FUSED IMIDAZOPHENOTHIAZINES: STUDIES ON THE BERNTHSEN THIONATION OF 1-METHYL-6-(*p*-TOLYLAMINO)BENZIMIDAZOLE AND 2-METHYL-1-PHENYLBENZIMIDAZOLE

Pilar López-Alvarado, Carmen Avendaño*, and J. Carlos Menéndez

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia.

Universidad Complutense, 28040 Madrid, Spain

Abstract - Thionation of 1-methyl-6-(p-tolylamino)benzimidazole (obtained from 1-methyl-6-aminobenzomidazole and p-tolyllead triacetate) afforded a 7:3 mixture of two isomeric imidazophenothiazines, by inclusion of sulphur into the C_7 and $C_{2'}$ or C_5 and $C_{2'}$ positions, respectively. The capability of 1-arylbenzimidazoles to cyclize to a fused imidazophenothiazine was also shown. These results are discussed in comparison to those previously obtained on 2-methyl-1-phenyl-5-phenylaminobenzimidazole, a more complex system where both diarylamine units are present.

INTRODUCTION

Although a wide range of phenothiazines has been described,[1-3] the number of polycyclic systems wearing a phenothiazine ring has remained relatively small. Imidazophenothiazines are particularly scarce, and, previously to our own research in this area,[4] only one derivative of imidazo[4,5,1-*k*,*l*]phenothiazine was known.[5] In a previous paper[4] we described that Bernthsen thionation of 2-methyl-1-phenyl-5-phenylaminobenzimidazole (**1**) is regiospecific, leading to the angular phenothiazine (**2**) as the only isolated product, in spite of the fact that three reaction pathways are possible, (Figure 1). This selectivity was somewhat surprising, since Bernthsen reaction usually yields mixtures of all the

possible thionation products,[1-3] and was tentatively attributed to steric hindrance at C_6 due to the

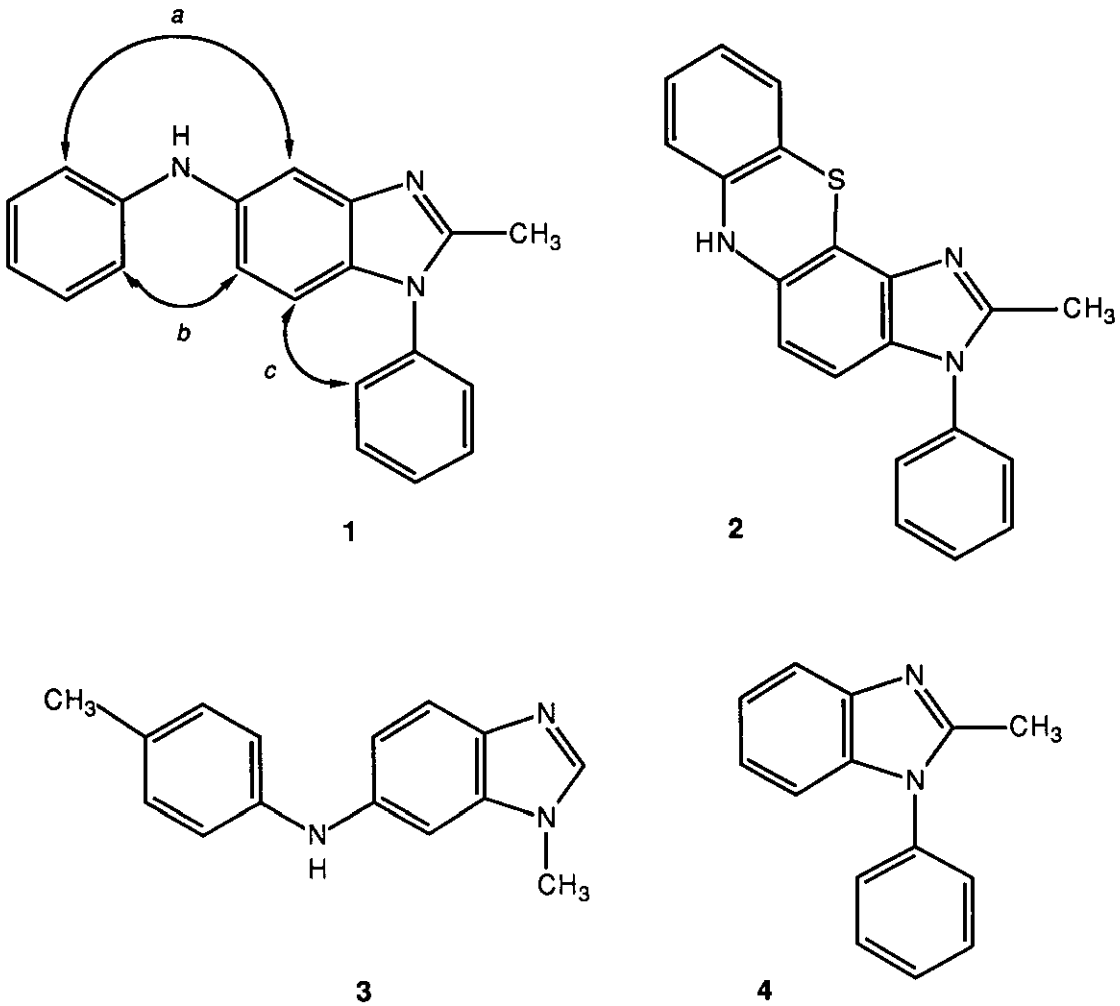
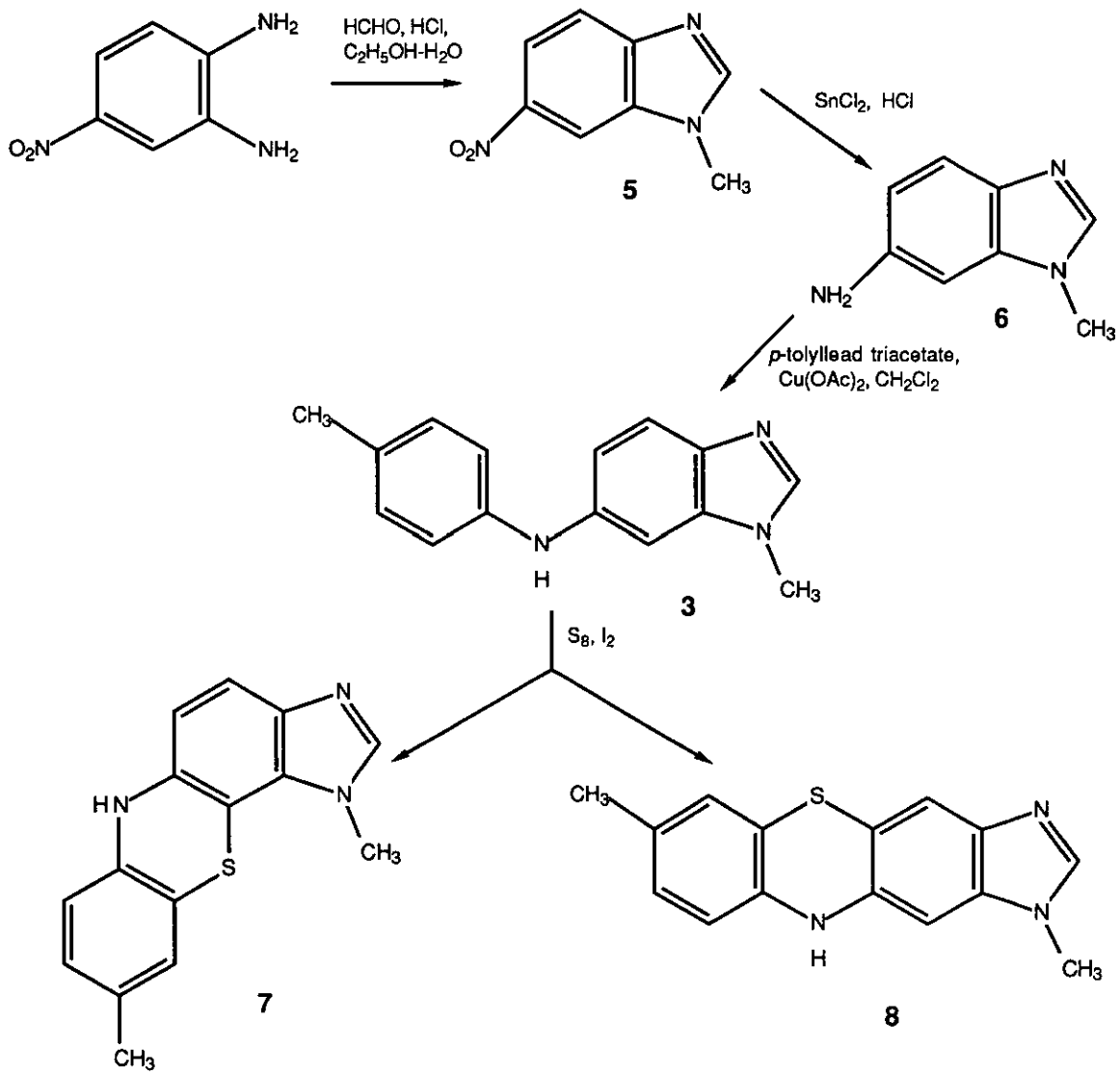


Figure 1

presence of the bulky phenyl group on the nearby nitrogen N_1. In order to test this hypothesis, we planned to investigate the outcome of Bernthsen thionation on simplified models of the two diarylamine portions of **1** (compounds **3** and **4**, Figure 1).

SYNTHESIS

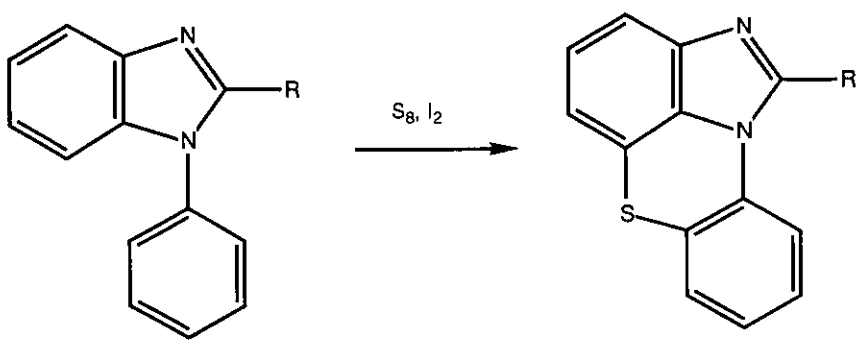
Compound (**3**) was prepared as outlined in Scheme 1. Synthesis of 1-methyl-6-nitrobenzimidazole (**5**), based upon chemoselective Eschweiler-Clark methylation of 4-nitro-1,2-phenylenediamine followed



Scheme 1

by cyclization with formaldehyde, was performed using a modification of a previously described procedure.[6] Reduction of **5** with stannous chloride in 35% hydrochloric acid gave the corresponding amine (**6**). In the arylation of **6** to **3**, the poor results obtained in the Ullmann-Goldberg procedure[7] made it necessary the use of an alternative method. It was found that the recently described[8] arylation with *p*-tolyllead triacetate, prepared using a modified previously reported procedure,[9] in the presence of copper (II) acetate at room temperature gave **3** in almost quantitative yield. Finally, Bernthsen thionation of **3** with sulphur and a trace of iodine in refluxing *o*-dichlorobenzene gave a 7:3 mixture of compounds (**7**) and (**8**). Phenothiazine (**7**) is derived from cyclization pathway *a* (Figure 1), while **8**, which is, to our knowledge, the first example of a linear imidazophenothiazine fused ring system, is formed through pathway *b*. This results confirm our initial hypothesis that the regiospecificity observed in the thionation of **1** to **2** was due to steric hindrance caused by the N_1-phenyl substituent.

Melting compound (**4**)[4] with sulphur and iodine afforded phenothiazine (**9**) as the only isolable product, showing that cyclization pathway *c*, although less favoured, is also possible (Scheme 2). It must be mentioned that the analogue of **9** with R=H has been previously obtained from 1-aminophenothiazine.[5] The successful thionation of benzimidazole (**4**) to **9** is of interest from the point of view of reactivity of benzimidazole, since an indole derivative analogous to **4**, namely 1-phenylindole, does not react under Bernthsen conditions.[10]

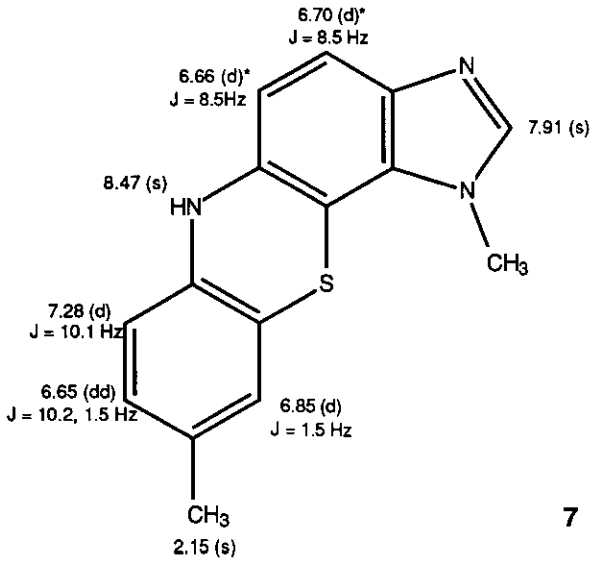


4 (R = CH_3) **9** (R = CH_3)

Scheme 2

STRUCTURAL STUDY

Structures of compounds (**7-9**) were confirmed by high-resolution mass spectrometry and ^{1}H-nmr spectroscopy. ^{1}H-nmr data of compounds (**7**) and (**8**) fully support the proposed structures. Thus, the angular structure of compound (**7**) was deduced by the appearance of two clean doublets at $\delta = 6.66$



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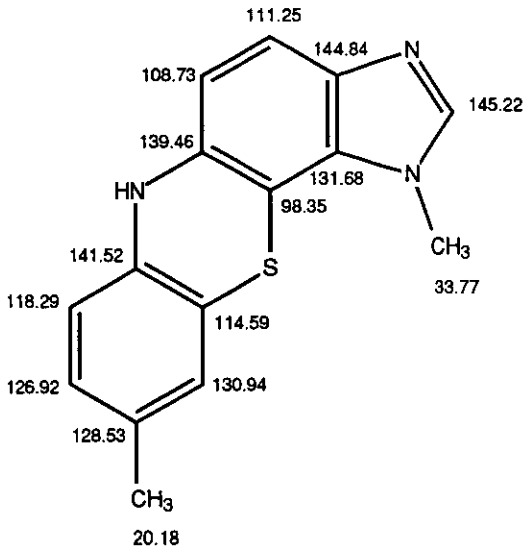

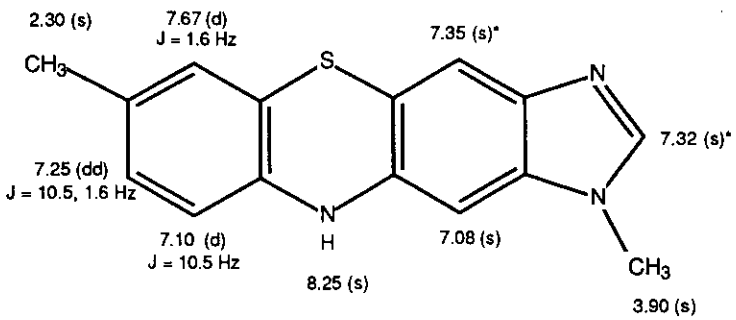

8

* Interchangeable assignments

Figure 2

and 6.70 ppm (J=8.5 Hz) attributed to C_4-H and C_5-H, while the linear structure of **8** was in agreement with the presence of two singlets at $\delta = 7.35$ and $\delta = 7.08$, assignable to C_4-H and C_{11}-H, respectively. ^{13}C-nmr data of **7** are also according with those previously discussed for compound (**2**)[4] (Figure 2).

The aromatic multiplet in the ^{1}H-nmr spectrum of compound (**9**) (seven protons relative to three methyl protons) could not be properly analyzed due to its complexity, and also because the unstability of **9** precluded further nmr experiments. It is noteworthy that the demethylated analog of **9** also showed a complex, non-analizable aromatic multiplet in its ^{1}H-nmr spectrum.[5a]

In conclusion, all these results support the assumption that substitution on N_1 strongly influences the regioselectivity of Bernthsen thionation of 5(6)-arylaminobenzimidazoles.

EXPERIMENTAL

Ir spectra were recorded on a Perkin-Elmer 577 spectrophotometer, with all compounds compressed into KBr pellets. ^{1}H-Nmr spectra were obtained on the following instruments: Hitachi Perkin-Elmer R-24B (60 MHz) and Varian VXR-300 (300 MHz). ^{13}C-Nmr spectrum (75.4 MHz) of compounds (**7**) was carried out on the latter instrument . $CDCl_3$ or DMSO-d_6 were used as solvents, and TMS was added in all cases as an internal standard. Only those J values that could be accurately measured are given. Low resolution mass spectra were obtained on a Hitachi Perkin-Elmer RMV-6M spectrometer at 75 eV, using the DIP mode for the introduction of the samples. High resolution mass measurements were performed on a VC/Micromass-ZAB/2F instrument. Elemental analyses were determined on a Perkin-Elmer 2400 CHN microanalyzer. Melting points were measured in open capillary tubes, using a Büchi inmersion apparatus, and are uncorrected. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Scharlau Cf 530). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh) or neutral alumina (activity I, Merck). All reagents were of commercial procedence (Aldrich, Merck, Probus) and were used as received. Solvents were purified and dried using standard procedures.[11] The expression "petroleum ether" refers to the fraction boiling at 40-60 °C.

1-Methyl-6-nitrobenzimidazole (**5**). A solution of 4-nitro-1,2-phenylenediamine (1 g, 6.53 mmol) in

ethanol (20 ml) and 35% hydrochloric acid (7 ml) was heated to 80 °C and treated dropwise with 35% aqueous formaldehyde (1.2 ml, 7.16 mmol). After 90 min at 80 °C, the reaction mixture was cooled and evaporated under reduced pressure, and the black residue was dissolved in water (15 ml).This solution was basified with 20% aqueous ammonium hydroxide and extracted with chloroform (4 x 25 ml). The organic layers were dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue was recrystallized from 8:2 ethanol-water to yield 0.46 g (40%) of **5** as slightly orange plates. mp 179-181 °C (ethanol) (lit.,[6,12] mp 182 °C). ^{1}H-Nmr (60 MHz, $CDCl_3$-DMSO-d_6, 3:1) δ: 8.45 (1H, d, J = 2.5 Hz, C_7-H), 8.35 (1H, s, C_2-H), 8.10 (1H, dd, J = 10 and 2.5 Hz, C_5-H), 7.75 (1H, d, J = 10 Hz, C_4-H), 3.95 (3H, s, CH_3) ppm.

6-Amino-1-methylbenzimidazole (**6**). A suspension of the nitro derivative **5** (1 g , 5.6 mmol) in 35% hydrochloric acid (10 ml) was heated at 100 °C until complete dissolution, and solid stannous chloride dihydrate (5.64 g, 29.7 mmol of $SnCl_2$) was added. Water (*ca.* 5 ml) was added dropwise until a clear solution was obtained again; the reacting mixture was heated at 100-110 °C for further 3.5 h, on cooling, a precipitate of 0.2 g of **6** hydrochloride (white crystals, ir (KBr): 3390-2500 (N^+-H), 1620 cm^{-1}) was obtained. This hydrochoride was dissolved in water (10 ml) and the solution was joined with the reaction filtrate, basified with 20% aqueous sodium hydroxide and extracted with chloroform (4 x 50 ml). The organic layers were dried over anhydrous sodium sulphate, evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with 95:5 chloroform-methanol to yield 0.72 g (86%) of **6** as yellowish crystals. mp 173-176 °C (ethanol). Ir (KBr): 3390, 3320, 3210 3100 (NH), 1625 cm^{-1}. ^{1}H-Nmr (60 MHz, DMSO-d_6) δ: 7.75 (1H, s, C_2-H), 7.25 (1H, d, J= 9Hz, C_4-H), 6.60 (1H, s, C_7-H), 6.50 (1H, dd, J = 9 Hz and 2 Hz, C_5-H), 3.90 (2H, s, NH_2), 3.60 (3H, s, CH_3) ppm. Anal. Calcd for $C_8H_9N_3$: C, 65.31; H, 6.12; N, 28.57. Found: C, 65.04 ; H, 6.19; N, 28.36.

p-Tolyllead triacetate. Anhydrous lead tetraacetate (4.5 g, 10 mmol) was kept at 20 torr for 1 h in the presence of solid sodium hydroxide in order to eliminate the acetic acid used to stabilize the commercial reagent, and was then inmediately treated, under a nitrogen atmosphere, with a solution of trichloroacetic acid (7.5 g, 45 mmol) in dry chloroform (20 ml). Dry toluene (12.5 ml) was then added, and the orange

solution thus obtained was stirred at room temperature for 5-10 h, until the addition of a drop of the reaction medium to 0.5 ml of water did not cause the formation of a dark brown precipitate of lead tetraacetate. The pale yellow reaction mixture was then washed with water (2 x 50 ml) and the organic layer was evaporated *in vacuo*. The residue was dissolved in chloroform (5 ml), and slow addition of petroleum ether (*ca.* 100 ml) caused the complete precipitation of a pale yellow solid. This compound was identified as the plumboxane mentioned by Pinhey and coworkers.[9] Yield, 3.95 g (63%). Ir (KBr): 3050, 1650 (C=O), 1480, 820 (C-Cl), 540 (Pb-O). Mp could not be recorded because the compound exploded at *ca.* 140 °C. The crude plumboxane (0.5 g, 0.39 mmol), dissolved in chloroform (4 ml) and acetic acid (2 ml), was stirred at room temperature for 15-20 min. The clear solution thus obtained was washed with water (3 x 5 ml), and the organic layer was diluted with chloroform (10 ml) and stirred with anhydrous sodium bicarbonate (1 g) for 45 min. The bicarbonate was filtered off and washed with chloroform (3 x 15 ml), and the joined chloroform layers were evaporated *in vacuo* at room temperature. The oily orange residue was dissolved in chloroform (5 ml) and precipitated by slow addition of petroleum ether until turbudity appeared. Cooling at 4 °C afforded *p*-tolyllead triacetate, as white crystals. Yield, 0.25 g (66%). mp 86-87 °C (lit.,[9] mp 86-87 °C).

1-Methyl-6-(*p*-tolylamino)benzimidazole (**3**). A solution of **6** (100 mg, 0.68 mmol) in dry dichloromethane (10 ml) was treated with *p*-tolyllead triacetate (0.36 g, 0.75 mmol) and 12 mg of copper (II) acetate. The reaction mixture was stirred at room temperature for 15 min and evaporated under reduced pressure. The residue was purified by flash chromatography on a column of silica gel (15 g) with a layer of activated neutral alumina (0.5 g) on top, which retained the copper species present in the crude reaction product. A mixture of chloroform-methanol (99:1) was used as eluent. Yield, 0.16 g (96%). mp 206-208 °C (ethyl acetate). Ir (KBr): 3250 (NH), 3180, 1615 cm^{-1}. ^{1}H-Nmr (60 MHz, DMSO-d_6) δ: 8.03 (1H, s, NH), 7.54 (1H, s, C_2-H), 7.30-6.70 (7H, m, ArH), 3.74 (3H, s, N_1-CH_3), 2.23 (3H, s, $C_{4'}$-CH_3). Ms, m/z (%): 273 (100, M^+), 236 (30), 222 (5), 221 (10), 111 (9). Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.95; H, 6.33; N, 17.72. Found: C, 75.72; H, 6.20; N, 17.58.

Bernthsen Thionation of 1-Methyl-6-(*p*-tolylamino)benzimidazole. Synthesis of 1,9-Dimethyl-6*H*-imidazo[4,5-*c*]phenothiazine (**7**) and 1,7-Dimethyl-10*H*-imidazo[4,5-*b*]phenothiazine (**8**). A solution

of **3** (0.3 g, 1.27 mmol), sulphur (0.07 g, 2.2 mmol) and iodine (8 mg) in dry *o*-dichlorobenzene (5 ml) was refluxed in an oil bath at 220 °C for 3-4 h, under a slow stream of dry nitrogen (hydrogen sulphide evolution was observed after the first 30-45 min). After evaporating *in vacuo* most of the *o*-dichlorobenzene, the residue was purified by flash column chromatography on silica gel, eluting with petroleum ether-ethyl acetate (9:1) to yield, two separated fractions that contained phenothiazines (**7**) and (**8**). Compound (**7**) was purified from the first fraction by a new flash chromatography on alumina, eluting with dichloromethane. Compound (**8**) was obtained by chromatography of the second fraction on silica gel, eluting with a gradient of dichloromethane-ethyl acetate (1:1)-net ethyl acetate, followed by methanol.

1,9-Dimethyl-6*H*-imidazo[4,5-*c*]phenothiazine (**7**). Yield, 140 mg (46%), as a thick oil. ^{1}H-Nmr (300 MHz, DMSO-d_6), and ^{13}C-nmr (75.4 MHz, DMSO-d_6), see Figure 2. High-resolution mass meassurement: Calcd for $C_{15}H_{13}N_3S$ (M^+): 267.0830. Found: 267.0817.

1,7-Dimethyl-10*H*-imidazo[4,5-*b*]phenothiazine (**8**). Yield, 60 mg (20%), as a thick oil. ^{1}H-Nmr (300 MHz, DMSO-d_6) (see Figure 2). High-resolution mass measurement: Calcd for $C_{15}H_{13}N_3S$ (M^+): 267.0830. Found: 267.0845.

1-Methylimidazo[4,5,1-*kl*]phenothiazine (**9**) . A mixture of 2-methyl-1-phenylimidazole[4] (0.2 g, 0.96 mmol), sulphur (0.19 g, 5.9 mmol) and iodine (20 mg) was melted in an oil bath at 215-220 °C, under a nitrogen stream, for 4 h (evolution of hydrogen sulphide was observed after the first 30-40 min). The crude reaction product was purified by flash chromatography on alumina eluting with dichloromethane, followed by flash chromatography on silica gel, eluting with petroleum ether-ethyl acetate (9:1). The residue from evaporation of the eluent was precipitated from acetone-petroleum ether to give 0.14 g (61%) of **9** as an amorphous solid. Ir (KBr): 3020, 2900, 1600, 1550, 1500, 880, 790. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ: 8.20-6.45 (7H, m, Ar-H), 2.25 (3H, s, CH_3). High-resolution mass measurement. Calcd for $C_{14}H_{11}N_2S$ (MH^+): 239.0643. Found: 239.0622.

ACKNOWLEDGEMENTS

We thank Dr. J. Gutiérrez Luis (Centro de Productos Naturales Orgánicos "Antonio González",

Universidad de La Laguna) for accurate mass measurements. Finantial support from CICYT (Project PA-86-0317) and Comunidad Autónoma de Madrid (research grant to PL-A) are also gratefully acknowledged.

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Received, 15th March, 1991