Synthesis of Thieno[2',3'(3',4' or 3',2'):5,6]azepino[2,1-*a*]isoindolediones from *N*-Thienyl-2(3)-ylmethylphthalimides

Pascal Pigeon and Bernard Decroix*

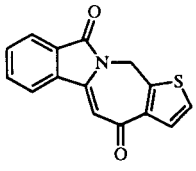
Laboratoire de Chimie, Faculté des Sciences de l'Université du Havre,
30, rue Gabriel Péri, 76600 Le Havre, France

Received July 20, 1995
Revised September 12, 1995

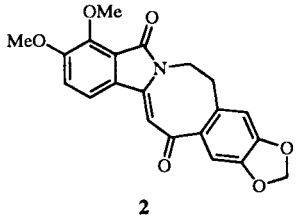
Reduction of *N*-thienylmethylphthalimides **5a-e** followed by the Wittig reaction gave the substituted acetic acids **8a-e**. Their corresponding acyl chlorides where cyclized in the presence of aluminium trichloride to furnish the cyclic ketones **9a-e**. Treatment of these ketones with bromine followed by triethylamine, or with selenium dioxide led to the thienoazepinoisoindolediones **1a-e**.

J. Heterocyclic Chem., **33**, 129 (1996).

During the course of our work concerning the synthesis of new fused polyheterocyclic compounds with potential therapeutic interest we described in previous papers some thieno or furodiazepines annelated to a pyrrole [1], pyrrolidine [2] or piperidine [3] rings and recently we synthesized piperidinothienoazepinones [4]. Now, we wish to report the synthesis of thienoazepinones fused to an isoindole ring as **1a**. This heterocycle is analogous to isoindolobenzazepine alkaloid isolated from *Berberidaceae* [5] and could be considered as precursor of isoindolothienoazocines or isoindolothienodiazocines compounds closes to the new class of isoindolobenzazocines alkaloid [6,7], as magallanesine **2** is the first example.



1a

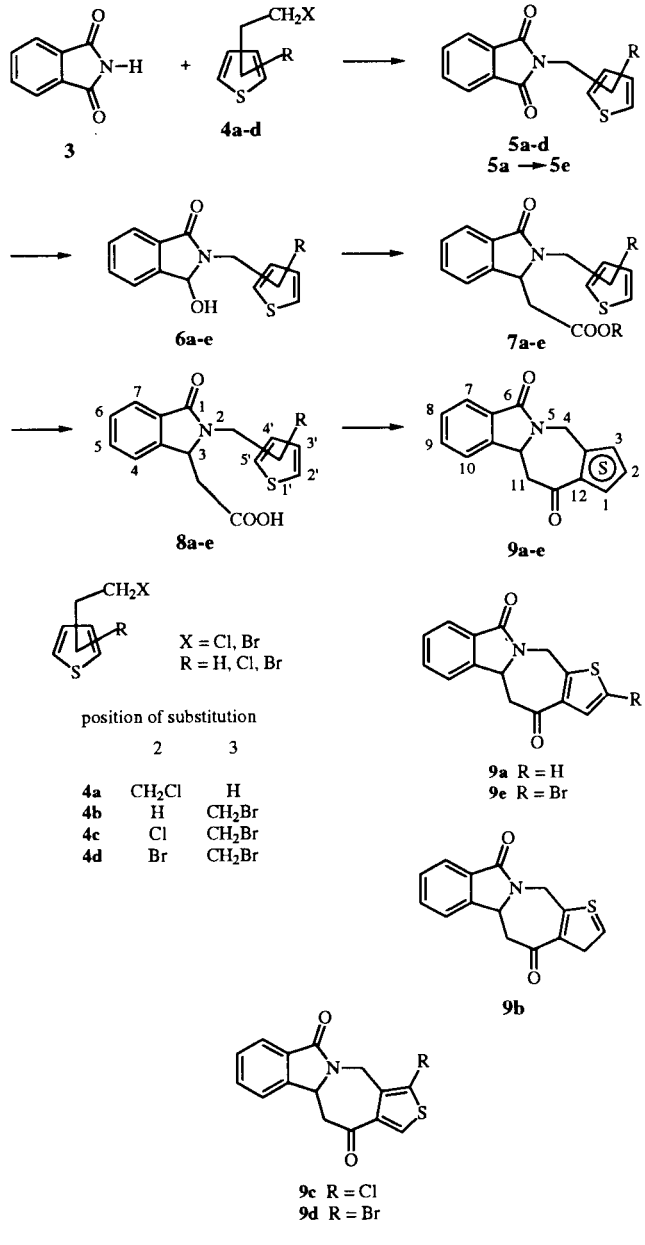


2

As shown in Scheme 1, the alkylation of phthalimide **3** was carried out with various halogenomethylthiophenes **4a-d** in dimethylformamide using potassium carbonate as base. The *N*-alkylated phthalimides **5a-d** were isolated in good yields (56 to 77%). The bromo compound **5d** could be prepared from **5b** but upon the conditions of the halogenation (see Scheme 2) we obtained a mixture of products, the 2-(2'-bromothien-3'-ylmethyl)phthalimide **5d**, 2-(2'-bromothien-4'-ylmethyl)phthalimide **5f** and 2-(2',5'-bromothien-3'-ylmethyl)phthalimide **5g** accompanied with a small amount of the starting material. Unfortunately, the bromo derivatives **5d,f,g** could not be separated whatever the conditions (chromatography, crystallization,...) so the alkylation with the appropriate halogenomethylthiophene was preferred.

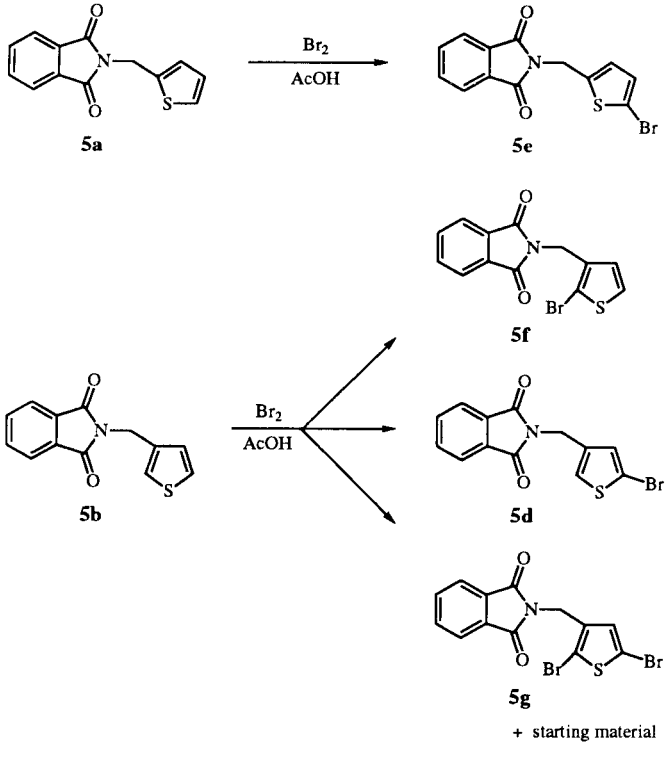
Nervertheless, bromination of **5a** with an equivalent of bromine in acetic acid gave the 5'-bromo derivative **5e** in a quantitative yield. The alkylated phthalimides **5a-e** were

Scheme 1



reduced with sodium borohydride to give the hydroxyisoindolones **6a-e** in good yields (94-99%). The Wittig reaction using ethoxycarbonylmethylidenetriphenylphosphorane led to the esters **7a-e**. Even if the triphenylphosphine oxide formed during the reaction and the esters could be separated, by chromatography on silica gel eluting with dichloromethane, the mixture was used without further purification for the next step. Thus, the hydrolysis of the crude product **7a-e** using a solution of potassium carbonate followed with an acidic treatment gave, the expected substituted acetic acids **8a-e** in good yield 65 to 90% calculated from **6a-e**.

Scheme 2

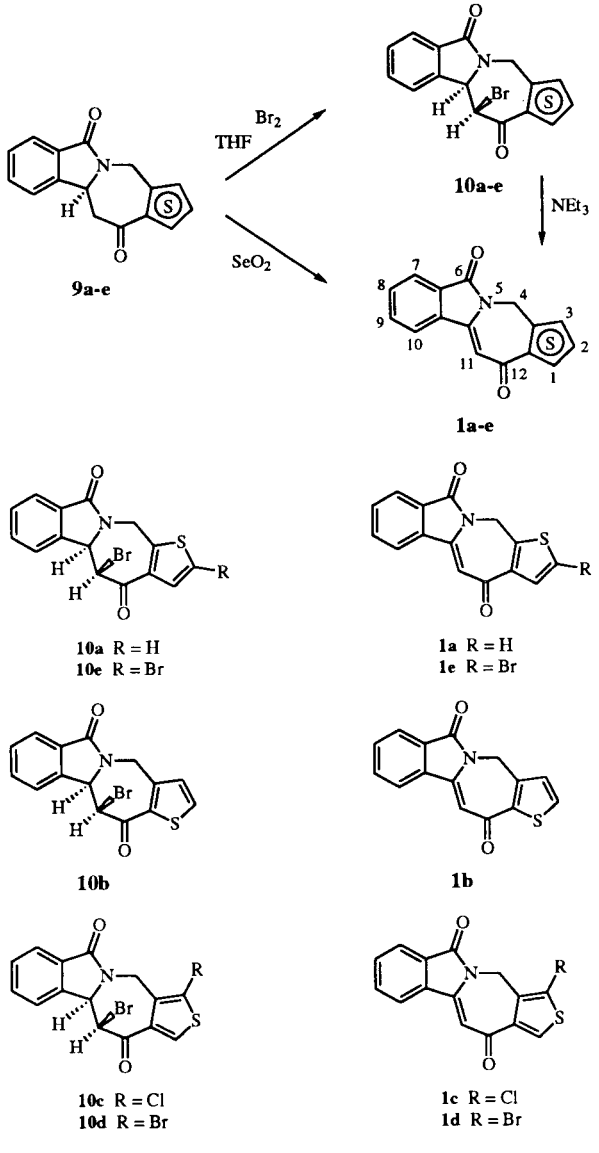


quantity of Br2	1 eq	1.25 eq	2.1 eq
5d	8%	5%	0%
5f	58%	74%	0%
5g	15%	21%	100%
starting material	19%	0%	0%

All of these compounds were characterized by ir and nmr spectroscopy and microanalyses. Details are reported in the experimental section but there are a number of interesting features. The -CH_2-N protons in compounds **5a-e** appear as a singlet with a chemical shift of about 4.8 ppm and they appear as an AB system in **6-8a-e** with chemical shifts of about 4.5 ppm and 5.0 ppm and a coupling constant of about 15 Hz. Furthermore, the proton attached to the carbon bearing the hydroxy or methylcarboxylic group appears as a doublet (5.6 ppm, $J_{H\text{-}OH}$ = 11.5 Hz) in **6a-e** and as a doublet of doublet (4.75 ppm, J = 7, 4.5 Hz) in **8a-e** because the two adjacent protons of the close methylene are non equivalent. Treatment of the acid **8** in polyphosphoric acid, according to our previous reports with other acids [3,4] gave no result, we observed a resinification of the starting material. On the other hand, the cyclization occured under Friedel-Crafts conditions. Acids **8a-e** were treated with thionyl chloride in dichloromethane and the resulting acid chloride in the presence of aluminium trichloride of high quality as a catalyst gave the cyclic ketones **9a-e** in very good yield (91 to 98%). Because the α-position of thiophene is more reactive than the β-position, the acid **8b** was cyclized into the ketone **9b**. When the α-position is blocked with a halogen (acids **8c** and **8d**) cyclization occured at the β-position in contrast to our previous work [8] in which the chlorothiophene derivative furnished the chloroketone whereas the bromothiophene derivative led to a mixture of the expected bromoketone (minus product), and the ketone corresponding to a cyclization with the α-position (major product; thus, the bromine was substituted). In a same manner, the bromoacid **8e** led to the bromoketone **9e**. Thus, whatever the halogen (bromine or chlorine), the cyclization occured exclusively with the free *ortho* position of the thiophene ring. The structure of this new tetracyclic system was supported by the ir and nmr spectra as well as by the microanalyses. The ketones **9a-b** display a characteristic doublet for each proton of an α, β-disubstituted thiophene ring with the usual coupling constant of J = 5.0 Hz. Furthermore for the ketone **9a** (for example) the protons attached to C_4 are non equivalent and appear as a AB system with chemical shifts of 4.93 and 5.34 ppm and a coupling constant of J = 17 Hz characteristic of *gem* protons. Otherwise, the protons attached to C_{11} appear as a doublet of doublet with chemical shifts of 2.99 ppm for H_{11a} and 3.47 ppm for H_{11b} and coupling constants of J = 15.9 Hz (H_{11a}, H_{11b}), J = 8.2 Hz (H_{11a}-H_{10b}) and J = 3.8 Hz (H_{11b}-H_{10b}). Finally, the proton H_{10b} appears as a doublet of doublet (J = 3.8, 8.2 Hz) with a chemical shift of 4.99 ppm. The spectra of **9b-e** revealed the same remarks (details are reported in the Experimental).

The H_{10b} proton might be particularly labile, so it was interesting to study the dehydrogenation of the ketones **9a-e** which could lead to the expected thienoazepinoisoindolediones **1a-e** (Scheme 3). Actually, treated with an equivalent of bromine in tetrahydrofuran we observed the substitution of the proton next to the ketone. Under this condition the halogenation of the thiophene did not occur. The ^1H nmr of the crude product shows the presence of a small amount of the α, β-unsaturated ketone **1** (20%) consecutively to an elimination of one molecule of hydrogen bromide. The separation of the bromo derivative **10a-e** (80%) from the mixture was difficult. The ^1H nmr spectrum of **10a** revealed the presence of only one isomer. The

Scheme 3



signal of H_{10b} with a chemical shift of 5.0 ppm is a doublet exhibiting a *cis* coupling constant measured at 1.2 Hz. For the other compounds **10b-e**, the signal of H_{10b} is a singlet. The molecular model of the *cis* configuration shows a dihedral angle close to 90° between H_{10b} and H_{11} and the coupling constant becomes non observable. The signal of H_{11} is a doublet (J = 1.2 Hz) for **10a** and a singlet for **10b-e**. These observations suggest a *cis* structure for **10a-e**. The interaction between the bromine atom and the electron doublet of the nitrogen atom favors the displacement of one molecule of hydrogen bromide to give the unsaturated compounds **1a-e**. In fact the dehydrohalogenation was achieved when triethylamine, used as a base, was added directly to the reaction mixture. In that latter case the thienoazepinoisoindolediones **1a-e** were isolated as crystals in excellent yields (90 to 98%). On the other hand these azepines could be obtained by a direct oxidization of the ketones **9** using selenium dioxide. The structure of the compounds **1a-e** were supported by ir and nmr spectroscopy and elemental analysis. For example, the ^1H nmr spectrum of **1a** shows a singlet for H_{11} with a chemical shift of 6.30 ppm. This deshielding is due to the double bond C_{10b}-C_{11} and to the proximity of the carbonyl group C_{12} = 0. It is interesting to note that the singlet observed for the two protons attached to C_4 with a chemical shift of 5.20 ppm. Otherwise, the signals of the protons of the thiophene ring and the benzene ring are similar to those observed in the corresponding cyclic ketone **9a**. Similar observations can be made in the ^1H nmr spectra of compounds **1b-e**.

In conclusion, an efficient synthesis of thieno[3',2'(2',3' or 3',4'):5,6]azepino[2,1-*a*]isoindolediones **9a-e** was described from phthalimide and halogenomethylthiophenes. Their facile dehydrogenation to **1a-e** were achieved according to two different methods in excellent yields. The reactivity of these ketones are under investigations and the results will be published soon.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin Elmer FTIR paragon 1000 spectrometer. The ^1H an ^{13}C nmr spectra were recorded on a Bruker AC-200 instrument in deuteriochloroform solution and chemical shift (δ) are expressed in ppm relative to internal TMS. 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. The elemental analyses were carried out by the microanalysis laboratory of INSA at Rouen, F 76130 M^T. S^T. Aignan. The halogenomethylthiophenes **4a-d** were synthesized as previously described [9,10,11].

2-Thienylmethylphthalimides **5a-d**.

General Procedure.

A mixture of halogenomethylthiophene **4a-d** (0.15 mole), phthalimide (33 g, 0.225 mole), potassium carbonate (15.5 g, 0.113 mole) and 100 ml of dry dimethylformamide was stirred under light reflux for 4 hours. After cooling, the mixture was poured into water. The precipitate was separated by filtration, washed with water, dried and chromatographed on silica gel eluting with dichloromethane to give crystals. Recrystallization from ethanol afforded the 2-thienylmethylphthalimides **5a-d** as white crystals.

2-(Thien-2'ylmethyl)phthalimide (**5a**).

This compound was obtained in a yield of 71%, mp 125° (lit [12] 124-125°).

2-(Thien-3'-ylmethyl)phthalimide (**5b**).

This compound was obtained in a yield of 69%, mp 129° (lit [13], 130-132°).

2-(2'-Chlorothien-3'-ylmethyl)phthalimide (**5c**).

This compound was obtained in a yield of 77%, mp 92°; ir: 1723 (C=O) cm^{-1}; ^1H nmr: δ 4.66 (s, 2H, CH_2), 6.84 (d, 1H, $H_{4'}$, J = 5.9 Hz), 6.90 (d, 1H, $H_{5'}$, J = 5.9 Hz), 7.48-7.60 (m, 2H, H_{arom}), 7.61-7.72 (m, 2H, H_{arom}).

Anal. Calcd. for $C_{13}H_8ClNO_2S$: C, 56.22; H, 2.90; N, 5.04. Found: C, 56.36; H, 3.15; N, 4.89.

2-(2'-Bromothien-3'-ylmethyl)phthalimide (**5d**).

This compound was obtained in a yield of 56%, mp 100° (lit [14] 99°).

2-(2'-Bromothien-5'-ylmethyl)phthalimide (**5e**).

A mixture of **5a** (0.243 g, 1 mmole), acetic acid (20 ml), bromine (0.18 g, 1.1 mmoles) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The crude product was dissolved in dichloromethane, washed with a solution of sodium hydrogenocarbonate, water, dried (magnesium sulfate). The solvent was evaporated to give **5e** (0.322 g, 100%) as white ctystals, mp 100°; ir: 1722 (C=O) cm^{-1}; ^1H nmr: δ 4.90 (s, 2H, CH_2) 6.87 (m, 2H, $H_{3'}$ and $H_{4'}$), 7.64-7.75 (m, 2H, H_{arom}), 7.78-7.88 (m, 2H, H_{arom}).

Anal. Calcd. for $C_{13}H_8BrNO_2S$: C, 48.47; H, 2.50; N, 4.35. Found: C, 48.28; H, 2.66; N, 4.21.

2-(2'-Bromothien-3'-ylmethyl)phthalimide (**5d**), 2-(2'-Bromothien-4'-ylmethyl)phthalimide (**5f**), 2-(2',5'-Dibromothien-3'-ylmethyl)phthalimide (**5g**).

The same method for bromination was used with 1.25 equivalents of bromine to furnish an inseparable mixture of **5d** (5%), **5f** (74%), **5g** (21%). With 2.1 equivalents of bromine, **5g** was obtained pure in a quantitative yield, mp 150°; ir: 1715 (C=O) cm^{-1}; ^1H nmr: δ 4.73 (s, 2H, CH_2), 6.95 (s, 1H, $H_{4'}$), 7.66-7.76 (m, 2H, H_{arom}), 7.78-7.88 (m, 2H, H_{arom}).

Anal. Calcd. for $C_{13}H_7Br_2NO_2S$: C, 38.93; H, 1.76; N, 3.49. Found: C, 39.06; H, 1.51; N, 3.39.

2,3-Dihydro-3-hydroxy-2-(thienylmethyl)-1*H*-isoindol-1-ones **6a-e**.

General Procedure.

To a mixture of phthalimidomethylthiophene **5a-e** (4 mmoles) in dry methanol (40 ml) at 0° was added sodium borohydride (0.9 g, 24 mmoles) in one portion. To this mixture were added 5 drops of ethanolic hydrochloric acid solution (prepared from 9 drops of concentrated hydrochloric acid in ethanol (15 ml) at regular (10 minute) intervals. The reaction was controlled by tlc. When the starting product had disappeared (30 minutes), the excess sodium borohydride was decomposed by careful addition of cold water (15 ml) and diluted hydrochloric acid. Sodium hydrogenocarbonate was added and the solvent was evaporated. The residue was triturated with water and the hydroxylactam **6a-e** was separated by filtration, washed with water, dried and recrystallized from ethanol.

2,3-Dihydro-3-hydroxy-2(thien-2'-ylmethyl)-1*H*-isoindol-1-one (**6a**).

This compound was obtained in a yield of 98%, mp 146°; ir: 3310 (OH), 1668 (C=O) cm^{-1}; ^1H nmr: δ 3.47 (d, 1H, OH, J = 11.7 Hz), 4.47 (d, 1H, CH_2, J = 15.3 Hz), 4.89 (d, 1H, CH_2, J = 15.3 Hz), 5.69 (d, 1H, H_3, J = 11.7 Hz), 6.90 (dd, 1H, $H_{4'}$, J = 3.5, 5.1 Hz), 7.02 (dd, 1H, $H_{3'}$, J = 1.3, 3.5 Hz), 7.17 (dd, 1H, $H_{5'}$, J = 1.3, 5.1 Hz), 7.40-7.60 (m, 3H, $H_{4,5,6}$), 7.66 (d, 1H, H_7, J = 7.3 Hz).

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.51; H, 4.39; N, 5.51.

2,3-Dihydro-3-hydroxy-2(thien-3'-ylmethyl)-1*H*-isoindol-1-one (**6b**).

This compound was obtained in a yield of 99%, mp 147°; ir: 3203 (OH), 1710 (C=O) cm^{-1}; ^1H nmr: δ 3.26 (d, 1H, OH, J = 11.8 Hz), 4.30 (d, 1H, CH_2, J = 14.9 Hz), 4.74 (d, 1H, CH_2, J = 14.9 Hz), 5.60 (d, 1H, H_3, J = 11.8 Hz), 7.00 (dd, 1H, $H_{4'}$, J = 1.6, 4.8 Hz), 7.18-7.24 (m, 2H, $H_{2',5'}$), 7.38-7.59 (m, 3H, $H_{4,5,6}$), 7.63 (d, 1H, H_7, J = 7.3 Hz).

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.39; H, 4.29; N, 5.40.

2,3-Dihydro-3-hydroxy-2-(2'-chlorothien-3'-ylmethyl)-1*H*-isoindol-1-one (**6c**).

This compound was obtained in a yield of 94%, mp 143°; ir: 3291 (OH), 1674 (C=O) cm^{-1}; ^1H nmr: δ 2.87 (d, 1H, OH, J = 11.2 Hz), 4.43 (d, 1H, CH_2, J = 15.1 Hz), 4.81 (d, 1H, CH_2, J = 15.1 Hz), 5.65 (d, 1H, H_3, J = 11.2 Hz), 6.92 (d, 1H, $H_{4'}$, J = 5.6 Hz), 7.02 (d, 1H, $H_{5'}$, J = 5.6 Hz), 7.43-7.60 (m, 2H, $H_{4,5,6}$), 7.74 (d, 1H, H_7, J = 7.0 Hz).

Anal. Calcd. for $C_{13}H_{10}ClNO_2S$: C, 55.82; H, 3.60; N, 5.01. Found: C, 55.85; H, 3.54; N, 5.14.

2,3-Dihydro-3-hydroxy-2-(2'-bromothien-3'-ylmethyl)-1H-isoindol-1-one (**6d**).

This compound was obtained in a yield of 95%, mp 153°; ir: 3312 (OH), 1682 (C=O) cm^{-1}; ^1H nmr: δ 3.23 (d, 1H, OH, J = 11.0 Hz), 4.37 (d, 1H, CH_2, J = 15.1 Hz), 4.72 (d, 1H, CH_2, J = 15.1 Hz), 5.64 (d, 1H, H_3, J = 11.0 Hz), 6.90 (d, 1H, $H_{4'}$, J = 5.6 Hz), 7.17 (d, 1H, $H_{5'}$, J = 5.6 Hz), 7.44-7.60 (m, 3H, $H_{4,5,6}$), 7.70 (d, 1H, H_7, J = 7.0 Hz).

Anal. Calcd. for $C_{13}H_{10}BrNO_2S$: C, 48.16; H, 3.11; N, 4.32. Found: C, 48.32; H, 3.20; N, 4.37.

2,3-Dihydro 3-hydroxy-2-(2'-bromothien-5'-ylmethyl)-1*H*-isoindol-1-one (**6e**).

This compound was obtained in a yield of 97%, mp 164°; ir: 3318 (OH), 1671 (C=O) cm^{-1}; ^1H nmr: δ 2.71 (d, 1H, OH, J = 11.8 Hz), 4.51 (d, 1H, CH_2, J = 15.5 Hz), 4.98 (d, 1H, CH_2, J = 15.5 Hz), 5.73 (d, 1H, H_3, J = 11.8 Hz), 6.81 (d, 1H, $H_{3'}$, J = 3.6 Hz), 6.87 (d, 1H, $H_{4'}$, J = 3.6 Hz), 7.46-7.60 (m, 3H, $H_{4,5,6}$), 7.75 (d, 1H, H_7, J = 7.2 Hz).

Anal. Calcd. for $C_{13}H_{10}BrNO_2S$: C, 48.16; H, 3.11; N, 4.32. Found: C, 48.21; H, 3.30; N, 4.20.

2,3-Dihydro-1-oxo-2-(thienylmethyl)-1*H*-isoindol-3-acetic Acids **8a-e**.

General Procedure.

A solution of carbethoxycarbonyltriphenylphosphorane (1 g, 2.87 mmoles), hydroxylactam **6a-e** (2.45 mmoles) in toluene (6 ml) was refluxed with stirring overnight. The solvent was evaporated under reduced pressure (at this step, the ester **7a-e** could be isolated by chromatography as an oil) and potassium carbonate (0.6 g), water (1.5 ml) and methanol (6 ml) were added. The mixture was stirred under reflux for 2 hours, then concentrated under reduced pressure. Water and dichloromethane was added and the organic layer was discarded. The aqueous layer was washed with dichloromethane and acidified with hydrochloric acid (10%) to *p*H 2. Compound **8** was extracted with dichloromethane rapidly before crystallization occurs. After

removal of the solvent, the residue was recrystallized from acetone to give pure **8a-e**.

2,3-Dihydro-1-oxo-2-(thien-2'-ylmethyl)-1*H*-isoindol-3-acetic Acid (**8a**).

This compound was obtained in a yield of 87%, mp 120°, ir: 2983 (OH), 1727 (COOH) 1658 (C=O) cm^{-1}; ^1H nmr: δ 2.67 (dd, 1H, CH_2(COOH), J = 7.0, 16.1 Hz), 2.94 (dd, 1H, CH_2(COOH), J = 5.2, 16.1 Hz), 4.54 (d, 1H, CH_2-N, J = 15.9 Hz), 4.89 (dd, 1H, H_3, J = 5.2, 7.0 Hz), 5.35 (d, 1H, CH_2-N, J = 15.9 Hz), 6.89 (dd, 1H, $H_{4'}$, J = 3.5, 5.1 Hz), 7.00-7.23 (m, 2H, $H_{3',5'}$), 7.41-7.52 (m, 3H, $H_{4,5,6}$), 7.83 (d, 1H, H_7, J = 7.8 Hz).

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.88. Found: C, 62.43; H, 4.38; N, 4.60.

2,3-Dihydro-1-oxo-2-(thien-3'-ylmethyl)-1*H*-isoindol-3-acetic Acid (**8b**).

This compound was obtained in a yield of 65%, mp 140°; ir: 3000 (OH), 1732 (COOH) 1651 (C=O) cm^{-1}; ^1H nmr: δ 2.49 (dd, 1H, CH_2(COOH), J = 7.1, 16.1 Hz), 2.79 (dd, 1H, CH_2(COOH), J = 5.4, 16.1 Hz), 4.34 (d, 1H, CH_2-N, J = 15.4 Hz), 4.75 (dd, 1H, H_3, J = 5.4, 7.1 Hz), 5.07 (d, 1H, CH_2-N, J = 15.4 Hz), 6.94 (dd, 1H, $H_{4'}$, J = 1.5, 4.8 Hz), 7.10-7.19 (m, 2H, $H_{2',5'}$), 7.32-7.45 (m, 3H, $H_{4,5,6}$), 7.73 (d, 1H, H_7, J = 6.8 Hz).

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.88. Found: C, 62.39; H, 4.47; N, 4.81.

2,3-Dihydro-1-oxo-2-(2'-chlorothien-3'-ylmethyl)-1*H*-isoindol-3-acetic Acid (**8c**).

This compound was obtained in a yield of 77%, mp 180°; ir: 3107 (OH), 1732 (COOH), 1666 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.65 (dd, 1H, CH_2(COOH), J = 7 2, 16.2 Hz), 3.04 (dd, 1H, CH_2(COOH), J = 4.2, 16.2 Hz), 4.39 (d, 1H, CH_2, J = 15.6 Hz), 4.71 (dd, 1H, H_3, J = 4.2, 7.2 Hz), 4.93 (d, 1H, CH_2-N, J = 15.6 Hz), 6.91 (d, 1H, $H_{4'}$, J = 5.8 Hz), 7.41 (d, 1H, $H_{5'}$, J = 5.8 Hz), 7.44-7.66 (m, 3H, $H_{4,5,6}$), 7.70 (d, 1H, H_7, J = 7.3 Hz).

Anal. Calcd. for $C_{15}H_{12}ClNO_3S$: C, 55.99; H, 3.76; N, 4.35. Found: C, 55.61; H, 3.62; N, 4.12.

2,3-Dihydro-1-oxo-2-(2'-bromothien-3'-ylmethyl)-1*H*-isoindol-3-acetic Acid (**8d**).

This compound was obtained in a yield of 90%, mp 182°; ir: 3102 (OH), 1732 (COOH), 1672 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.65 (dd, 1H, CH_2(COOH), J = 7.3, 16.1 Hz), 3.05 (dd, 1H, CH_2(COOH), J = 4.0, 16.1 Hz), 4.37 (d, 1H, CH_2-N, J = 15.6 Hz), 4.71 (dd, 1H, H_3, J = 4.0, 7.3 Hz), 4.93 (d, 1H, CH_2-N, J = 15.6 Hz), 6.89 (d, 1H, $H_{4'}$, J = 5.4 Hz), 7.42-7.62 (m, 4H, $H_{4,5,6,5'}$), 7.71 (d, 1H, H_7, J = 7.3 Hz).

Anal. Calcd. for $C_{15}H_{12}BrNO_3S$: C, 49.19; H, 3.30; N, 3.82. Found: C, 49.01; H, 3.41; N, 3.97.

2,3-Dihydro-1-oxo-2-(2'-bromothien-5'-ylmethyl)-1*H*-isoindol-3-acetic Acid (**8e**).

This compound was obtained in a yield of 73%, mp 115°; ir: 2923 (OH), 1716 (COOH), 1652 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.75 (dd, 1H, CH_2(COOH), J = 6.7, 16.7 Hz), 3.04 (dd, 1H, CH_2(COOH), J = 4.8, 16.7 Hz), 4.63 (d, 1H, CH_2-N, J = 15.9 Hz), 4.83 (dd, 1H, H_3, J = 4.8, 6.7 Hz), 5.08 (d, 1H, CH_2-N, J = 15.9 Hz), 6.90-7.08 (m, 2H, $H_{3',4'}$), 7.41-7.64 (m, 3H, $H_{4,5,6}$), 7.72 (d, 1H, H_7, J = 7.0 Hz).

Anal. Calcd. for $C_{15}H_{12}BrNO_3S$: C, 49.19; H, 3.30; N, 3.82. Found: C, 48.91; H, 3.06; N, 3.61.

Thienoazepinoisoindolediones **9a-e**.

General Procedure.

A mixture of compound **8a-e** (3.5 mmoles), in dry dichloromethane (20 ml) and thionyl chloride (0.30 ml) was stirred under reflux until all of the solid had disappeared. Reflux was continued for an additional 30 minutes. After cooling the solution was evaporated under reduced pressure. The residue was dissolved into dry dichloromethane (20 ml) to furnish a solution of the corresponding acyl chloride. This solution was added drop by drop to a stirred mixture of aluminium trichloride (99.99%, 1.5 g, 11 mmoles) and dry dichloromethane (50 ml). Stirring was continued for 1 hour. The solution was poured into cold water and decanted. The aqueous layer was extracted once more with dichloromethane. The combined organic layer was washed with water, dried (magnesium sulfate), and evaporated. The resulting solid **9a-e** was recrystallized in the appropriate solvent.

4,10b-Dihydro-11*H*-thieno[3',2':5,6]azepino[2,1-*a*]isoindole-6,12-dione (**9a**).

This compound was obtained in a yield of 92%, mp 161° (ethanol); ir: 1694 (C=O), 1667 (C=O) cm^{-1}; ^1H nmr: δ 2.99 (dd, 1H, H_{11a}, J = 8.2, 15.9 Hz), 3.47 (dd, 1H, H_{11b}, J = 3.8, 15.9 Hz), 4.93 (d, 1H, CH_2N, J = 17.0 Hz), 4.99 (dd, 1H, H_{10b}, J = 3.8, 8.2 Hz), 5.34 (d, 1H, CH_2N, J = 17.0 Hz), 7.11 (d, 1H, H_2, J = 5.4 Hz), 7.37 (d, 1H, H_1, J = 5.4 Hz), 7.41-7.64 (m, 3H, $H_{8,9,10}$), 7.80 (d, 1H, H_7, J = 7.3 Hz); ^{13}C nmr: δ 40.9 (CH_2), 47.4 (CH), 57.0 (CH), 122.4 (CH), 123.8 (CH), 123.9 (CH), 128.9 (CH), 129.0 (CH), 131.6 (C), 132.4 (CH), 140.1 (C), 144.3 (C), 146.2 (C), 168.1 (N-C=O), 192.0 (C=O).

Anal. Calcd. for $C_{15}H_{11}NO_2S$: C, 66.90; H, 4.12; N, 5.20. Found: C, 66.55; H, 3.81; N, 5.33.

4,10b-Dihydro-11*H*-thieno[2',3':5,6]azepino[2,1-*a*]isoindole-6,12-dione (**9b**).

This compound was obtained in a yield of 93%, mp 175°(ethanol); ir: 1682 (C=O), 1634 (C=O) cm^{-1}; ^1H nmr: δ 2.92 (dd, 1H, H_{11a}, J = 9.1, 16.4 Hz), 3.46 (dd, 1H, H_{11b}, J = 3.2, 16.4 Hz), 4.74 (d, 1H, CH_2N, J = 17.8 Hz), 4.94 (dd, 1H, H_{10b}, J = 3.2, 9.1 Hz), 5.36 (d, 1H, CH_2N, J = 17.8 Hz), 7.04 (d, 1H, H_3, J = 5.1 Hz), 7.38-7.62 (m, 4H, $H_{2,8,9,10}$), 7.78 (d, 1H, H_7, J = 6.7 Hz); ^{13}C nmr: δ 43.3 (CH_2), 47.7 (CH_2), 56.7 (CH), 122.3 (CH), 124.0 (CH), 129.0 (CH), 129.8 (CH), 131.6 (C), 132.4 (CH), 134.2 (CH), 140.7 (C), 142.8 (C), 144.6 (C), 168.7 (N-C=O), 190.3 (C=O).

Anal. Calcd. for $C_{15}H_{11}NO_2S$: C, 66.90; H, 4.12; N, 5.20. Found: C, 67.15; H, 4.01; N, 5.02.

3-Chloro-4,10b-dihydro-11*H*-thieno[3',4':5,6]azepino[2,1-*a*]-isoindole-6,12-dione (**9c**).

This compound was obtained in a yield of 98%, mp 238°(chloroform); ir: 1694 (C=O), 1667 (C=O) cm^{-1}; ^1H nmr: δ 3.02 (dd, 1H, H_{11a}, J = 6.8, 15.3 Hz), 3.50 (dd, 1H, H_{11b}, J = 4.4, 15.3 Hz), 4.72 (d, 1H, CH_2N, J = 16.4 Hz), 4.96 (dd, 1H, H_{10b}, J = 4.4, 6.8 Hz), 5.20 (d, 1H, CH_2N, J = 16.4 Hz), 7.41-7.64 (m, 3H, $H_{8,9,10}$), 7.77-7.84 (m, 2H, $H_{1,7}$); ^{13}C nmr: δ 39.1 (CH_2), 46.4 (CH_2), 57.1 (CH), 122.2 (CH), 124.0 (CH), 129.0 (CH), 130.0 (C), 130.1 (CH), 131.7 (C), 132.2 (CH), 132.8 (C), 140.5 (C), 143.7 (C), 167.8 (N-C=O), 191.2 (C=O).

Anal. Calcd. for $C_{15}H_{10}ClNO_2S$: C, 59.31; H, 3.32; N, 4.61. Found: C, 59.38; H, 3.15; N, 4.58.

3-Bromo-4,10b-dihydro-11*H*-thieno[3',4':5,6]azepino[2,1-*a*]-isoindole-6,12-dione (**9d**).

This compound was obtained in a yield of 91%, mp 223°(chloroform); ir: 1692 (C=O), 1671 (C=O) cm^{-1}; ^1H nmr: δ 3.03 (dd, 1H, H_{11a}, J = 6.7, 15.3 Hz), 3.51 (dd, 1H, H_{11b}, J = 4.7, 15.3 Hz), 4-68 (d, 1H, CH_2N, J = 16.4 Hz), 4.95 (dd, 1H, H_{10b}, J = 4.7, 6.7 Hz), 5.18 (d, 1H, CH_2N, J = 16.4 Hz), 7.39-7.64 (m, 3H, $H_{8,9,10}$), 7.78 (d, 1H, H_7, J = 7.3 Hz), 7.93 (s, 1H, H_1); ^{13}C nmr: δ 40.7 (CH_2), 46.3 (CH_2), 57.2 (CH), 112.4 (C-Br), 122.2 (CH), 123.9 (CH), 128.9 (CH), 131.7 (CH), 132.2 (CH), 133.1 (CH), 135.6 (C), 141.1 (C), 143.7 (C), 167.8 (N-C=O), 190.9 (C=O).

Anal. Calcd. for $C_{15}H_{10}BrNO_2S$: C, 51.74; H, 2.89; N, 4.02. Found: C, 51.84; H, 2.97; N, 4.05.

2-Bromo-4,10-dihydro-11*H*-thieno[3',2':5,6]azepino[2,1-*a*]isoindole-6,12-dione (**9e**).

This compound was obtained in a yield of 98%, mp 200°(chloroform); ir: 1668 (C=O, C=O) cm^{-1}; ^1H nmr: δ 2.99 (dd, 1H, H_{11b}, J = 7.6, 15.7 Hz), 3.46 (dd, 1H, H_{11b}, J = 4.0, 15.7 Hz), 4.77 (d, 1H, CH_2N, J = 17.2 Hz), 4.97 (dd, 1H, H_{10b}, J = 4.0, 7.6 Hz), 5.26 (d, 1H, CH_2N, J = 17.2 Hz), 7.27 (s, 1H, H_1), 7.39-7.63 (m, 3H, $H_{8,9,10}$), 7.77 (d, 1H, H_7, J = 7.3 Hz); ^{13}C nmr: δ 40.6 (CH_2), 47.1 (CH_2), 56.7 (CH), 110.9 (C-Br), 122.2 (CH), 124.0 (CH), 129.0 (CH), 131.1 (CH), 131.3 (C), 132.4 (CH), 140.3 (C), 143.9 (C), 147.6 (C), 168.1 (N-C=O), 190.4 (C=O).

Anal. Calcd. for $C_{15}H_{10}BrNO_2S$: C, 51.74; H, 2.89; N, 4.02. Found: C, 51.91; H, 2.92; N, 4.19.

Bromination of Ketones **9a-e** to Bromoderivatives **10a-e**.

General Procedure.

A mixture of compound **9a-e** (1 mmole), in tetrahydrofuran (40 ml) and bromine (0.18 g, 1.1 mmoles) was stirred for 40 minutes at room temperature. The solvent was evaporated under reduced pressure and a yellow solid appeared which was triturated with ether to furnish the bromo derivative **10a-e** (90-85%) contaminated with **1a-e** (10-15%). These compounds could not be separated.

11-Bromo-4,10b-dihydro-11*H*-thieno[3',2':5,6]azepino[2,1-*a*]-isoindole-6,12-dione (**10a**).

This compound had a ^1H nmr: δ 5.00 (d, 1H, H_{10b}, J = 1.3 Hz), 5.02-5.14 (m, 2H, H_{11} and H_4), 5.32 (d, 1H, H_4, J = 17.2 Hz), 7.21 (d, 1H, H_1, J = 5.4 Hz), 7.43-7.69 (m, 4H, $H_{4,8,9,10}$), 7.89 (d, 1H, H_7, J = 7.0 Hz).

11-Bromo-4,10b-dihydro-11*H*-thieno[2',3':5,6]azepino[2,1-*a*]-isoindole-6,12-dione (**10b**).

This compound had a ^1H nmr: δ 4.98 (d, 1H, H_4, J = 17.4 Hz), 5.03 (s, 1H, H_{10b}), 5.11 (s, 1H, H_{11}), 5.30 (d, 1H, H_4, J = 17.4 Hz), 7.08 (d, 1H, H_3, J = 4.9 Hz), 7.42-7.75 (m, 4H, $H_{2,8,9,10}$),7.87 (d, 1H, H_7, J = 6.8 Hz).

11-Bromo-3-chloro-4,10b-dihydro-11*H*-thieno[3',4':5,6]-azepino[2,1-a]isoindole-6,12-dione (**10c**).

This compound had a ^1H nmr: δ 4.82 (d, 1H, H_4, J = 16.2 Hz), 5.00 (s, 2H, $H_{10b,11}$), 5.19 (d, 1H, H_4, J = 16.4 Hz), 7.41-7.64 (m, 3H, $H_{8,9,10}$), 7.89 (d, 1H, H_7, J = 6.3 Hz), 8.01 (s, 1H, H_1).

3,11-Dibromo-4,10b-dihydro-11*H*-thieno[3',4':5,6]azepino-[2,1-*a*]isoindole-6,12-dione (**10d**).

This compound had a ^1H nmr: δ 4.81 (d, 1H, H_4, J = 16.4 Hz), 5.01 (s, 1H, H_{10b}), 5.19 (d, 1H, H_4, J = 16.4 Hz), 5.28 (s, 1H, H_{11}), 7.41-7.65 (m, 3H, $H_{8,9,10}$), 7.90 (d, 1H, H_7, J = 8.2 Hz), 8.16 (s, 1H, H_2).

2,11-Dibromo-4,10b-dihydro-11*H*-thieno[3',2':5,6]azepino-[2,1-*a*]isoindole-6,12-dione (**10e**).

This compound had a ^1H nmr: δ 4.93 (d, 1H, H_4, J = 17.3 Hz), 4.98 (d, 1H, H_{10b}, J = 1.3 Hz), 5.09 (m, 1H, H_{11}), 5.29 (d, 1H, H_4, J = 17.3 Hz), 7.42-7.71 (m, 4H, $H_{1,8,9,10}$), 7.90 (d, 1H, H_7, J = 7.0 Hz).

Preparation of Ketoeneamides **1a-e**.

General Procedure.

A mixture of compound **9a-e** (1 mmole), in tetrahydrofuran (40 ml) and bromine (0.18 g, 1.1 mmoles) was stirred for 40 minutes at room temperature. Then, triethylamine (1 ml) was added and the solution was stirred for a night. After evaporation of the solvent, the resultant solid was dissolved in dichloromethane, washed with a solution of sodium hydrogenocarbonate, dried magnesium sulfate). Evaporation of the solvent gave a solid which was recrystallized from chloroform to afford pure compounds **1a-e**.

4*H*-Thieno[3',2':5,6]azepino[2,1-*a*]isoindole-6,12-dione (**1a**).

This compound was obtained in 98% yield, mp 215°; ir: 1726 (C=O), 1613 (C=O) cm^{-1}; ^1H nmr: δ 5.20 (s, 2H, H_4), 6.30 (s, 1H, H_{11}), 7.14 (d, 1H, H_1, J = 5.2 Hz), 7.47 (d, 1H, H_2, J = 5.2 Hz), 7.55-7.78 (m, 3H, $H_{8,9,10}$), 7.86 (m, 1H, H_7).

Anal. Calcd. for $C_{15}H_9NO_2S$: C, 67.40; H, 3.39; N, 5.24. Found: C, 66.99; H, 3.17; N, 5.17.

4*H*-Thieno[2',3':5,6]azepino[2,1-*a*]isoindole-6,12-dione (**1b**).

This compound was obtained in 95% yield, mp 221°; ir: 1709 (C=O), 1629 (C=O) cm^{-1}; ^1H nmr: δ 5.13 (s, 2H, H_4), 6.33 (s, 1H, H_{11}), 7.07 (d, 1H, H_3, J = 4.8 Hz), 7.55-7.79 (m, 4H, $H_{2,8,9,10}$), 7.86 (m, 1H, H_7).

Anal. Calcd. for $C_{15}H_9NO_2S$: C, 67.40; H, 3.39; N, 5.24. Found: C, 67.23; H, 3.28; N, 5.03.

3-Chloro-4*H*-thieno[3',4':5,6]azepino[2,1-*a*]isoindole-6,12-dione (**1c**).

This compound was obtained in 96% yield, mp 215°; ir: 1736 (C=O), 1638 (C=O) cm^{-1}; ^1H nmr: δ 5.09 (s, 2H, H_4), 6.32 (s, 1H, H_{11}), 7.41-7.82 (m, 4H, $H_{3,8,9,10}$), 7.90 (m, 1H, H_7).

Anal. Calcd. for $C_{15}H_8ClNO_2S$: C, 59.71; H, 2.67; N, 4.64. Found: C, 59.41; H, 2.53; N, 4.60.

3-Bromo-4*H*-thieno[3',4':5,6]azepino[2,1-*a*]isoindole-6,12-dione (**1d**).

This compound was obtained in 95% yield, mp 259°; ir: 1729 (C=O), 1626 (C=O) cm^{-1}; ^1H nmr: δ 5.10 (s, 2H, H_4), 6.28 (s, 1H, H_{11}), 7.60-7.78 (m, 3H, $H_{8,9,10}$), 7.90 (m, 1H, H_7), 8.04 (s, 1H, H_1).

Anal. Calcd. for $C_{15}H_8BrNO_2S$: C, 52.04; H, 2.33; N, 4.05. Found: C, 52.43; H, 1.98; N, 4.05.

2-Bromo-4*H*-thieno[3',2':5,6]azepino[2,1-*a*]isoindole-6,12-dione (**1e**).

This compound was obtained in 93% yield, mp 245°; ir: 1723 (C=O), 1612 (C=O) cm^{-1}; ^1H nmr: δ 5.11 (s, 2H, H_4), 6.28 (s, 1H, H_{11}), 7.43-7.71 (m, 4H, $H_{1,8,9,10}$), 7.90 (m, 1H, H_7).

Anal. Calcd. for $C_{15}H_8BrNO_2S$: C, 52.04; H, 2.33; N, 4.05. Found: C, 52.21; H, 2.06; N, 4.04.

REFERENCES AND NOTES

[1] C. Chedru, B. Decroix, J. Morel and F. Povazanec, *J. Heterocyclic Chem.*, **31**, 1027 (1994).

[2] D. Lebosquain and B. Decroix, *Heterocycles*, **36**, 2303 (1993).

[3] S. Marchalin and B. Decroix, *J. Heterocyclic Chem.*, **31**, 495 (1994).

[4] D. Berkes and B. Decroix, *Bull. Soc. Chim. France*, **131**, 986 (1994).

[5] E. Valencia, I. Weiss, S. Firdous, A. J. Freyer, M. Shamma, A. Urzua and V. Fajardo, *Tetrahedron*, **40**, 3957 (1984).

[6] E. Valencia, V. Fajardo, A. J. Freyer and M. Shamma, *Tetrahedron Letters*, **26**, 993 (1985).

[7] R. Yoneda, Y. Sakamoto, Y. Oketo, K. Minami, S. Harusawa and T. Kurihara, *Tetrahedron Letters*, **35**, 3749 (1994).

[8] S. Marchalin, B. Decroix and J. Morel, *Acta Chem. Scand.*, **47**, 287 (1993).

[9] G. Marchand, B. Decroix and J. Morel, *Chem. Scr.*, **23**, 80, (1984).

[10] B. Yom-Tov and S. Gronowitz, *Chem. Scr.*, **3**, 37 (1973).

[11] F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.*, **70**, 3768 (1948).

[12] J. Cymerman-Craig and J. W. Loder, *J. Am. Chem. Soc.*, **76**, 237 (1954).

[13] T. Aubert, M. Farnier and R. Guilard, *Tetrahedron*, **47**, 53 (1991).

[14] H. Finch, D. H. Reece and J. T. Sharp, *J. Chem. Soc., Perkin Trans 1*, 1193 (1994).