SYNTHESIS OF SUBSTITUTED PYRAZOLO[3,4-*b*]- AND PYRAZOLO[4,3-*c*]PHENOTHIAZINE DERIVATIVES

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Abstract - The synthesis of new pyrazolo[*b*]- and [*c*]phenothiazines by the Bernthsen thionation of *N*-arylindazoles obtained using organometalic compounds is reported.

Phenothiazines have a wide range of pharmacological and biological activities which makes them well known therapeutic agents.[1] However, although a significant number of derivatives have been prepared,[2] these are only, to the best of our knowledge, imidazo[3] and pyrrolo[4] derivatives. Therefore, in connection with our experience in the synthesis of pyrazolo[*a*]acridin-9(10*H*)-ones,[5,6] we got involved in the preparation of a new class of tetracycles bearing a pyrazolic ring fused to a phenothiazine moiety.

Our approach towards pyrazolophenothiazine derivatives (**4**) and (**5**), (Scheme 1), is based on the *N*-arylation of primary aromatic amines (**2**) followed by the Bernthsen thionation of the so-formed *N*-arylindazoles (**3**); and uses as commun starting material, commercially available 6-nitroindazole (**1a**).

Compound (**1a**) was first either chlorinated to give 3-chloro-6-nitroindazole (**1b**) (70% yield) or methylated with methyl sulfate to yield a mixture of two isomeric indazoles, 1-methyl and 2-methyl-6-nitroindazoles (**1c** and **1d**) (about 45% yield). Nitroindazoles (**1b**, **1c**, and **1d**) were then reduced with stannous chloride in acidic methanol to yield the corresponding 6-aminoindazoles (**2b**, **2c**, and **2d**) in good yields (75-85%). Palladium catalyzed hydrogenation could also have been of convenient use.[7] The next step was the arylation of the primary amine moety in order to prepare the corresponding diarylamino derivatives. For this purpose we first used the Ullmann's procedure,[8] however, since this method did not led to satisfactory results, we turned to the copper catalyzed arylation by organometalic compounds.[9] This method, which has recently been used for the synthesis of imidazophenothiazines,[3c] gave much better results.

Thus, aminoindazole derivatives were arylated with aryllead or arylbismuth reagents under mild conditions in dichloromethane at room temperature with copper (II) acetate as catalyst.[10] Indeed, the *N*-arylation can be performed either with aryllead (**6a** and **6b**) or with aryl bismuth (**7**), (Table 2). Using *p*-tolyllead triacetate (**6a**) with compounds (**2b**) and (**2c**), we obtained the corresponding 3-chloro-6-*p*-tolylamino-1*H*-indazole (**3b**) (50% yield) and 1-methyl-6-*p*-tolylamino-1*H*-indazole (**3c**) (67% yield). Diarylamines (**3d**, **3e**, and **3f**) were prepared in the same way (55-75% yield). Then, the Bernthsen thionation with sulphur and iodine in refluxing *o*-dichlorobenzene was used to cyclize the *N*-arylindazoles (**3b-f**).

Scheme 1

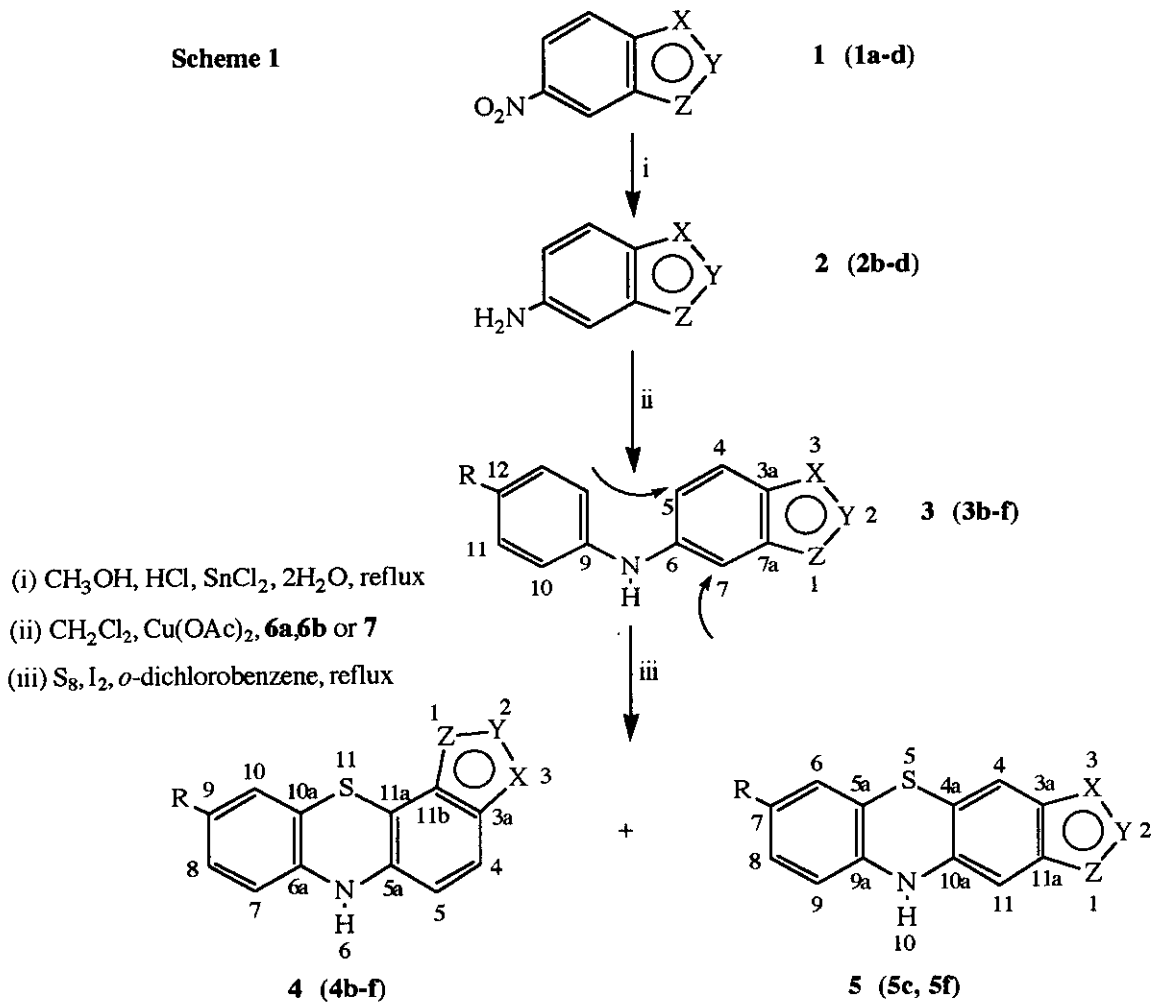


Table 1 Compounds prepared

1	2	3	4	5	X	Y	Z	R
1a[a]	-	-	-	-	CH	N	NH	-
1b	2b	3b	4b	-	CCl	N	NH	CH_3
1c	2c	3c	4c	5c	CH	N	NCH_3	CH_3
1d	2d	3d	4d	-	CH	NCH_3	N	H
1c	2c	3e	4e	-	CH	N	NCH_3	OCH_3
1c	2c	3f	4f	5f	CH	N	NCH_3	H

[a] commercial compound

In this case, (see Scheme 1), two isomers can be formed depending on the cyclization positions 5 or 7 in diarylamine (**3**): the linear [*b*] isomer (cyclization in 5), and the "bent" [*c*] isomer (cyclization in 7).

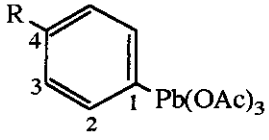
Under Bernthsen 's conditions **3b**, **3d** and **3e** led to a single isomer, the "bent" products (**4b**, **4d** and **4e**), i.e. the pyrazolo[4,3-*c*]phenothiazines, (30-55% yield), while **3c** and **3f** gave the "bent" products (**4c** and **4f**) only as the major isomer (about 45% yield); indeed pyrazolo[3,4-*b*]phenothiazines (**5c** and **5f**) were also formed in about 10% yield.

Although linear isomers might also be formed from **3b**, **3d** and **3e**, the large difficulties associated with their purification could account for their absence; indeed these isomers undergo facile oxydation, leading therefore to many side products.

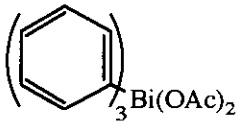
Structures of pyrazolo[*b*]- and [*c*]phenothiazines were determined unambiguously by ^{1}H and ^{13}C nmr. In particular, the multiplet pattern of the C-ring protons was investigated. Indeed two singlets are expected in the case of the [*b*] fusion (for 4-H and 11-H), while two doublets are expected in the case of the [*c*] fusion (for 4-H and 5-H). Actually doublets appear at 7.39 and 6.65 ppm which correspond to 4-H and 5-H of the "bent" structure (**4c**); while singlets at 7.34 and 6.71 ppm are only observed respectively for 4-H and 11-H with the linear compound (**5c**).

In conclusion, we reported a preparation of a new class of heterocycles, the pyrazolo[*b*]- and [*c*]phenothiazines, which uses organometalic reagents. Additional studies are currently in progress to expand the scope of this approach to the synthesis of other heterocycles.

Table 2



R	Compound
CH_3	**6a**
OCH_3	**6b**



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EXPERIMENTAL

All melting points are given uncorrected. Mass spectra were recorded on a NERMAG R1010 H spectrometer. ^{1}H and ^{13}C spectra were recorded on a Bruker AMX-400 spectrometer in DMSO-d_6; chemical shifts are reported in parts per millions (δ) with reference to tetramethylsilane (as internal standard). 6-Nitroindazole (**1a**) was purchased from Aldrich. Triphenylbismuth diacetate (**7**) was prepared according to a known procedure.[11]

3-Chloro-6-nitroindazole (1b)[12]

Chlorine was bubbled at 80 °C for 30 min through a solution of 6-nitroindazole (**1a**) (6 g, 0.036 mol) in acetic acid (100 ml). The solution was then evaporated and the residue was treated with a solution of 1N sodium bicarbonate (100 ml). The obtained precipitate was filtered off and extracted continuously with chloroform (500 ml). After evaporation, crystallization of the residue from acetic acid (40 ml) yielded 3-chloro-6-nitroindazole (**1b**) (5 g, 70%); mp 199 °C. Anal. Calcd for $C_7H_4N_3O_2Cl$: C, 42.53; H, 2.02; N, 21.26. Found: C, 42.41; H, 2.34; N, 21.40. ^{1}H-Nmr δ: 7.75 (1H, d, J = 8.9 Hz, 4-H), 8.00 (1H, dd, J = 1.8; 8.9 Hz, 5-H),

8.45 (1H, d, J = 1.2 Hz, 7-H). ^{13}C-Nmr δ: 107.83 (7-C), 115.70 (5-C), 120.13 (4-C), 122.47 (3a-C), 132.99 (3-C), 139.70 (1a-C), 146.93 (6-C).

6-Amino-3-chloroindazole (2b)

A suspension of 3-chloro-6-nitroindazole (**1b**) (3 g, 0.015 mol) in methanol (30 ml) and 36% hydrochloric acid (30 ml) was heated at 100° C until complete dissolution. Solid stannous chloride dihydrate (17.8 g, 0.079 mol) was then added and the reaction mixture was heated at 100-110 °C for 1 h before cooling and evaporation under reduced pressure. The residue was dissolved in water and basified with 3N potassium hydroxide (100 ml). The aqueous solution was extracted with ether (3 x 50 ml). The organic layers were dried over anhydrous sodium sulphate, concentrated, and the residue was recrystallized from ethanol/water (80/20) to give (**2b**) (2 g, 80%); mp 184 °C. Anal. Calcd for $C_7H_6N_3Cl$: C, 50.15; H, 3.58; N, 25.07. Found: C, 50.43; H, 3.45; N, 25.32. ^{1}H-Nmr δ: 6.47 (1H, d, J = 1.5 Hz, 7-H), 6.58 (1H, dd, J = 1.5; 8.6 Hz, 5-H), 7.26 (1H, d, J = 8.7 Hz, 4-H), 12.41 (1H, s, 1-H). ^{13}C-Nmr δ: 90.42 (7-C), 111.97 (3a-C), 113.40 (5-C), 118.64 (4-C), 131.97 (3-C), 143.57 (1a-C), 148.86 (6-C).

1-Methyl-6-nitroindazole (1c) and 2-methyl-6-nitroindazole (1d)[13]

Methyl sulphate (17.5 g, 0.138 mol) was added slowly at 45 °C to a solution of 6-nitroindazole (**1a**) (5 g, 0.03 mol) in an alkaline solution, (potassium hydroxide (15 g, 0.3 mol) and water (17 ml)). The solution was kept under stirring at 45 °C during 30 min and then cooled. The mixture of 1- and 2-methyl isomers was then filtered, dried and separated by flash chromatography on silica gel with ether/toluene (40/60) as eluent. 1-methyl-6-nitroindazole (**1c**) appeared first, followed by 2-methyl-6-nitroindazole (**1d**).

1c, 2.28 g (42%); mp 125 °C (from ether/toluene). Anal. Calcd for $C_8H_7N_3O_2$: C, 54.23; H, 3.95; N, 23.72. Found: C, 54.41; H, 3.68; N, 23.49. ^{1}H-Nmr δ: 4.19 (3H, s, 1-CH_3), 7.93 (1H, dd, J = 1.8; 8.8 Hz, 5-H), 8.00 (1H, dd, J = 0.8; 8.8 Hz, 4-H), 8.28 (1H, d, J = 1.0 Hz, 3-H), 8.72 (1H, d, J = 1.0 Hz, 7-H). ^{13}C-Nmr δ: 35.75 (1-CH_3), 106.43 (7-C), 114.30 (5-C), 121.62 (4-C), 126.20 (3a-C), 132.71 (3-C), 137.92 (C-1a), 145.45 (6-C).

1d, 2.39 g (44%); mp 160 °C (from diethyl ether/toluene). Anal. Calcd for $C_8H_7N_3O_2$: C, 54.23; H, 3.95; N, 23.62. Found: C, 54.57; H, 4.18; N, 23.52. ^{1}H-Nmr δ: 4.28 (3H, s, 2-CH_3), 7.80 (1H, dd, J = 1.7; 9.0 Hz, 5-H), 7.97 (1H, dd, J = 0.4; 9.0 Hz, 4-H), 8.59 (1H, d, J = 0.4 Hz, 7-H), 8.60 (1H, s, 3-H). ^{13}C-Nmr δ: 40.84 (2-CH_3), 114.53 (5-C), 114.55 (7-C), 122.20 (4-C), 124.07 (3a-C), 126.12 (3-C), 146.04 (6-C), 147.82 (1a-C).

6-Amino-1-methylindazole (2c) and 6-amino-2-methylindazole (2d)

Aminomethylindazoles (**2c** and **2d**) were obtained by reduction of compounds (**1c** and **1d**) as described above for the preparation of 6-amino-3-chloroindazole (**2b**).

2c, 2.18 g (87%); mp 130 °C (from water). Anal. Calcd for $C_8H_9N_3$: C, 65.30; H, 6.12; N, 28.57. Found: C, 65.53; H, 6.37; N, 28.36. ^{1}H-Nmr δ: 3.81 (3H, s, 1-CH_3), 6.44 (1H, m, 7-H), 6.49 (1H, dd, J = 1.8; 8.5 Hz, 5-H), 7.35 (1H, dd, J = 0.6; 8.5 Hz, 4-H), 7.68 (1H, d, J = 1.0 Hz, 3-H). ^{13}C-Nmr δ: 34.68 (1-CH_3), 89.51 (7-C), 112.19 (5-C), 120.77 (4-C), 125.97 (3a-C), 131.91 (C-3), 141.64 (C-1a), 147.73 (C-6).

2d, 1.92 g (77%); mp 155 °C (from water). Anal. Calcd for $C_8H_9N_3$: C, 65.30; H, 6.12; N, 28.57. Found: C, 65.41, H, 6.04; N, 28.71. ^{1}H-Nmr δ: 3.98 (3H, s, 2-CH_3), 6.47 (1H, m, 7-H), 6.50 (1H, dd, J = 1.9; 8.7 Hz, 5-H), 7.33 (1H, dd, J = 0.9; 8.7 Hz, 4-H), 7.97 (1H, d, J = 0.3 Hz, 3-H). ^{13}C-Nmr δ: 39.23 (2-CH_3), 94.09 (7-C), 115.78 (5-C), 115.78 (3a-C), 120.30 (4-C), 123.81 (3-C), 146.25 (6-C), 150.17 (1a-C).

p-Tolyllead triacetate (6a)[14]

Lead tetraacetate (4.5 g, 10 mmol) was kept one night under 20 mm Hg over potassium hydroxide pellets. Then, it was added immediately to a stirred solution of trichloroacetic acid (7.5 g, 45 mmol) in dry chloroform (20 ml) under nitrogen atmosphere. After complete dissolution of lead tetraacetate, anhydrous toluene (12.5 ml, 0.11 mmol) was added and the mixture stirred at room temperature until all lead tetraacetate had reacted, 5-10 h, (the presence of unreacted lead tetraacetate in the solution can be checked from the precipitate which is formed when dropping a sample of the reaction mixture into water). The yellow solution was then washed with water (2 x 50 ml) and concentrated under reduced pressure. The residue was dissolved in cold light petroleum, (bp 60-70 °C, 100 ml), to precipitate the aryllead oligomer as a white powder. The precipitate of plumboxane was recovered by filtration and added to a stirred solution of glacial acetic acid (10 ml) in chloroform (25 ml). After 15 min at room temperature, the clear solution obtained was washed with water (2 x 25 ml) and the organic phase concentrated in vacuo (2-5 ml). The residue was then diluted with light petroleum until a white precipitate appeared and the solution kept for one night at 4°C to afford *p*-tolyllead triacetate (**6a**) as white crystals (2.8 g, 50%); mp 86-87 °C (from light petroleum/toluene). Anal. Calcd for $C_{13}H_{16}O_6Pb$: C, 32.84; H, 3.37. Found: C, 32.63; H, 6.58. ^{1}H-Nmr δ: 1.88 (9H, s, 3xOAc), 2.34 (3H, s, 4-CH_3), 7.69 (2H, d, J = 7.9 Hz, 2-H), 7.37 (2H, d, J = 8.0 Hz, 3-H). ^{13}C-Nmr δ: 20.78 (4-CH_3), 22.28 ($\underline{C}H_3CO$), 79.28 (1-C), 130.34 (2-C), 130.71 (3-C), 140.55 (4-C), 176.57 ($\underline{C}OCH_3$).

p-Methoxyphenyllead triacetate (6b)[15]

Lead tetraacetate (25 g, 55 mmol), dried as previously described, was added to a stirred solution of dichloroacetic acid (7.5 g, 45 mmol) in dry chloroform (100 ml) under a nitrogen atmosphere. When all lead tetraacetate had dissolved, anhydrous anisole (8 g, 74 mmol) was added during 15 min and the solution stirred at room temperature until lead tetraacetate can no longer be detected (see above for **6a**). The orange solution was washed with water (2 x 110 ml) and the organic layer separated and concentrated under reduced pressure until a volume of 10 ml was reached. Then, the mixture was treated with hexane (bp 67-70 °C, 400 ml), and kept cooled over night. The yellow precipitate (plumboxane) was collected and stirred with a mixture of glacial acetic acid (125 ml) and chloroform (100 ml) for 1 h. The solution was washed with water (2 x 100 ml), the organic layer concentrated under reduced pressure (volume 10 ml), diluted with hexane (200 ml), and cooled. A white precipitate was collected and dried to give *p*-methoxyphenyllead triacetate (**6b**) (14.2 g, 60%); mp 138 °C (from methanol). Anal. Calcd for $C_{13}H_{16}O_7Pb$: C, 31.77; H, 3.26. Found: C, 31.98; H, 3.55. ^{1}H-Nmr δ: 1.88 (9H, s, 3xOAc), 3.79 (3H, s, 4-OCH_3), 7.16 (2H, d, J = 8.3 Hz, 3-H), 7.74 (2H, d, J = 8.5 Hz, 2-H). ^{13}C-Nmr δ: 21.94 ($\underline{C}H_3CO$), 55.40 (4-OCH_3), 55.60 (1-C), 115.34 (3-C), 134.16 (2-C), 157.87 (4-C), 160.77 ($\underline{C}OCH_3$).

General method for the preparation of *N*-arylindazoles:

3-Chloro-6-*p*-tolylamino-1*H*-indazole (3b)

A solution of 6-amino-3-chloroindazole (**2b**) (0.8 g, 4.8 mmol) in dry dichloromethane (30 ml) was treated with *p*-tolyllead triacetate (**6a**)(2.51 g, 5.28 mmol) and copper(II) acetate (87 mg, 0.48 mmol). The mixture was stirred at room temperature under a slow stream of dry nitrogen for 4 h and evaporated under reduced pressure. The residue was extracted with ethyl acetate, filtered, and the filtrate was concentrated to yield **3b** . The resulting solid was purified by chromatography on silica gel, (elution with dichloromethane/ethanol, 9/1) (0.55 g, 50%); mp 176 °C (from dichloromethane/ethanol). Anal. Calcd for $C_{14}H_{12}N_3Cl$: C, 65.24; H, 4.66; N, 16.30. Found: C, 65.13; H, 4.73; N, 16.19. ^{1}H-Nmr δ: 2.25 (3H, s, 12-CH_3), 6.77 (1H, dd, J = 1.7; 8.7 Hz, 5-H), 6.94 (1H, br s, 7-H), 7.04-7.14 (4H, AA'BB' type spectrum, 10-H and 11-H), 7.42 (1H, d, J = 8.7 Hz, 4-H), 8.34 (1H, s, 8-H), 12.63 (1H, s, 1-H). ^{13}C-Nmr δ: 20.38 (12-CH_3), 91.49 (7-C), 113.34 (3a-C), 114.57 (5-C), 119.14 (10-C), 119.25 (4-C), 129.72 (11-C), 130.15 (12-C), 132.01 (3-C), 139.78 (9-C), 142.94 (7a-C), 144.68 (6-C).

1-Methyl-6-*p*-tolylamino-1*H*-indazole (3c)

6-Amino-1-methylindazole (**2c**) (0.8 g, 5.4 mmol), was treated as above with *p*-tolyllead triacetate (**6a**) (2.84 g, 6 mmol); after evaporating the resulting residue was flash chromatographed on silica gel with ethyl acetate to afford compound (**3c**) (0.86 g, 67%); mp 144 °C (from ethyl acetate). Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.95; H, 6.33; N, 17.72. Found: C, 75.93; H, 6.35; N, 17.68. ^{1}H-Nmr δ: 2.25 (3H, s, 12-CH_3), 3.88 (3H, s, 1-CH_3), 6.82 (1H, dd, J = 1.6; 8.6 Hz, 5-H), 7.02 (1H, s, 7-H), 7.10 (4H, s, 10-H and 11-H), 7.54 (1H, d, J = 8.7 Hz, 4-H), 7.80 (1H, s, 3-H). ^{13}C-Nmr δ: 34.99 (1-CH_3), 20.32 (12-CH_3), 91.59 (7-C), 113.60 (5-C), 117.66 (3a-C), 118.17 (10-C), 121.30 (4-C129.25 (12-C), 129.66 (11-C), 132.06 (3-C), 140.42 (9-C), 140.98 (7a-C), 143.10 (6-C).

1-Methyl-6-*p*-methoxyphenylamino-1*H*-indazole (3e)

Compound (**2c**) (0.8 g, 5.4 mmol) was treated with *p*-methoxyphenyllead triacetate (**6b**) (2.95 g, 6 mmol). After evaporating, the residue was flash chromatographed with ethyl acetate to give indazole (**3e**) (0.77 g, 56%); mp 150 °C (from ethyl acetate). Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.15; H, 5.93; N, 16.60. Found: C, 71.31 H, 5.89; N, 16.72. ^{1}H-Nmr δ: 3.73 (3H, s, 12-OCH_3), 3.85 (3H, s, 1-CH_3), 6.76 (1H, dd, J = 1.5; 8.5 Hz, 5-H), 6.88 (1H, s, 7-H), 6.91 (2H, d, J = 9.0 Hz, 10-H), 7.16 (2H, d, J = 8.8 Hz, 11-H), 7.78 (1H, s, 3-H), 8.09 (1H, s, 8-H). ^{13}C-Nmr δ: 34.96 (1-CH_3), 55.20 (12-OCH_3), 90.13 (7-C), 113.22 (5-C), 114.59 (11-C), 117.29 (3a-C), 120.94 (10-C), 121.30 (4-C), 132.05 (3-C), 135.82 (9-C), 141.11 (7a-C), 144.24 (6-C), 154.10 (12-C).

1-Methyl-6-phenylamino-1*H*-indazole (3f)

6-Amino-1-methylindazole (**2c**) (0.8 g, 5.4 mmol) was treated with triphenylbismuth diacetate (**7**) (3.35 g, 6 mmol) and copper(II) acetate (98 mg, 0.54 mmol). After chromatography with ethyl acetate aryl compound (**3f**) was obtained (0.9 g, 74%); mp 143-144°C (from ethyl acetate). Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.34; H,

5.83; N, 18.83. Found: C, 75.24; H, 5.96; N, 18.75. ^{1}H-Nmr δ: 3.90 (3H, s, 1-CH_3), 6.87 (1H, dt, J = 7.7 Hz, 12-H), 6.88 (1H, dd, J = 1.9; 8.6 Hz, 5-H), 7.12 (1H, t, J = 0.9 Hz, 7-H), 7.18 (1H, dt, J = 7.7 Hz, 10-H), 7.27 (2H, t, J = 7.7 Hz, 11-H), 7.57 (1H, d, J = 8.7 Hz, 4-H), 7.82 (1H, d, J = 1.0 Hz, 3-H), 8.37 (1H, s, 8-H). ^{13}C-Nmr δ: 35.12 (1-CH_3), 92.97 (7-C), 114.28 (5-C), 117.35 (10-C), 118.12 (3a-C), 120.16 (12-C), 121.44 (4-C), 129.31 (11-C), 132.18 (3-C), 140.97 (7a-C), 142.42 (9-C-9), 143.10 (6-C).

2-Methyl-6-phenylamino-1*H*-indazole (3d)

Arylation of 6-amino-2-methylindazole (**2d**) (0.8 g, 5.4 mmol) with aryl bismuth reagent (**7**) (3.35 g, 6 mmol) afforded compound (**3d**) (0.8 g, 66%); mp 144°C (from ethyl acetate). Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.34; H, 5.83; N, 18.83. Found: C, 75.21; H, 5.98; N, 18.95. ^{1}H-Nmr δ: 4.04 (3H, s, 1-CH_3), 6.80 (1H, t, J = 7.3 Hz, 12-H), 6.81 (1H, dd, J = 1.6; 7.4 Hz, 5-H), 7.09 (2H, d, J = 7.5 Hz, 10-H), 7.11 (1H, s, 7-H), 7.23 (2H, t, J = 7.5 Hz, 11-H), 7.54 (1H, d, J = 8.9 Hz, 4-H), 8.13 (3H, s, 3-H), 8.15 (1H, s, 8-H). ^{13}C-Nmr δ: 39.58 (2-CH_3), 98.27 (7-C), 116.76 (10-C), 117.06 (5-C), 117.19 (3a-C), 119.50 (4-C), 120.94 (12-C), 124.25 (3-C), 129.13 (11-C), 140.66 (6-C), 143.72 (9-C), 149.26 (7a-C).

General method for thionation:

3-Chloro-9-methyl-1*H*,6*H*-pyrazolo[4,3-*c*]phenothiazine (4b)

A mixture of compound (**3b**) (0.5 g, 1.9 mmol), sulphur (0.125 g, 3.9 mmol) and iodine (50 mg, 0.19 mmol) was refluxed in dry *o*-dichlorobenzene (5 ml) under nitrogen during 5 h. Chromatography on silica gel of the solution with dichloromethane as eluent, afforded *o*-dichlorobenzene followed by compound (**4b**) (0.168 g, 30%); mp 210 °C (from dichloromethane). Anal. Calcd for $C_{14}H_{10}N_3ClS$: C, 58.43; H, 3.48; N, 14.61. Found: C, 58.61; H, 3.27; N, 14.35. Ms m/z: 287 (M^+). ^{1}H-Nmr δ: 2.13 (3H, s, 9-CH_3), 6.61 (1H, d, J = 7.8 Hz, 7-H), 6.67 (1H, d, J = 8.7 Hz, 5-H), 6.79 (1H, s, 10-H), 6.82 (1H, d, J = 8.9 Hz, 8-H), 7.26 (1H, d, J = 8.6 Hz, 4-H), 8.69 (1H, s, 6-H), 13.04 (1H, s, 1-H). ^{13}C-Nmr δ: 20.02 (9-CH_3), 94.22 (11a-C), 112.37 (5-C), 114.66 (10a-C), 114.93 (7-C), 115.78 (3a-C), 117.47 (4-C), 126.96 (10-C), 128.51 (8-C), 131.69 (9-C), 132.85 (3-C), 138.89 (11b-C), 139.61 (6a-C), 141.98 (5a-C).

1,9-Dimethyl-1*H*,6*H*-pyrazolo[4.3-*c*]phenothiazine (4c) and 1,7-dimethyl-1*H*,10*H*-pyrazolo-[3,4-*b*]phenothiazine (5c)

1-Methyl-6-*p*-tolylamino-1*H*-indazole (**3c**) (0.8 g, 3.37 mmol) was treated in the same way as (**4b**) by sulphur (0.180 g, 5.57 mmol) and iodine (80 mg, 0.3 mmol) in dry *o*-dichlorobenzene (8 ml), over 8 h under reflux. The black solution was extracted with ether and filtered to obtain:

A) A filtrate which was concentrated under reduced pressure and purified on silica gel with ether; the solvent of the reaction, *o*-dichlorobenzene, was eluted first, followed by the "bent" phenothiazine (**4c**) (0.37 g, 41%); mp 181°C (from ether). Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.41; H, 4.87; N, 15.73. Found: C, 67.35; H, 5.01; N, 15.86. Ms m/z: 268 (M^+). ^{1}H-Nmr δ: 2.16 (3H, s, 9-CH_3), 4.23 (3H, s, 1-CH_3), 6.65 (1H, d, J = 8.5 Hz, 5-H), 6.76 (1H, dd, J = 1.6; 8.5 Hz, 7-H), 6.86 (1H, dd, J = 1.8; 7.8 Hz, 8-H), 6.87 (1H, s, 10-H), 7.39 (1H, d, J = 8.5 Hz, 4-H), 7.83 (1H, s, 3-H), 8.66 (1H, s, 6-H). ^{13}C-Nmr δ:

19.93 (1-CH_3), 38.65 (9-CH_3), 94.63 (11a-C), 111.63 (5-C), 114.45 (7-C), 115.50 (10a-C), 119.68 (4-C), 126.80 (10-C), 128.41 (8-C), 131.35 (9-C), 132.77 (3-C), 136.79 (11b-C), 140.67 (6a-C), 142.35 (5a-C).

B) An insoluble green part which was chromatographed with ethyl acetate to isolate the linear isomer: 1,7-dimethyl-1*H*,10*H*-pyrazolo[3,4-*b*]phenothiazine (**5c**) (0.01 g, 11%); mp 195 °C (from ethyl acetate). Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.41; H, 4.87; N, 15.73. Found: C, 67.69; H, 5.20; N, 15.98. Ms m/z: 268 (M^+). ^{1}H-Nmr δ: 2.15 (3H, s, 7-CH_3), 3.86 (3H, s, 1-CH_3), 6.67 (1H, d, *J* = 7.5 Hz, 9-H), 6.71 (1H, s, 11-H), 6.82 (1H, s, 6-H), 6.83 (1H, d, *J* = 7.8 Hz, 8-H), 7.34 (1H, s, 4-H), 7.72 (1H, s, 3-H), 8.83 (1H, s, 10-H). ^{13}C-Nmr δ: 20.03 (1-CH_3), 35.19 (7-CH_3), 92.10 (5-C), 112.88 (11a-C), 114.55 (7-C), 116.88 (10a-C), 117.53 (11b-C), 119.60 (3a-C), 126.34 (10-C), 127.91 (8-C), 130.51 (9-C), 131.64 (3-C), 138.98 (6a-C), 140.13 (4-C), 141.84 (5a-C).

1-Methyl-1*H*, 6*H*-pyrazolo[4,3-*c*]phenothiazine (4f) and 1-methyl-1*H*,10*H*-pyrazolo[3,4-*b*]phenothiazine (5f)

We used the same conditions as for **4c** *and* **5c** *but with 1-methyl-6-phenylamino-1H-indazole* (**3f**) (0.8 g, 3.75 mmol), sulphur (0.2 g, 6.2 mmol) and iodine (80 mg, 0.3 mmol). Extraction and filtration of the mixture with diethyl ether gave:

A) A soluble part which was concentrated and purified by column chromatography with ether as for compound (**4b**), to give the "bent" phenothiazine (**4f**) (0.44 g, 46%); mp 185 °C (from ether). Anal. Calcd for $C_{14}H_{11}N_3S$: C, 66.40; H, 4.35; N, 16.60. Found: C, 66.56; H, 4.27; N, 16.82. Ms m/z: 254 (M^+). ^{1}H-Nmr δ: 4.24 (3H, s, 1-CH_3), 6.67 (1H, d, *J* = 8.5 Hz, 5-H), 6.76 (1H, dd, *J* = 0.8; 7.8 Hz, 7-H), 6.83 (1H, dt, *J* = 1.3;7.7 Hz, 9-H), 7.04 (1H, dd, *J* = 1.5; 7.3 Hz, 10-H), 7.05 (1H, ddd, *J* = 1.4; 7.8; 9.2 Hz, 8-H), 7.40 (1H, d, *J* = 8.5 Hz, 4-H), 7.84 (1H, s, 3-H), 8.78 (1H, s, 6-H). ^{13}C-Nmr δ: 38.76 (1-CH_3), 94.91 (11a-C), 111.98 (5-C), 114.72 (7-C), 115.71 (10a-C), 119.89 (4-C), 121.28 (3a-C), 122.47 (9-C), 126.66 (10-C), 128.13 (8-C), 132.91 (3-C), 136.85 (11b-C-), 142.09 (5a-C), 143.32 (6a-C).

B) The green part which gave finally 1-methyl-1*H*,10*H*-pyrazolo[3,4-*b*]phenothiazine (**5f**) purified on silica gel with ethyl acetate (8 mg, 9%); mp > 260 °C (from ethyl acetate). Anal. Calcd for $C_{14}H_{11}N_3S$: C, 66.40; H, 4.35; N, 16.60. Found: C, 66.57; H, 4.71; N, 16.36. Ms m/z: 254 (M^+). ^{1}H-Nmr δ: 3.87 (3H, s, 1-CH_3), 6.74 (1H, s, 11-H), 6.78 (1H, dd, *J* = 1.2; 7.8 Hz, 9-H), 6.79 (1H,br t, *J* = 7.2 Hz, 7-H), 6.99 (1H, dd, *J* = 1.6; 8.4 Hz, 6-H), 7.02 (1H, dt, *J* = 1.5; 7.7 Hz, 8-H), 7.35 (1H, s, 4-H), 7.73 (1H, d, *J* = 0.7 Hz, 3-H), 8.96 (1H, s, 10-H). ^{13}C-Nmr δ: 35.25 (1-CH_3), 92.41 (5-C), 112.85 (11a-C), 114.73 (7-C), 117.04 (10a-C), 117.64 (11b-C), 119.81 (3a-C), 121.62 (9-C), 126.17 (10a-C), 127.49 (8-C), 131.72 (3-C), 140.15 (4-C), 141.21 (5a-C), 141.52 (6a-C).

2-Methyl-1*H*, 6*H*-pyrazolo[4,3-*c*]phenothiazine (4d)

Cyclization and work-up as for **4c** *and* **5c** *gave only the* [4,3-*c*] "bent" isomer (**4d**) after purification, (0.5 g, 55%); mp 147 °C (from ether). Anal. Calcd for $C_{14}H_{11}N_3S$: C, 66.40; H, 4.35; N, 16.60. Found: C, 66.75; H, 4.23; N, 16.85. Ms m/z: 254 (M^+). ^{1}H-Nmr δ: 4.05 (3H, s, 2-CH_3), 6.54 (1H, d, *J* = 8.8 Hz, 5-H),

6.61 (1H, dd, J = 1.1; 7.9 Hz, 7-H), 6.71 (1H, dt, J = 1.3;7.4 Hz, 9-H), 6.87 (1H, dd, J = 1.3; 7.6 Hz, 10-H), 6.94 (1H, dt, J = 1.6; 7.6 Hz, 8-H), 7.34 (1H, d, J = 8.6 Hz, 4-H), 8.09 (1H, s, 3-H), 8.37 (1H, s, 6-H). ^{13}C-Nmr δ: 39.85 (2-CH_3), 96.98 (11a-C), 116.22 (10a-C), 113.64 (5-C), 114.53 (7-C), 118.05 (3a-C), 118.92 (4-C), 121.87 (9-C), 125.20 (3-C), 126.48 (10-C), 127.49 (8-C), 138.19 (5a-C), 142.43 (6a-C), 145.62 (11b-C).

9-Methoxy-1-methyl-1*H*, 6*H*-pyrazolo[4,3-*c*]phenothiazine (4e)

The *N*-aryl compound (**3e**) was cyclized as above, but chromatographed with dichloromethane/ethanol (95/5) to yield compound (**4e**) (0.32 g, 36%); mp 175 °C (from dichloromethane/ethanol). Anal. Calcd for $C_{15}H_{13}N_3OS$: C, 63.60; H, 4.60; N, 14.84. Found: C, 63.42; H, 4.91; N, 14.52. Ms m/z: 284 (M^+). ^{1}H-Nmr δ: 3.68 (3H, s, 9-OCH_3), 4.23 (3H, s, 1-CH_3), 6.64 (1H, d, J = 8.5 Hz, 5-H), 6.67 (1H, dd, J = 2.6;9.0 Hz, 7-H), 6.69 (1H, d, J = 2.6 Hz, 10-H), 6.71 (1H, d, J = 8.6 Hz, 8-H), 7.39 (1H, d, J = 8.5 Hz, 4-H), 7.82 (1H, s, 3-H), 8.57 (1H, s, 6-H). ^{13}C-Nmr δ: 38.74 (1-CH_3), 55.52 (9-OCH_3), 94.14 (11a-C), 111.88 (5-C), 111.89 (10-C), 113.79 (8-C), 115.31 (7-C), 116.81 (10a-C), 119.87 (4-C), 120.99 (3a-C), 132.88 (3-C), 136.90 (11b-C), 155.18 (9-C), 136.63 (6a-C), 142.84 (5a-C).

ACKNOWLEDGEMENTS

The authors wish to thank Dr. J.P. Finet of the "Laboratoire de structure et réactivité des espèces paramagnétiques, Université St Jérôme, Marseille" for very helpful discussions about the use of organometalic compounds, and Dr. L. Debrauwer of "Laboratoire des Xénobiotiques, INRA, Toulouse" for recording Mass spectra.

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Received, 26th October, 1994