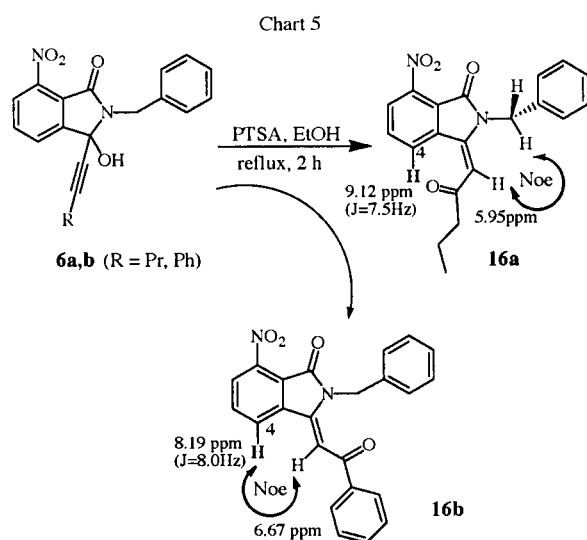


i) $\text{HS-CH}_2\text{CO}_2\text{Me}$, PTSA, CH_2Cl_2 , r. t, 24 h; ii) NaH, $\text{Br-CH}_2\text{CO}_2\text{Et}$, DMF, r. t, 24 h; iii) K_2CO_3 , MeOH, H_2O , reflux, 4 h then 2M HCl at $0-2^\circ$ to pH 2; iv) $\text{HS-CH}_2\text{CO}_2\text{H}$, PTSA, CH_2Cl_2 , r. t, 24 h; v) SOCl_2 , CH_2Cl_2 , reflux, 5 h (or 2 h then AlCl_3 at $-5-0^\circ$ to r. t for 2 h).



i) NaH, $\text{BrCH}_2\text{CO}_2\text{Et}$, DMF, r. t, 24 h; ii) $\text{HSCH}_2\text{CO}_2\text{Me}$ or $\text{HSCH}_2\text{CO}_2\text{H}$, PTSA, CH_2Cl_2 , r. t to reflux 24 h; iii) NaBH_4 , $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, MeOH, $-5-0^\circ$, 40 minutes to 1 h.

Treatment of **7A** with sodium hydride in *N,N*-dimethylformamide followed by addition of ethyl bromoacetate, furnished the *O*-alkylated product **12** in 88% yield. On the other hand, reduction of the nitro-alcohol **7A** using sodium borohydride in methanol did not occur but with 3 equivalents of an additional nickel(II) chloride hexahydrate, the reaction furnished the amino ω -carbinol lactam derivative **14** accompanied with the amide-alcohol **15** in a 2/1 ratio (75%), which were separated by chromatography on silica gel. The addition of an ethanolic hydrochloric acid solution at regular times during the reduction, to avoid the opened amide-alcohol **15** as described for related amide-alcohol compounds [10,11] did not give satisfactory results.



As shown in Chart 5, another reaction confirmed the structure of **7B**. In fact, the ω -alkynyl- ω -carbinol lactams **6a** or **6b** in refluxing ethanol for 2 hours with a catalytic quantity of *p*-toluenesulfonic acid, undergoes Meyer-Schuster rearrangement [14] leading to enamides **16a** (88%) or **16b** (92%). The proton nmr spectra of these enamides **16a,b** indicate the presence of a single isomer. Moreover, based on the signal of the olefinic proton [14-20] and aromatic proton H_4 [14, 17-20] we assess that 2-oxobutylidene and 2-oxo-2-phenylethylidene side chain in enamides **16a** or **16b** have a *S-cis* conformation but respectively a *E* and *Z* configuration. In fact, the 1H nmr spectrum of **16a** shows a high value for the chemical shift of H_4 at $\delta = 9.12$ ppm, with the usual benzene coupling constant of $J = 7.5$ Hz, due to the proximity of the carbonyl functional group [17]. The same is observed for enamide **16b** but the aromatic proton appears at $\delta = 8.19$ ppm with coupling constant of $J = 8.0$ Hz [18]. Furthermore, the vinylic proton appears at $\delta = 5.95$ ppm in **16a** but at $\delta = 6.67$ ppm in **16b**. These values are correlated with related model compounds as *E*-2,3-dihydro-3-(2"-oxo-2"-phenylbutylidene)-2-[(2'-bromothien-3'-ylmethyl)-1*H*-isoindol-1-one [17] and *Z*-3-(benzoylmethylene)phthalide [18] in which H_4 appears at $\delta = 8.85$ ppm and $\delta = 7.4$ -8.2 ppm while the vinylic

proton appears at $\delta = 6.59$ ppm and $\delta = 6.75$ ppm respectively. Moreover, these attributions were also confirmed by using NOE difference measurements of products **16a** and **16b**. These results corroborate unambiguously the structures of **7A** and **7B** discussed above.

In summary, we have demonstrated that *N*-benzyl-3-nitrophthalimide (**5**) led regioselectively to hydroxylactams **7A** and **7B** under borohydride reduction. This result is similar to that reported for the reduction of 3-nitrophthalimide [21,22]. The major ω -carbinol lactam **7A**, could be obtained as a single product when the reduction was performed at low temperature. Nevertheless, the addition of an organolithium derivative to the imide **5** led exclusively to the regioisomer **6a** or **6b** corresponding to the previous minor **7B**. The thioglycolic acid derivative **9**, obtained by the nucleophilic attack of the sulfur atom onto an *N*-acyliminium ion generated in acidic medium, gave under Friedel-Crafts cyclization conditions a substituted isoin-dolo[1,2-*d*][3,5]benzothiazocine derivative **2B**.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The 1H and ^{13}C nmr spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform solution and chemical shifts (δ) are expressed in ppm relative to internal tetramethylsilane. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. E. Merck silica gel 60 F (70-300 mesh) was used for column chromatography. Elemental analyses were carried out by the microanalysis laboratory of INSA at Rouen, F 76130 M^t. S^t. Aignan, France.

N-Benzyl-3-nitrophthalimide (**5**).

Method A: To a stirred mixture of 3-nitrophthalimide (**4**) (20 mmol) and 18-C-6 (1% w/w) in 30 ml of dry toluene were added solid potassium carbonate (2.68 g, 22 mmol) and 0.1 equivalent per mmol of potassium iodide. After stirring for 15 minutes, 24 mmol of benzyl chloride in 30 ml of dry toluene was added dropwise over a period of 20 minutes. The mixture was then refluxed for 24 hours and cooled. After filtration over a short column of celite, the organic phase was concentrated under reduced pressure and the crude resulting solid was purified by flash chromatography on silica gel with dichloromethane as eluent to give **5**. Recrystallization from ethanol afforded pure **5** (74%).

Method B: A mixture of benzylamine (10 mmol), phthalic anhydride (**3**) (1.48 g, 10 mmol) and triethylamine (0.5 ml) in toluene (70 ml) was refluxed with a Dean-Stark apparatus for 3 hours. The reaction mixture was cooled, and concentrated *in vacuo*. The residue was dissolved into dichloromethane, washed with 10% hydrochloric acid solution then with a 10% sodium hydrogen carbonate solution. The organic layer was dried over magnesium sulfate, and concentrated *in vacuo*. Recrystallization of the residue from ethanol gave **5**. This product was obtained in 87% yield, mp 144°; ir: ν 3035 (CH), 2950 (CH), 1718 (C=O),

1538 (NO₂) cm⁻¹; ¹H nmr: δ 4.82 (s, 2H, CH₂-N), 7.24-7.29 (m, 3H, H_{benzene}), 7.39-7.43 (m, 2H, H_{benzene}), 7.82-7.90 (dd, 1H, J = 7.5 and 7.8 Hz, H_{5-phthalimide}), 8.03-8.11 (dd, 2H, J = 7.5 and 7.8 Hz, H_{4- and 6-phthalimide}); ¹³C nmr: δ 42.9 (CH₂), 126.7 (CH), 128.2 (CH), 128.4 (CH), 128.6 (2CH), 128.8 (2CH), 135.1 (C), 135.6 (CH+C), 145.1 (C), 162.9 (C), 165.9 (C=O), 176.5 (CO).

Anal. Calcd. for C₁₅H₁₀N₂O₄ (282.26): C, 63.83; H, 3.57; N, 9.92. Found: C, 63.66; H, 3.39; N, 9.89.

General Procedure for Synthesis of Hydroxylactams (**6a**) and (**6b**).

To a stirred solution of pentynyl(or phenylethynyl)lithium (11 mmoles) (generated *in situ* by reaction of *n*-butyllithium 1.65 M solution in hexane (11 mmoles) and 1-pentyne(or phenylacetylene) (11 mmoles) in 50 ml of dry dichloromethane) was added in portions *N*-benzyl-3-nitrophthalimide (**5**) over a period of 15 minutes at 0°. The mixture was stirred at 0° for 1 hour then at room temperature for 3 hours. The reaction mixture was poured into 40 ml of 1M ammonium chloride solution, and was extracted twice with dichloromethane (20 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to afford hydroxylactams **6a** or **6b**, which were recrystallized from a mixture of diethyl ether and dichloromethane.

2,3-Dihydro-3-hydroxy-7-nitro-3-(pentynyl)-2-phenylmethyl-1*H*-isoindol-1-one (**6a**).

Compound **6a** was obtained as a single regioisomer in 87% yield; mp 151°; ir: ν 3326 (br, OH), 2229 (C≡C), 1686 (C=O), 1532 (NO₂) cm⁻¹; ¹H nmr: δ 0.83 (t, 3H, J = 7.5 Hz, CH₃), 1.32 (h, 2H, J = 7.5 Hz, CH₂), 1.60 (s, 1H, OH), 1.99 (t, 2H, J = 7.5 Hz, CH₂-C≡), 4.87 (s, 2H, CH₂-N), 7.17-7.33 (m, 3H, H_{benzene}), 7.41-7.55 (m, 2H, H_{benzene}), 7.68-7.75 (dd, 1H, J = 7.5 and 8.1 Hz, H_{5-phthalimide}), 8.15 (dd, 1H, J = 1.1 and 7.5 Hz, H_{6-phthalimide}), 8.31 (dd, 1H, J = 1.1 and 8.10 Hz, H_{4-phthalimide}); ¹³C nmr: δ 13.3 (CH₃), 20.3 (CH₂), 21.3 (CH₂), 43.8 (CH₂), 74.3 (C), 82.4 (C≡), 87.9 (C≡), 127.2 (CH), 128.1 (CH), 128.2 (2CH), 128.4 (2CH), 129.8 (CH), 131.3 (CH), 133.5 (C), 137.2 (C), 140.3 (C), 143.2 (C), 164.2 (CO).

Anal. Calcd. for C₂₀H₁₈N₂O₄ (350.37): C, 68.56; H, 5.17; N, 7.99. Found: C, 68.39; H, 5.09; N, 7.88.

2,3-Dihydro-3-hydroxy-7-nitro-3-(phenylethynyl)-2-phenylmethyl-1*H*-isoindol-1-one (**6b**).

Compound **6b** was obtained as a single regioisomer in 90% yield; mp 165°; ir: ν 3368 (br, OH), 2234 (C≡C), 1672 (C=O), 1529 (NO₂) cm⁻¹; ¹H nmr: δ 4.86 (d, 1H, J = 15.6 Hz, CH₂-N), 5.02 (d, 1H, J = 15.6 Hz, CH₂-N), 5.04 (br, 1H, OH), 7.03-7.14 (m, 2H, H_{benzene}), 7.15-7.36 (m, 6H, H_{benzene}), 7.42-7.55 (m, 2H, H_{benzene}), 7.67-7.75 (dd, 1H, J = 7.5 and 8.1 Hz, H_{5-phthalimide}), 8.17 (d, 1H, J = 7.5 Hz, H_{6-phthalimide}), 8.31 (d, 1H, J = 8.1 Hz, H_{4-phthalimide}); ¹³C nmr: δ 43.9 (CH₂), 81.9 (C≡), 86.1 (C≡), 120.1 (C), 127.3 (CH), 128.3 (3CH), 128.6 (3CH), 128.9 (CH), 129.6 (CH), 130.3 (CH), 131.7 (CH), 132.3 (2CH), 133.3 (C), 136.7 (2C), 139.3 (C), 143.3 (C), 163.7 (CO).

Anal. Calcd. for C₂₃H₁₆N₂O₄ (384.39): C, 71.86; H, 4.19; N, 7.28. Found: C, 71.80; H, 4.11; N, 7.21.

Preparation of ω-Carbinol Lactams **7A** and **7B**.

To a stirred solution of *N*-benzyl-3-nitrophthalimide (**5**) (2.82 g, 10 mmoles) in dry methanol (40 ml) at -5-0° was added by portions 6 equivalents of sodium borohydride (2.27 g, 60 mmoles).

After addition of sodium borohydride, 3 drops of ethanolic hydrochloric acid solution were added during 10 minutes (prepared from 9 drops of concentrated hydrochloric acid in 15 ml of ethanol) until the reaction was complete. The excess sodium borohydride was decomposed by careful addition of 10% hydrochloric acid solution to pH 2. After removal of the solvent, the residue was diluted with water (40 ml) and the whole was extracted with 30 ml of dichloromethane. The organic layers were washed with water and brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting solid as a mixture of ω-carbinol lactams **7A** and **7B** (65/35) (94%), was separated by preparative tlc using precoated plate of silica gel and chloroform as eluent, to give pure **7A** and **7B**. If the reaction was performed at -15 to -10°, only **7A** was isolated in an 84% yield. This product was identical to the one obtained above *via* preparative tlc separation.

2,3-Dihydro-3-hydroxy-4-nitro-2-phenylmethyl-1*H*-isoindol-1-one (**7A**).

This product was obtained as a white solid, mp 188°; ir: ν 3326 (br, OH), 3028 (CH), 2968 (CH), 1705 (C=O), 1529 (NO₂) cm⁻¹; ¹H nmr: δ 3.02 (br, 1H, OH), 4.33 (d, 1H, J = 15.1 Hz, CH₂-N), 5.12 (d, 1H, J = 15.1 Hz, CH₂-N), 6.19 (s, 1H, CH(OH)), 7.24-7.32 (m, 5H, H_{benzene}), 7.62-7.69 (dd, 2H, J = 6.9 and 7.8 Hz, H_{6-phthalimide}), 8.07 (d, 1H, J = 6.9 Hz, H_{5-phthalimide}), 8.21 (d, J = 7.8 Hz, 2H, H_{7-phthalimide}); ¹³C nmr: δ 41.4 (CH₂), 78.5 (CH), 125.2 (CH), 125.8 (CH), 126.4 (2CH), 126.8 (2CH), 127.3 (CH), 129.4 (CH), 133.5 (C), 135.4 (C), 138.5 (C), 142.9 (C), 163.2 (C=O).

Anal. Calcd. for C₁₅H₁₂N₂O₄ (284.27): C, 63.38; H, 4.25; N, 9.85. Found: C, 63.22; H, 4.07; N, 9.81.

2,3-Dihydro-3-hydroxy-7-nitro-2-phenylmethyl-1*H*-isoindol-1-one (**7B**).

This product was obtained as a white-yellow solid, mp 198°; ir: ν 3319 (br, OH), 3025 (CH), 2977 (CH), 1701 (C=O), 1532 (NO₂) cm⁻¹; ¹H nmr: 4.28 (d, 1H, J = 14.8 Hz, CH₂-N), 4.93 (d, 1H, J = 14.8 Hz, CH₂-N), 5.56 (s, 1H, CH(OH)), δ 6.52 (br, 1H, OH), 7.16-7.25 (m, 5H, H_{benzene}), 7.57-7.66 (m, 3H, H_{phthalimide}); ¹³C nmr: δ 42.9 (CH₂), 78.7 (CH), 122.1 (CH), 125.8 (CH), 126.3 (CH), 127.1 (2CH), 127.3 (2CH), 131.7 (CH), 135.8 (C), 135.9 (C), 144.4 (C), 146.6 (C), 161.1 (C=O).

Anal. Calcd. for C₁₅H₁₂N₂O₄ (284.27): C, 63.38; H, 4.25; N, 9.85. Found: C, 63.19; H, 4.11; N, 9.62.

2,3-Dihydro-3-methoxycarbonylmethylthio-7-nitro-2-phenylmethyl-1*H*-isoindol-1-one (**8a**).

To a stirred solution of hydroxylactam **7B** (1.41 g, 5 mmoles) in 30 ml of dry dichloromethane were added methyl thioglycolate (0.61 g, 6 mmoles) and a catalytic amount of *p*-toluenesulfonic acid. After stirring overnight at room temperature, the solvent was evaporated and the residue was washed with a saturated solution of sodium hydrogencarbonate, dried over magnesium sulfate and concentrated *in vacuo*. The solid residue was recrystallized from ethanol to give **8a** in 78% yield, mp 139°; ir: ν 3300 (br, OH), 1740 (C=O), 1694 (C=O), 1536 (NO₂) cm⁻¹; ¹H nmr: δ 2.60 (d, 1H, J = 15.3 Hz, CH₂-S), 2.71 (d, 1H, J = 15.3 Hz, CH₂-S), 3.47 (s, 1H, CH₃), 4.23 (d, 1H, J = 14.8 Hz, CH₂-N), 5.24 (d, 1H, J = 14.8 Hz, CH₂-N), 5.28 (s, 1H, CH), 7.13-7.31 (m, 5H, H_{benzene}), 7.59-7.78 (m, 3H, H_{phthalimide}); ¹³C nmr: δ 28.8

(CH₃), 43.2 (CH₂), 53.2 (CH₂), 62.2 (CH), 123.4 (CH), 127.4 (CH), 127.8 (CH), 128.4 (C), 128.6 (2CH), 129.1 (2CH), 132.8 (CH), 136.1 (C), 144.8 (C), 146.4 (C), 161.7 (CO), 169.2 (CO).

Anal. Calcd. for C₁₈H₁₆N₂O₅S (372.14): C, 58.05; H, 4.33; N, 7.52. Found: C, 58.16; H, 4.21; N, 7.41.

3-Ethoxycarbonylmethoxy-2,3-dihydro-7-nitro-2-phenylmethyl-1*H*-isoindol-1-one (**8b**).

To a stirred and cooled solution of hydroxylactam **7B** (2 g, 7 mmol) in 30 ml of dry *N,N*-dimethylformamide was added, under nitrogen atmosphere, by portions sodium hydride (60% dispersion in mineral oil) (0.4 g, 10 mmol). After 15 minutes of reaction, a solution of ethyl bromoacetate (1.67 g, 10 mmol) in 10 ml of dry *N,N*-dimethylformamide was added dropwise over a period of 5 minutes. After 24 hours of reaction at room temperature, the solution was poured into water and the resulting precipitates were filtered off by suction, air dried and recrystallized from diethyl ether to give **8b** as a white solid in 82% yield, mp 192°; ir: ν 3039 (CH), 2989 (CH), 1726 (C=O), 1693 (C=O), 1530 (NO₂) cm⁻¹; ¹H nmr: δ 1.16 (t, 3H, J = 7.2 Hz, CH₃), 3.67 (d, 1H, J = 5.8 Hz, CH₂-O), 3.85 (d, 1H, J = 15.8 Hz, CH₂-O), 4.06 (q, 2H, J = 7.2 Hz, CH₂), 4.38 (d, 1H, J = 14.8 Hz, CH₂-N), 5.14 (d, 1H, J = 14.8 Hz, CH₂-N), 6.33 (s, 1H, CH), 7.08-7.57 (m, 5H, H_{benzene}), 7.69-7.77 (dd, 3H, J = 7.3 and 8.1 Hz, H_{5-phthalimide}), 8.12 (d, 1H, J = 7.3 Hz, H_{6-phthalimide}), 8.28 (d, 1H, J = 8.1 Hz, H_{4-phthalimide}); ¹³C nmr: δ 34.6 (CH₃), 44.1 (CH₂), 61.7 (CH₂), 63.7 (CH₂), 86.8 (CH), 127.5 (CH), 128.3 (CH), 129.1 (2CH), 129.6 (2CH), 132.3 (CH), 134.1 (C), 135.4 (C), 136.7 (CH), 136.8 (C), 144.6 (C), 164.7 (CO), 168.4 (CO).

Anal. Calcd. for C₁₉H₁₈N₂O₆ (370.36): C, 61.61; H, 4.89; N, 7.56. Found: C, 61.46; H, 4.91; N, 7.39.

3-Carboxymethylthio-2,3-dihydro-7-nitro-2-phenylmethyl-1*H*-isoindol-1-one (**9**).

Method A: A mixture of hydroxylactam **7B** (1.41 g, 5 mmol), thioglycolic acid (0.55 g, 6 mmol) and a catalytic amount of *p*-toluenesulfonic acid in 30 ml of dry dichloromethane was stirred overnight at room temperature. The solvent was evaporated and the residue was triturated with ether and filtered off by suction. The solid obtained was recrystallized from ethanol to give **9** in 80% yield, mp 162°; ir: ν 3109 (br, OH), 1716 (C=O), 1665 (C=O), 1539 (NO₂) cm⁻¹; ¹H nmr: δ 2.65 (s, 2H, CH₂-S), 4.37 (d, 1H, J = 14.7 Hz, CH₂-N), 5.28 (d, 1H, J = 14.7 Hz, CH₂-N), 5.35 (s, 1H, OH), 5.84 (s, 1H, CH), 7.21-7.38 (m, 3H, H_{benzene}), 7.66-7.71 (m, 3H, H_{5-phthalimide}+2H_{benzene}), 8.15 (d, 1H, J = 7.5 Hz, H_{6-phthalimide}), 8.26 (d, 1H, J = 7.8 Hz, H_{4-phthalimide}); ¹³C nmr: δ 29.1 (CH₂), 44.5 (CH₂), 69.0 (CH), 127.2 (CH), 128.2 (CH), 129.3 (CH), 128.7 (2CH), 129.1 (2CH), 130.9 (CH), 133.5 (C), 135.8 (C), 136.9 (C), 144.9 (C), 163.4 (CO), 174.6 (CO).

Anal. Calcd. for C₁₇H₁₄N₂O₅S (358.37): C, 56.97; H, 3.93; N, 7.81. Found: C, 56.87; H, 3.89; N, 7.77.

Method B: A mixture of methyl ester **8a** (1.86 g, 5 mmol), potassium carbonate (1.38 g, 10 mmol), and water (6 ml) in 20 ml of methanol was heated under reflux for 4 hours. After cooling, the solution was concentrated *in vacuo* and the residue was diluted with water (30 ml) and dichloromethane (50 ml). After separation, the aqueous layer was washed with dichloromethane and acidified to pH 2 with 2*M* hydrochloric acid solution. The mixture was extracted with dichloromethane and, after the

classical work up, the resulting residue was recrystallized from ethanol to give **9** as described above in 76% yield.

5,11*b*-Dihydro-8-nitroisoindolo[1,2-*d*][3,5]benzothiazocine-7,14(13*H*)-dione (**2B**).

Method A: A stirred suspension of thioglycolic acid derivative **9** (1.61 g, 4.5 mmol) in dry dichloromethane (25 ml) was treated slowly with freshly distilled thionyl chloride (0.73 g, 6 mmol) and the mixture was heated under reflux for 2 hours. After cooling, the solution was concentrated *in vacuo* and the residue was dissolved in dry dichloromethane (35 ml). The mixture was treated with aluminium trichloride (1.1 g, 8.2 mmol) over a period of 10 minutes at -5-0°. After 2 hours of reaction at room temperature, the solution was poured into cold water and decanted. The aqueous layer was extracted with dichloromethane and the organic layers were washed with water, brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting solid was recrystallized from ethanol to give **2B** in 56% yield.

Method B: The identical product to **2B** was obtained in 62% yield when a mixture of thioglycolic acid derivative **9** and thionyl chloride in dry dichloromethane was heated under reflux for 5 hours. The ketone **2B** was isolated as a white-yellow solid, mp 92°; ir: ν 3012 (CH), 1711 (C=O), 1675 (C=O), 1534 (NO₂) cm⁻¹; ¹H nmr: δ 2.90 (d, 1H, J = 16.1 Hz, CH₂-S), 3.19 (d, 1H, J = 16.1 Hz, CH₂-S), 4.66 (d, 1H, J = 16.8 Hz, CH₂-N), 5.41 (d, 1H, J = 16.8 Hz, CH₂-N), 6.17 (s, 1H, CH), 7.04 (m, 1H, H_{benzene}), 7.16-7.54 (m, 3H, H_{benzene}), 7.71-7.79 (dd, 1H, J = 7.8 and 8.1 Hz, H_{10-phthalimide}), 8.18 (d, 1H, J = 7.8 Hz, H_{9-phthalimide}), 8.36 (d, 1H, J = 8.1 Hz, H_{11-phthalimide}); ¹³C nmr: δ 40.9 (CH₂), 45.1 (CH₂), 65.4 (CH), 125.4 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.8 (C), 129.6 (CH), 130.1 (CH), 130.9 (CH), 133.5 (C), 135.7 (C), 136.5 (C), 142.2 (C), 162.7 (CO), 204.6 (CO).

Anal. Calcd. for C₁₇H₁₂N₂O₄S (340.36): C, 59.99; H, 3.55; N, 8.23. Found: C, 59.87; H, 3.49; N, 8.01.

3-Ethoxycarbonylmethoxy-2,3-dihydro-4-nitro-2-phenylmethyl-1*H*-isoindol-1-one (**12**).

Product **12** was obtained as a yellow solid in a yield of 88% (diethyl ether-hexane) by using the same procedure as that described for **8b**, mp 169°; ir: ν 3028 (CH), 2980 (CH), 1732 (C=O), 1698 (C=O), 1528 (NO₂) cm⁻¹; ¹H nmr: δ 1.21 (t, 3H, J = 7.5 Hz, CH₃), 3.71 (d, 1H, J = 14.7 Hz, CH₂-O), 3.81 (d, 1H, J = 14.7 Hz, CH₂-O), 4.00 (q, 2H, J = 7.5 Hz, CH₂), 4.49 (d, 1H, J = 15.2 Hz, CH₂-N), 5.19 (d, 1H, J = 15.2 Hz, CH₂-N), 6.21 (s, 1H, CH), 7.14-7.28 (m, 5H, H_{benzene}), 7.61-7.84 (m, 2H, H₆ and 5-phthalimide), 8.09 (d, J = 7.5 Hz, 1H, H_{7-phthalimide}); ¹³C nmr: δ 14.5 (CH₃), 40.4 (CH₂), 61.9 (CH₂-N), 63.3 (CH₂-O), 82.6 (CH), 126.6 (CH), 127.9 (2CH), 128.2 (CH), 129.7 (2CH), 130.8 (CH), 132.8 (C), 133.8 (C), 137.9 (CH), 144.9 (C), 146.9 (C), 163.7 (CO), 172.5 (CO).

Anal. Calcd. for C₁₉H₁₈N₂O₆ (370.36): C, 61.61; H, 4.89; N, 7.56. Found: C, 61.52; H, 4.78; N, 7.42.

Reduction of 2,3-Dihydro-3-hydroxy-4-nitro-2-phenylmethyl-1*H*-isoindol-1-one (**7A**).

To a stirred solution of α -hydroxylactam **7A** (1.42 g, 5 mmol) and nickel chloride hexahydrate (3.56 g, 15 mmol) in dry methanol (40 ml) at -5-0° was added, by portions over a period of 10 minutes, 3 equivalents of sodium borohydride (0.57 g, 15 mmol). After 1 hour of reaction at 0° then 1 hour at room temperature, the excess sodium borohydride was decomposed by careful addition of 10% hydrochloric acid solution (40 ml). After removal of the solvent under reduced pressure, the black residue

was diluted with water (40 ml) and the whole was extracted twice with 30 ml of dichloromethane to remove the unreacted α -hydroxylactam **7A**. The aqueous layer was washed with dichloromethane and treated with 10% ammonia solution to pH 8-9, the suspension formed was extracted with dichloromethane, and the organic layer was washed with water, brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting solid as a mixture of ω -carbinol lactam **14** and the opened amide-alcohol **15** (66/34) (75%), was separated by chromatography on a silica gel column using dichloromethane as eluent to give pure **14** and **15**.

4-Amino-2,3-dihydro-3-hydroxy-2-phenylmethyl-1H-isindol-1-one (**14**).

This product was obtained as a white solid, mp 262°; ir: ν 3295 (br, OH and NH₂), 3015 (CH), 2978 (CH), 1678 (C=O), cm⁻¹; ¹H nmr: δ 2.71 (br, 2H, NH₂), 4.59 (d, 1H, J = 15.1 Hz, CH₂-N), 4.89 (d, 1H, J = 15.1 Hz, CH₂-N), 5.12 (d, 1H, J = 6.5 Hz, OH(CH)), 5.81 (d, 1H, J = 6.5 Hz, CH(OH)), 6.70-6.75 (dd, 2H, J = 4.3 and 4.6 Hz, H₆-phthalimide), 7.01 (d, 1H, J = 4.3 Hz, H₅-phthalimide), 7.09-7.29 (m, 5H, H_{benzene}), 7.37 (d, 1H, J = 4.6 Hz, H₇-phthalimide); ¹³C nmr: δ 44.5 (CH₂), 69.8 (CH), 114.7 (CH), 121.4 (CH), 127.9 (CH), 128.6 (2CH), 129.3 (2CH), 129.8 (C), 130.1 (CH), 132.1 (C), 136.4 (C), 140.1 (C), 167.3 (C=O).

Anal. Calcd. for C₁₅H₁₄N₂O₂ (254.28): C, 70.85; H, 5.54; N, 11.01. Found: C, 70.75; H, 5.43; N, 10.95.

3-Amino-2-hydroxymethyl-(N-benzyl)benzamide (**15**).

This product was obtained as a yellow solid mp 273°; ir: ν 3454 (br, OH), 3350 (NH₂), 3029 (CH), 2989 (CH), 1686 (C=O) cm⁻¹; ¹H nmr: δ 4.68 (s, 2H, CH₂-O), 4.71 (s, 2H, CH₂-NH), 5.13 (br, 1H, OH), 5.25 (br, 2H, NH₂), 6.57-6.94 (dd, 1H, J = 7.5 and 8.1 Hz, H₅-benzene), 6.75 (d, 1H, J = 8.1 Hz, H₄-benzene), 6.88 (br, 1H, NH), 7.01-7.42 (m, 6H, H₆-benzene + H_{benzene}); ¹³C nmr: δ 45.9 (CH₂), 49.6 (CH₂), 110.7 (CH), 113.3 (CH), 127.1 (CH), 127.8 (2CH), 128.1 (C), 128.7 (2CH), 132.9 (CH), 137.1 (C), 142.6 (C), 145.9 (C), 170.1 (C=O).

Anal. Calcd. for C₁₅H₁₆N₂O₂ (256.30): C, 70.29; H, 6.29; N, 10.92. Found: C, 70.11; H, 6.21; N, 11.01.

General Procedure for Preparation of Enamides (**16a**) and (**16b**).

To a stirred suspension of ω -alkynyl- ω -carbinol lactam **6a** or **6b** (2.21 mmoles) in dry ethanol (15 ml) was added a catalytic quantity of *p*-toluenesulfonic acid (0.05 g) and the mixture was heated under reflux for 2 hours. After cooling, the solution was concentrated *in vacuo* and the residue was dissolved in dichloromethane (30 ml). The organic layer was washed with 2M sodium bicarbonate solution, brine, water, dried over magnesium sulfate and concentrated under reduced pressure. The resulting solid was recrystallized from dry diethyl ether to give **16a** or **16b**.

2,3-Dihydro-7-nitro-3-(2'-oxobutylidene)-2-phenylmethyl-1H-isindol-1-one (**16a**).

This compound was obtained as a white solid in 88% yield, mp 180° (diethyl ether); ir: ν 3032 (CH), 2995 (CH), 1715 (C=O), 1675 (C=O), 1615 (C=C), 1533 (NO₂) cm⁻¹; ¹H nmr: δ 0.72 (t, 3H, J = 7.4 Hz, CH₃), 1.41 (m, 2H, J = 7.4 Hz, CH₂), 2.35 (d, 2H, J = 7.4 Hz, CH₂-CO), 4.87 (s, 2H, CH₂-N), 5.95 (s, 1H, C=CH), 7.05-7.18 (m, 5H, H_{benzene}), 7.57-7.66 (dd, 1H, J = 7.5 and 8.1 Hz, H₅-phthalimide), 7.71 (d, 1H, J = 8.1 Hz, H₆-phthalimide), 9.12 (d, 1H, J = 7.5 Hz, H₄-phthalimide); ¹³C nmr: δ 13.6 (CH₃), 17.8 (CH₂), 32.1 (CH₂), 47.2 (CH₂), 93.1 (C=), 115.9 (C=), 125.6

(CH), 126.9 (2CH), 127.9 (CH), 129.1 (C), 131.2 (C), 134.2 (C), 135.1 (2CH), 135.8 (CH), 135.9 (C), 143.4 (C), 164.3 (CO), 183.3 (CO).

Anal. Calcd. for C₂₀H₁₈N₂O₄ (350.37): C, 68.56; H, 5.17; N, 7.99. Found: C, 68.44; H, 5.11; N, 7.90.

2,3-Dihydro-7-nitro-3-(2'-oxo-2'-phenylethylidene)-2-phenylmethyl-1H-isindol-1-one (**16b**).

This compound was obtained as a yellow solid in 92% yield; mp 217° (ethanol), ir: ν 3025 (CH), 2992 (CH), 1732 (C=O), 1650 (C=O), 1603 (C=C), 1539 (NO₂) cm⁻¹; ¹H nmr: δ 5.11 (s, 2H, CH₂-N), 6.67 (s, 1H, C=CH), 7.15-7.45 (m, 8H, H_{benzene}), 7.50-7.55 (m, 2H, H_{benzene}), 7.70-7.77 (dd, 1H, J = 7.4 and 8.0 Hz, H₅-phthalimide), 8.06 (d, 1H, J = 7.4 Hz, H₆-phthalimide), 8.19 (d, 1H, J = 8.0 Hz, H₄-phthalimide); ¹³C nmr: δ 44.2 (CH₂), 100.1 (CH=), 124.6 (CH), 126.5 (2CH), 126.7 (CH), 127.6 (2CH), 128.1 (2CH), 128.5 (CH), 128.8 (2CH), 131.5 (CH), 132.3 (C), 133.1 (CH), 135.1 (C), 136.1 (C), 137.3 (C), 141.1 (C), 147.3 (C), 164.7 (CO), 189.2 (CO).

Anal. Calcd. for C₂₃H₁₆N₂O₄ (384.39): C, 71.86; H, 4.19; N, 7.28. Found: C, 71.79; H, 4.20; N, 7.22.

REFERENCES AND NOTES

- [1] E. Valencia, I. Weiss, S. Firdous, A. J. Freyer and M. Shamma, *Tetrahedron*, **40**, 3957 (1984).
- [2] P. H. Mazzocchi, C. R. King and H. L. Aammon, *Tetrahedron Letters*, **20**, 2473 (1987).
- [3] S. V. Kessar, T. Singh and R. Vohra, *Tetrahedron Letters*, **28**, 5323 (1987).
- [4] H. Ishibashi, H. Kawanami, H. Iriyama and M. Ikeda, *Tetrahedron Letters*, **36**, 6733 (1995).
- [5] S. M. Weinreb and J. Auerbach, *J. Am. Chem. Soc.*, **97**, 2503 (1975).
- [6] P. Netchitaïlo, M. Othman and B. Decroix, *J. Heterocyclic Chem.*, **34**, 321 (1997).
- [7] P. Pigeon and B. Decroix, *J. Heterocyclic Chem.*, **34**, 375 (1997).
- [8] S. Mamouni, A. Daïch and B. Decroix, *Synth. Commun.*, **27**, 2241 (1997).
- [9] J. P. Gesson, J. C. Jacquesy and D. Rambaud, *Bull. Soc. Chim. Fr.*, **129**, 227 (1992).
- [10] S. Mamouni, A. Daïch and B. Decroix, *J. Heterocyclic Chem.*, **33**, 1251 (1996).
- [11] J. B. P. A. Wijnberg, H. E. Schoemaker and W. N. Speckamp, *Tetrahedron*, **31**, 1437 (1975).
- [12] W. N. Speckamp and H. Hiemstra, *Tetrahedron*, **41**, 436 (1985).
- [13] P. Pigeon and B. Decroix, *Synth. Commun.*, **27**, 1423 (1997).
- [14] E. A. Omar, C. Tu, C. T. Wigal and L. L. Braun, *J. Heterocyclic Chem.*, **29**, 947 (1992).
- [15] A. Mamouni, A. Daïch, and B. Decroix, *Synth. Commun.*, **28**, 1839 (1998).
- [16] A. Couture, E. Deniau, P. Grandclaoudon and S. Lebrun, *Tetrahedron Letters*, **37**, 7749 (1996).
- [17] P. Pigeon and B. Decroix, *Tetrahedron Letters*, **37**, 7707 (1996).
- [18] N. G. Kundu, M. Pal and B. Nandi, *J. Chem. Soc. Perkin Trans. I*, 561 (1998).
- [19] V. Scartoni, R. Fiashi, D. Catalano L. Morelli, and A. Marsili, *J. Chem. Soc. Perkin Trans. I*, 1547 (1979).
- [20] I. Y. Jeong, W. S. Lee, S. Goto, S. Sano, M. Shiro and Y. Nagao, *Tetrahedron*, **54**, 14437 (1998).
- [21] T. Watanabe, F. Hamaguchi and S. Ohki, *Chem. Pharm. Bull.*, **20**, 2123 (1972).
- [22] T. Watanabe, F. Hamaguchi and S. Ohki, *Chem. Pharm. Bull.*, **26**, 530 (1978).