FUSED IMIDAZOPHENOTHIAZINES: SYNTHESIS OF 2-METHYL-3-PHENYL-6*H*-IMIDAZO[4,5-*c*]PHENOTHIAZINE

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Abstract — A new and reliable procedure for the multigram-scale preparation of 2-methyl-1-phenyl-5-phenylaminobenzimidazole (6) is reported. Bernthsen thionation of 6 leads to 2-methyl-3-phenyl-6*H*-imidazo[4,5-*c*]phenothiazine (9), whose structure was established through a detailed mono- and bidimensional ^{1}H-nmr and ^{13}C-nmr spectroscopic study of model compounds.

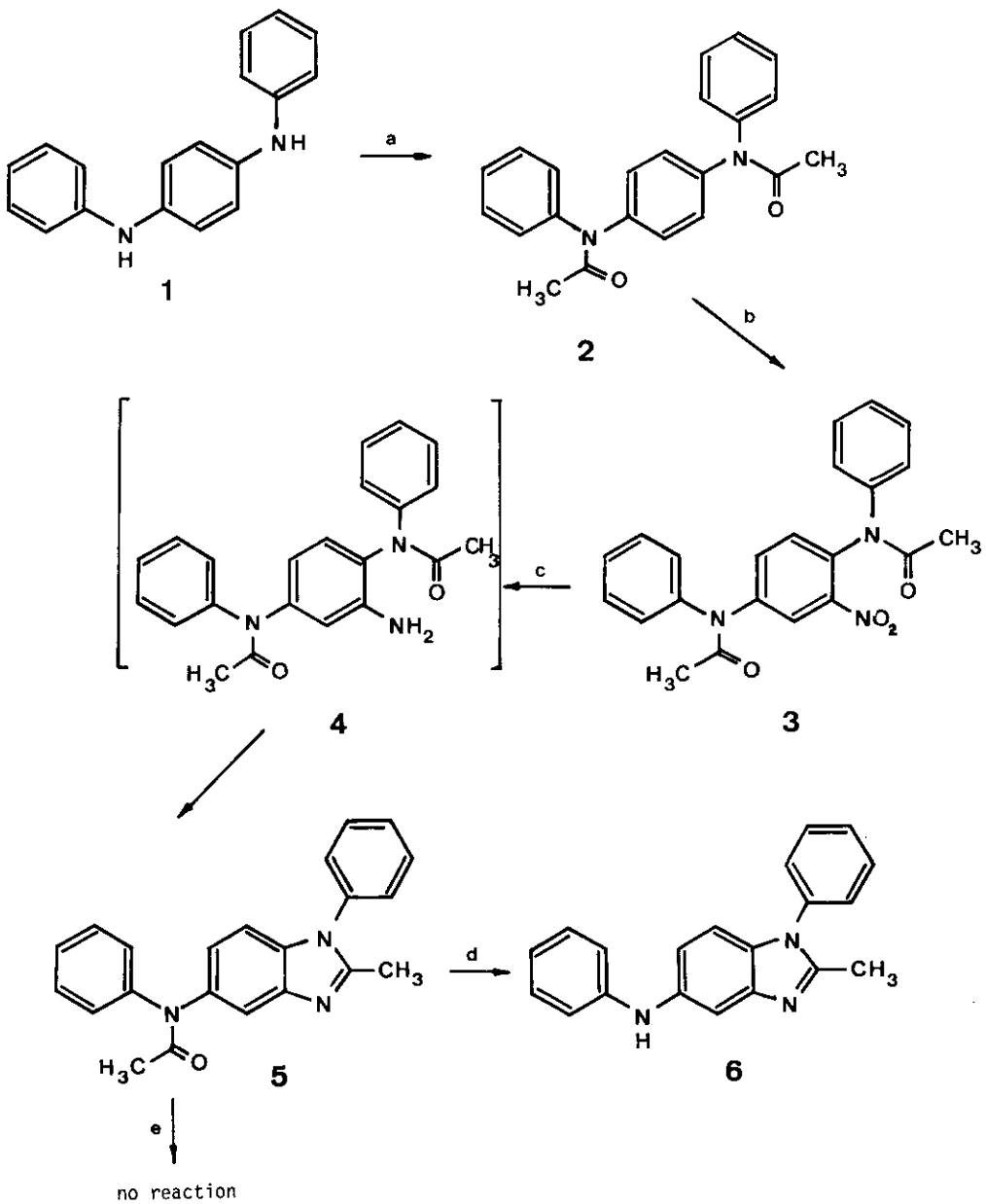
INTRODUCTION

The chemistry of phenothiazine compounds[1-3] has been considered of interest for over a century due to their wide range of applications, which include several useful pharmacological activities (antihistaminic,[4] neuroleptic[5] and anthelmintic[6]), and also their use as photosensitizers in solar energy converters.[7] In spite of the wide range of structural types covered by these studies, there is, to our knowledge, only one example of a mixed phenothiazine-imidazole fused ring system, namely imidazo[4,5,1-*k*,*l*]phenothiazine.[8] We wish to report here the first study of the regioselectivity of Bernthsen thionation[1-3] of an anilinobenzimidazole derivative, as exemplified by the transformation of 2-methyl-1-phenyl-5-phenylaminobenzimidazole (6) into 2-methyl-3-phenyl-6*H*-imidazo[4,5-*c*]phenothiazine (9).

SYNTHESIS

Through reinvestigation of an early report by Brunck,[9] in which experimental details were absent, we have developed a new and reliable procedure for the preparation of the phenothiazine precursor (6) in 38 % overall yield from commercially available *N,N'*-diphenyl-1,4-phenylenediamine (1) (Scheme 1). Treatment of 1 with acetic anhydride in the presence of sodium acetate gave the diacetyl derivative (2), which was chemoselectively nitrated to 3. Nitration of 2 to 3 with concentrated nitric acid, as described by Brunck,[9] showed the lack of reproducibility of his procedure, due mainly to the very short reaction times required in order to minimize polynitration. Another disadvantage of this method is that it is not ameneable to work at a scale higher than *ca.* 2 g, due to the incontrollable formation of tarry polynitrated compounds. All these problems made necessary to develop a more convenient procedure for the preparation of 3. After some experimentation with mixtures of nitric acid and several solvents, it was found that treatment of 2 with a 30 % solution of nitric acid in acetic acid at room temperature for 14 h gave 64 % yield (overall from 1) of the desired mononitro derivative (3). This is an easily reproducible method that can be readily performed in a multigram scale, significantly improving the yield of 3 and simplifying the experimental work. The structure of compound 3 was confirmed by its ^{1}H-nmr spectrum (270 MHz, $CDCl_3$), in which the three protons of the nitrated central ring can be easily distinguished from the rest of aromatic protons (H-3 (d):δ 7.82 ppm, $J_{3,5}$ = 1.7 Hz; H-5 (dd):δ 7.25 ppm, $J_{5,6}$ = 9.2 Hz; H-6 (d): δ 7.07 ppm).

With adequate amounts of 3 in hand, attention was turned towards achieving its reductive cyclization to a benzimidazole derivative. Among the many methods available for the reduction of aromatic nitro compounds to amines,[10,11] reaction with stannous chloride in concentrated hydrochloric acid was initially chosen. However, application of this procedure to 3 invariably led to complex mixtures, from which it was difficult to isolate the benzimidazole derivative (5). It was subsequently found that a new, high-yielding reductive cyclization could be effected by use of triethylammonium formate and palladium on charcoal[12,13] as reducing agent. The intermediate amine (4) was not isolated. Deprotection of 5 to the deacetyl derivative (6) was achieved by hydrolysis with sulfuric acid in aqueous ethanol.


a
b
c
d
e
no reaction
a. Ac_2O, NaOAc b. HNO_3, AcOH c. HCO_2NHEt_3, C-Pd
d. H_2SO_4, EtOH-H_2O e. S_8, I_2

Scheme 1

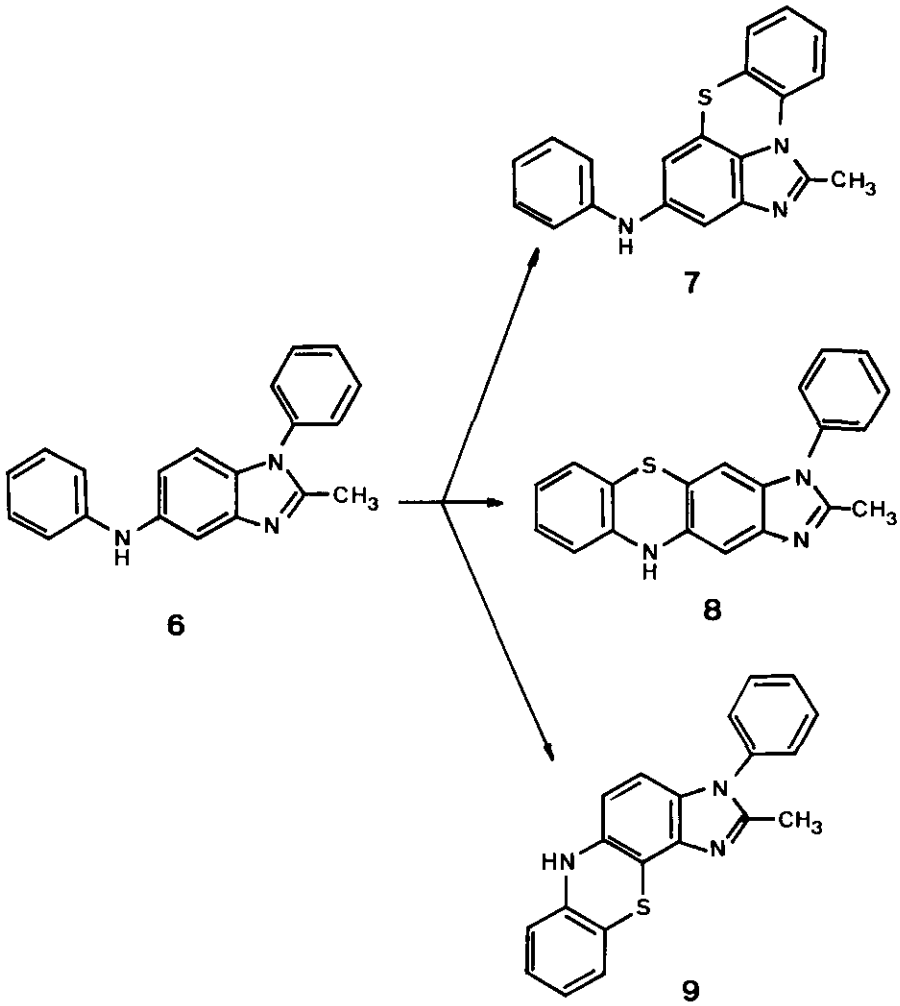
Bernthsen thionation[1-3] of 6 to the corresponding phenothiazine derivative was initially attempted by treatment with sulphur and iodine in refluxing *o*-dichlorobenzene, following the method described by Shavyrina.[14] Better results were obtained by melting the mixture of starting materials in the absence of solvents under an inert atmosphere. In spite of the high temperatures used (210-220 °C), ring closure was incomplete, but more drastic conditions could not be employed without extensive decomposition of the starting material. The use of a slow stream of dry nitrogen gave better results than static nitrogen atmospheres or a pressurized reaction vessel, which can be explained if removal of hydrogen sulfide formed during the reaction helps to displace the equilibrium towards the desired product.

An attempted thionation of the acetyl derivative (5) under the same conditions was unsuccessful. The use of higher temperatures led only to decomposition of 5, but no trace of a phenothiazine compound was formed.

STRUCTURAL STUDIES

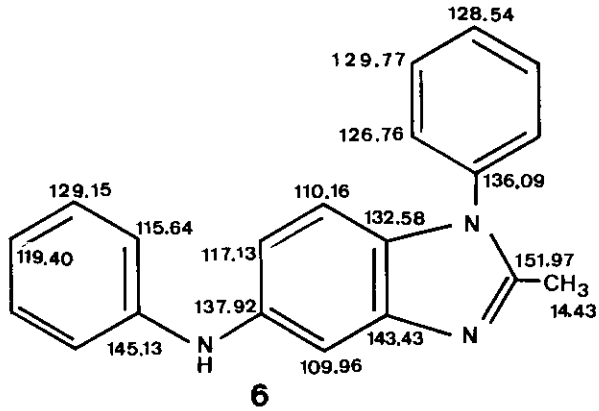
Thionation of 6 can lead, in principle, to three different phenothiazine derivatives (Scheme 2). In order to discriminate among the structures (7, 8 and 9) a detailed spectroscopic study was necessary. Because of the complexity of the spectra, due to the large number of aromatic signals and the well-known[2,15] instability of phenothiazine systems, much of the spectroscopic information had to be obtained by comparing spectral data of the phenothiazine derivative with those of its precursor (6). In order to assist the assignment of the spectra of 6, a model compound, 2-methyl-1-phenylbenzimidazole (10, Figure 1), was prepared by cyclization of commercially available *N*-phenyl-1,2-phenylenediamine with acetic acid, following the procedure described by Efros[16] for benzimidazole synthesis.

Most signals of the ^{13}C-nmr spectrum (75 MHz) of 6 could be unequivocally assigned with the help of its ^{13}C-nmr proton-coupled spectrum and study of literature data and the ^{13}C-nmr spectrum of 10 (Figure 1). Thus, quaternary carbon atoms of 6 (C-2, C-3a, C-5, C-7a, C-1' and C-1") showed δ values in good agreement with previously published data for benzimidazole systems,[17] 1-phenylimidazole,[17] and diarylamines,[18,19] and were assigned by examination of long-range (^{2}J and ^{3}J) coupling constants (Table 1). The

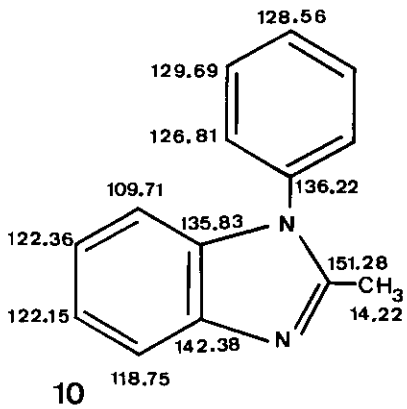


Scheme 2

signal corresponding to C-7 could be differentiated from all other non-quaternary carbon atoms because it was the only one that showed a clean doublet in the coupled ^{13}C-nmr spectrum, in agreement with the absence of protons in the atoms C-3a and C-5.



6



10

Figure 1

Signal	^1J	^2J	^3J
C-2	---	7.1 (CH_3)	---
C-3a	---	---	5.0 (H-7)
C-5	---	---	7.1 (H-7)
C-7a	---	---	7.1 (H-4, H-6)
C-1'	---	---	9.1 (H-3', H-5')
C-1"	---	---	9.1 (H-3", H-5")
C-7	163.2	---	---
C-4	160.1	---	4.0 (H-6)
C-6	160.1	---	5.0 (H-4)
C-2'	161.2	---	6.0 (H-4', H-6')
C-3'	163.2	---	8.1 (H-5')
C-4'	162.2	---	7.1 (H-2', H-6')
C-2"	158.1	---	6.1 (H-4", H-6")
C-3"	158.1	---	7.1 (H-5")
C-4"	160.2	---	7.1 (H-2", H-6")

Table 1: J_{C-H} values for compound 6 (Hz)

The intensity pattern in the ^{13}C decoupled spectrum of 6 was the criterion used to distinguish between the signals corresponding to C-2' (6'), C-3' (5'), C-2" (6") and C-3" (5") and the rest of carbon atoms. Their multiplicity in the proton-coupled ^{13}C-nmr spectrum was used to differentiate between the carbons *ortho* (dt) and *metha* (dd) of both phenyl substituents. Finally, the two remaining doublet-triplets at 119.40 ppm and 128.54 ppm were assigned to C-4" and C-4', respectively, on the basis of the study of an heteronuclear (^{13}C-^{1}H) correlation experiment (see below). This assignment is also supported by the absence of a signal at about 119 ppm in the ^{13}C-nmr spectrum of compound (10).

On the basis of the ^{13}C-nmr assignments discussed above, the information derived from a 2D ^{13}C-^{1}H heteronuclear correlation experiment (Figure 2) allowed the attribution of the ^{1}H-nmr spectrum (300 MHz) of compound (6). Examination of Figure 2 shows a correlation between the signals due to C-3' (5'), C-4' and C-4 and the multiplet centered at 7.54 ppm in the ^{1}H-nmr spectrum, which therefore corresponds to the protons H-3', H-5', H-4' and H-4. A correlation is also observed between the signal at 126.8 ppm (C-2', C-6') and the one centered at 7.38 ppm, which is thus attributed to H-2' and H-6'. The connection

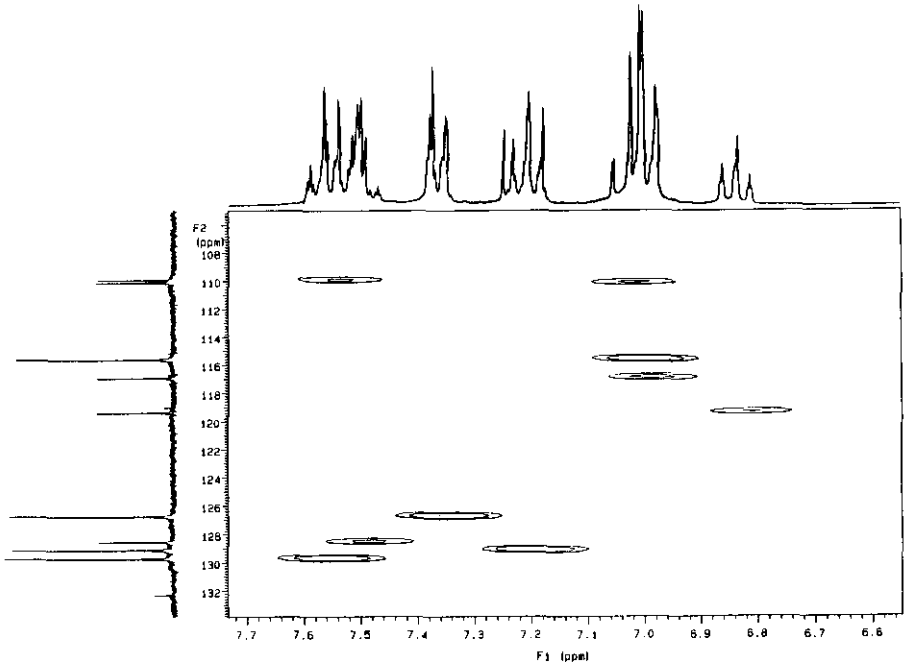
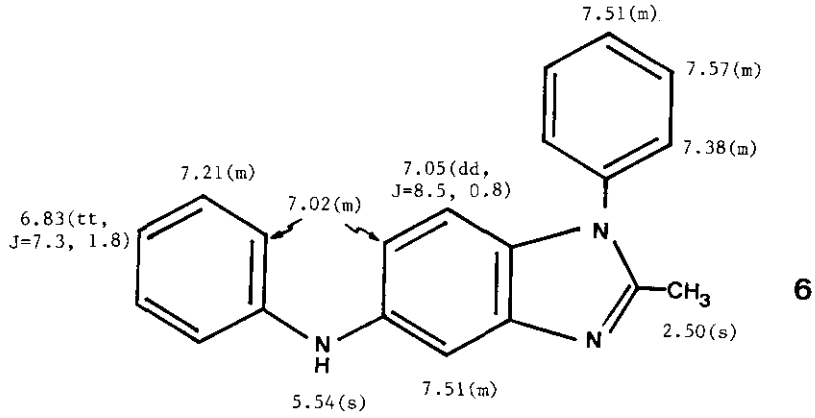


Figure 2

between the signal at 129.2 ppm (C-3", C-5") and that centered at 7.21 ppm allows to attribute the latter signal to H-3" and H-5". Finally, the observed correlation between the multiplet centered at δ = 7.02 ppm in the ^{1}H-nmr spectrum and the signals due to C-6, C-7 and C-2" (6") allows to assign the partially overlapped doublet of doublets ($J_{6,7}$ = 8.5 and $J_{4,7}$ = 0.7 Hz) at 7.05 ppm to H-7 and the rest of the multiplet to H-6, H-2" and H-6". The triplet of triplets at 6.83 ppm ($J_{3",4"}$ = 7.3 and $J_{2",4"}$ = 1.8 Hz) was attributed to H-4". The absence of this signal in the ^{1}H-nmr spectrum of 10 confirms this assignment.

^{1}H-Nmr data of compounds 6 and 10 are summarized in Figure 3



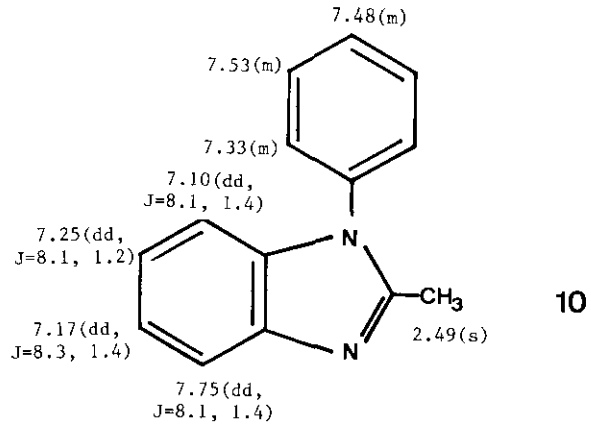


Figure 3

Nmr data of the compound obtained by thionation of 6 are in agreement with the singly-fused angular structure (9). Structure (7) could be ruled out due to the absence of signals attributable to the anilino group both in the ^{1}H-nmr and ^{13}C-nmr spectra of the thionation product. The linear arrangement (8) could also be excluded, taking into account the absence of two singlets assignable to H-4 and H-11 in the ^{1}H-nmr spectrum, and the presence of two clean doublets at δ = 6.58 (J = 8.2 Hz) and δ = 6.74 (J = 7.9 Hz), attributed to H-4 and H-5 of the angular structure. The ^{1}H-nmr assignments are in agreement with nmr data for other phenothiazines,[18,19] and can be found in Figure 4, together with a tentative assignment of the ^{13}C-nmr spectrum of 9. Although the instability of 9 in solution made impossible to obtain a reliable proton-coupled ^{13}C-nmr spectrum, the doublets assigned to C-4 and C-5 could be clearly distinguished from the rest of the signals. This lack of ^{3}J couplings is in agreement with structure (9), although this piece of information alone would not be sufficient to discard the linear structure (8).

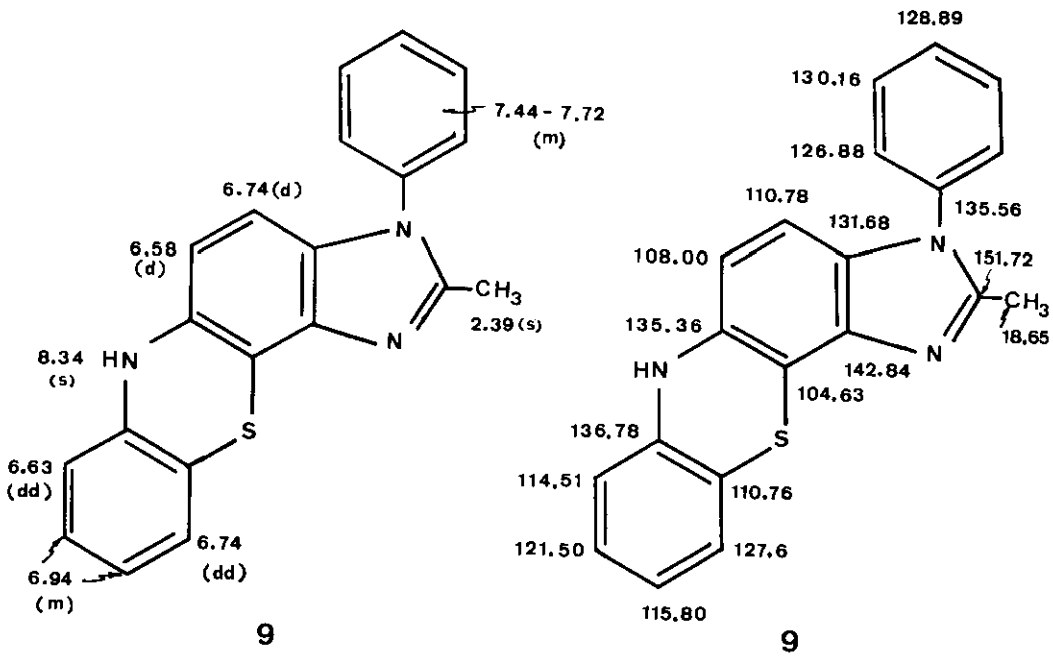


Figure 4

Further evidence in favour of structure (9) could be found in its ir spectrum, in which the absorption band due to the aromatic C-H out of plane bending vibration at 780 cm^{-1} is compatible with a 1,2,3,4-tetrasubstituted benzene system, but not with a 1,2,4,5-tetrasubstituted derivative, such as 8.[20,21]

EXPERIMENTAL

Ir spectra were recorded on a Perkin-Elmer 577 spectrophotometer. All compounds were compressed into KBr pellets. ^{1}H-Nmr spectra were obtained on the following instruments: Hitachi Perkin-Elmer R-24B (60 MHz), JEOL JNM-GSX-270 (270 MHz) and Varian VXR-300 (300 MHz). ^{13}C-Nmr and heteronuclear correlation experiments were carried out on the latter instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C). $CDCl_3$ or d_6-DMSO 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 columns (SDS 60 ACC).

N, N'-Diacetyl-*N, N'*-diphenyl-1,4-phenylenediamine (2). A magnetically stirred mixture of *N, N'*-diphenyl-1,4-phenylenediamine (1) (20 g, 76.8 mmol), acetic anhydride (30 ml, 0.318 mol) and anhydrous sodium acetate (0.5 g, 3.67 mmol) was heated in an oil bath at 120-130 °C for 3 h. The cooled reaction mixture was then poured on ice-water (300 g) to give a viscous precipitate, which was solidified by addition of 50 ml of a 15 % aqueous NaOH solution. The compound was filtered, washed with water and dried to yield 28.9 g (97 %) of 2, which was used for the next step without further purification. A small sample was recrystallized from ethanol to give a solid of mp 188-189 °C (ethanol) (lit.[22] mp 191.7 °C). Ir (KBr): 1660 (C=O) cm^{-1}. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 7.80-6.60 (m, 14H, Ar-H); 2.05 (s, 6H, 2 $COCH_3$).

2-Nitro-*N*, *N'*-diacetyl-*N*, *N'*-diphenyl-1,4-phenylenediamine (3). Method A. A mixture of powdered diacetyl compound (2) (2 g, 5.81 mmol) and 5 ml of concentrated nitric acid (density 1.40 g ml^{-1}) was warmed at 45 °C for 90 sec, which caused almost complete dissolution of 2 and formation of nitrous vapors. The reaction mixture was stirred at room temperature for 60 sec, then poured on water (100 ml) and the brown precipitate was collected by filtration, washed with water (5 x 50 ml) and dried *in vacuo* over phosphorous pentoxide. This material was dissolved in benzene (15 ml) and the solution was slowly treated with light petrol (bp 40-60 °C) until the precipitation of a black, tarry residue was completed. The solid precipitated by cooling the supernatant golden liquid was filtered to yield the desired nitro derivative (3) (0.8 g, 35 %).

Method B. Concentrated nitric acid (15 ml) was added dropwise over 10 min to a solution of 2 (10 g, 25 mmol) in glacial acetic acid (50 ml). The mixture was magnetically stirred at room temperature for 14 h, and then poured on cool water (250 ml). The precipited orange solid was filtered and purified, either by crystallization from benzene-light petrol (bp 40-60 °C), as described above (this technique requires to divide the crude product into two-gram fractions) or by flash chromatography on silica gel, eluting with ether. Yield, 6.85 g (64 %). mp 160-161 °C (ethanol) (lit.,[9] mp 160 °C). Ir (KBr): 1680 (C=O), 1670 (C=O), 1530 (NO_2), and 1370 (NO_2) cm^{-1}. ^{1}H-Nmr (270 MHz, $CDCl_3$) δ : 7.82 (d, 1H, $J_{3,5}$ = 1.7 Hz, H-3); 7.25 (dd, 1H, $J_{5,6}$ = 9.2 Hz, $J_{5,3}$ = 1.7 Hz, H-5); 7.70-7.30 (m, 10H, 2 C_6H_5); 7.07 (d, 1H, $J_{6,5}$ = 9.2 Hz, H-6), 2.04 and 2.02 (2 s, 6H, 2 $COCH_3$) ppm.

2-Methyl-1-phenyl-5-(*N*-phenylacetamido)benzimidazole (5). A mixture of 3 (2.95 g, 7.58 mmol) and freshly distilled dimethylformamide (8 ml) was heated in an oil bath at 80 °C for 10 min. The clear solution thus obtained was cooled in an ice bath and treated with 10 % palladium on charcoal (34 mg, 31.8 μ mol of palladium) and dry triethylamine (4.55 ml, 32.9 mmol), followed by dropwise addition of 97 % formic acid (0.94 ml, 24.9 mmol). The suspension was magnetically stirred and heated in an oil bath at 120 °C for 12 h. The reaction mixture was diluted with dichloromethane (25 ml) and filtered through celite, which was washed with dichloromethane (3 x 10 ml). The combined filtrates were concentrated *in vacuo* to yield a brown, viscous residue which, on treatment with ethyl acetate (15 ml), gave 1.1 g of 5 as off-white crystals, which were filtered and washed with a small amount of acetone. The residue from the mother liquors, after purification by flash

chromatography (ethyl acetate on silica gel), gave additional 0.97 g of 5. Overall yield, 2.07 g (80 %). mp 170-172 °C (ethanol) (lit.,[9] mp 170 °C). Ir (KBr): 1675 (C=O), 1590 cm^{-1}. ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 7.67-7.52 (m, 5H, Ar-H); 7.36-7.27 (m, 6H, Ar-H); 7.19-7.10 (m, 2H, Ar-H); 2.49 (s, 3H, $COCH_3$); 2.08 (s, 3H, C-2-CH_3) ppm. ^{13}C-nmr (75 MHz, $CDCl_3$) δ : 170.95 (CO-CH_3), 153.33 (C-2), 143.38 (C-3a*), 143.19 (C-1"*), 138.04 (C-5**), 135.76 (C-1'**), 130.11 (C-3"), 129.17 (C-3'), 128.94 (C-1"+), 127.03 (C-1'+), 126.51 (C-4'), 123.08 (C-4), 119.24 (C-4"), 117.45 (C-6), 110.84 (C-7), 24.00 (CO-CH_3), 14.53 (C-2-CH_3). See numbering system in Figure 2. Assignments marked with *, ** and + can be interchanged. Ms, m/z (%): 341 (M^+, 63), 300 (30.5), 299 (100), 118 (19), 77 (17).

2-Methyl-1-phenyl-5-phenylaminobenzimidazole (6). A solution of the acetyl derivative (5) (1.6 g, 4.69 mmol) in ethanol (10 ml), water (9 ml) and 96 % aqueous sulfuric acid (1 ml) was refluxed for 16 h in an oil bath at 90-95 °C, cooled and concentrated. Addition of ethanol to the residue caused the precipitation of 1.7 g (92 %) of 6-hydrogen sulfate as bluish crystals (mp 210-212 °C), which were filtered and washed with water. The hydrogen sulfate was dissolved in boiling water (10 ml) and the solution was filtered and treated, while still warm, with solid sodium hydroxide (0.4 g) in small portions. The solid that precipitated after cooling was filtered to give 1.05 g (75 %) of 6 as the free base. An analytical sample was obtained by flash chromatography on silica gel eluting with chloroform. mp 164-166 °C (ethanol). Ir (KBr): 3270 (N-H), 1600 cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$), see Figure 3. ^{13}C-nmr (75 MHz, $CDCl_3$), see Figure 2. Anal. Calcd for $C_{20}H_{17}N_3$: C, 80.27; H, 5.68; N, 14.05. Found : C, 79.98; H, 5.69; N, 13.82.

2-Methyl-3-phenyl-6*H*-imidazo[4,5-*c*]phenothiazine (9). A mixture of the diarylamine (6) (0.45 g, 1.51 mmol), ground sulfur (0.17 g, 5.41 mmol) and iodine (20 mg, 0.08 mmol) was melted in an oil bath at 215-220 °C under a slow stream of dry nitrogen for 6 h (a strong evolution of hydrogen sulfide was detected after the first 30-45 min). The crude reaction product was flash chromatographed[23] on silica gel (20 g) eluting with light petrol (bp 40-60 °C)-ethyl acetate (8:2) or with net dichloromethane to yield 0.2 g of 9 (70 % yield, based on unrecovered starting material) and 0.2 g of recovered 6. mp 208-210 °C. Ir (KBr): 3250 (N-H), 780 (C-H) cm^{-1}. ^{1}H-Nmr (300 MHz, d_6-DMSO) and ^{13}C-nmr (75 MHz, d_6-DMSO), see Figure 4.[22] Ms, m/z (%) : 331 (6), 330 (24), 329 (M^+, 100), 297 (19), 255 (9), 164 (20), 77 (10). High-resolution mass measurement : Calcd for $C_{20}H_{15}N_3S$: m/z = 329.09866. Found:

m/z = 329.1005.

2-Methyl-1-phenylbenzimidazole (10). A solution of *N*-phenyl-1,2-phenylenediamine (1 g, 5.43 mmol) in glacial acetic acid (6 ml) was refluxed in an oil bath at 120-125 °C for 10 h. The solvent was evaporated and the residue was dissolved in hot water (15 ml) and basified with ammonia. This aqueous solution was extracted with chloroform (3 x 35 ml), which was dried (sodium sulphate) and concentrated to yield a red, viscous residue. Flash chromatography on silica gel (30 g) eluting with chloroform afforded 1.09 g (97 %) of 10 as a slightly pink, crystalline solid. mp 73-74 °C (light petrol, bp = 40-60 °C). Ir (KBr) : 1625, 1600 cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$), see Figure 3. ^{13}C-Nmr (75 MHz, $CDCl_3$), see Figure 2. Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.76; H, 5.77; N, 13.46. Found: C, 80.87; H, 5.80; N, 13.18.

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23. Flash chromatography of compound (9) was carried out in a light-protected column, and nmr experiments were performed in DMSO-d_6,[18] in an attempt to minimize photo-oxidation.

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