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Synthesis and Acid Catalysed Condensation of 3-(1-Hydroxy-4-chlorobenzyl) -1-methylindole

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Abstrak

3-(1-Hidroksi-4-klorobenzil)-1-metilindola (3) telah disintesis dari indola dalam tiga tahap. Tahap pertama adalah metilasi indola menghasilkan N-metilindola (4) dengan rendemen 87%. Formilasi Vilsmeier-Hack N-metilindola (4) pada tahap kedua menghasilkan indola keton barn (S) dengan rendemen 67%. Reduksi senyawa karbonil (S) pada tahap ketiga dengan pereaksi natrium borohidrida menghasilkan indola alkohol barn (3) dengan rendemen 99%. Kondensasi alkohol sekunder (3) dengan katalis asam p-toluen sulfonat telah dikaji, dan alkohol tersebut memberikan senyawa baru berupa di-(1-metilindol-3-il)-(p-klorophenil)metana (7) dengan rendemen 71%.

***Kata Kunch** 3-(1-hidroksi p-klorobenzil)-1-metilindola, asam p-toluen sulfonat, Kndensasi, di-(1-metilindol-3-il)-(p-klorophenil)metana*

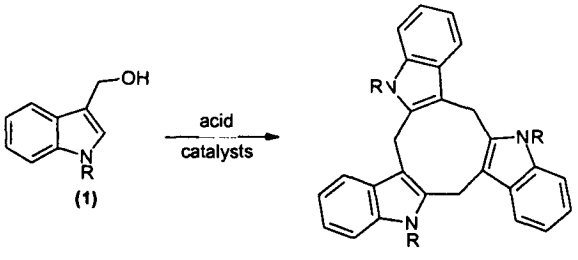
Abstract

3-(1-Hydroxy-4-chlorobenzyl)-1-methylindole (3) has been synthesised in three steps. The first step involved methylation of indole to give N-methylindole (4) in 87% yield which on Vilsmeier-Haack formylation in the next step gave new ketone (S) in 67% yield. Sodium borohydride reduction of the new carbonyl compound (S) in the last step afforded the new indole alcohol (3) in 99% yield. Treatment of the secondary alcohol (3) with p-toluene sulfonic acid has been examined which afford di-(1-methylindol-3 yl)-(p-chlorophenyl)methane (7) in 71% yield.

***Keywords:** 3-(1-Hdroxy-p-chlorobenzyl)-1-methyllindole, p-toluene sulfonic acid, condensation, di-(1-methyilindol-3-yl)-(p-chlorophenyl)methane*

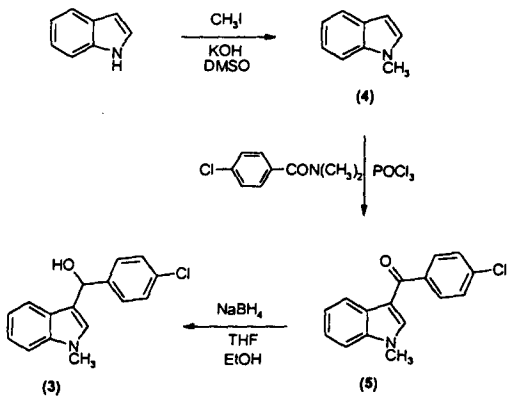
1. Introduction

Condensation of 3-hydroxymethyl-1-methylindole **(1a)** catalysed by *p*-toluene sulfonic acid has been reported to give indole cyclic trimer **(2a)** in a good yield[1]. The structure of the indolocyclotriveratrylene **(2a)** was established by ^{1}H NMR, ^{13}C NMR, MS, IR, UV spectroscopy, microanalysis and X-ray crystallography. Following the same procedure, *N*-substituted-3-hydroxymethylindoles **(1b-c)** also gave in good yields new indolocyclotriveratrylenes **(2b-c)**[2-4]. In contrast, under the same conditions the presence of an electron withdrawing group in the primary indole alcohol **(1d)** effectively deactivates the indole so that no reaction occurred even after prolonging the reaction for one day. The same result was also occurred when indole alcohol **(1d)** was treated with concentrated hydrochloric acid for one day. However, treatment of primary indole alcohol **(1d)** with boron trifluoride diethyl etherate for two hours gave a new trimer **(2d)** in 40% yield[5] (Scheme 1).



Scheme 1

This paper describes the synthesis of 3-(1-hydroxy-*p*-chlorobenzyl)-1-methylindole **(3)** and its reactivity when treated with *p*- toluene sulfonic acid under the same conditions. The synthesis of the secondary alcohol **(3)** is outlined in Scheme 2.



Scheme 2

2. Experimental

General. Ultraviolet-visible spectra were recorded in dichloromethane or methanol on Hitachi U-3200 Spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Infrared spectrometer. ^{1}H and ^{13}C NMR spectra were obtained in the designated solvents on a Bruker AC300F spectrometer at 300 MHz. EI mass spectra analyses were performed by at Organic Mass Spectrometry Unit, The University of New South Wales, Australia. Analyses were caried out on an AEI MS 12 mass spectrometer at 70 eV ionisation voltage and 8000V accelerating voltage with ion source temperature of 210 °C. Microanalysis were performed by Reet Bergman of Microanalytical Unit, Research School of Chemistry, The Australia National University, Australia. Melting points were determined on Mel-Temp melting point apparatus and were not corrected. Gravity column chromatography was carried out on Merck 70-230 mesh silica gel. Compounds were detected by short and long ultraviolet light and with iodine vapor. Anhydrous dimethyl sulfoxide was dried and stored under activated 4Å molecular sieves. Light petroleum refers to the fractions which boils 60-80 °C, and dichloromethane were redistilled prior to use.

Synthesis of *N*-methylindole (4). Freshly crushed potassium hydroxide (0.20 mol) and indole (0.049 mol) in dry dimethyl sulfoxide (30 mL) were stirred for one hour at room temperature. Iodomethane (0.10 mol) was added and the mixture was stirred for an additional one hour. Water was added and the oily product was extracted several times with diclorometane. The combined extract was washed several times with saturated brine solution, dried over magnesium sulfate, and evaporated under reduced pressure. The crude product was purified by distillation under reduced pressure to give the indole (**4**) as a light yellow oil (5.59g, 87%), b. p. 63-65 °C/0.6 mmHg) (Lit[5]. 128-129 °C/20 mmHg). ^{1}H NMR ($CDCl_3$): δ 3.91, s, 3H; 6.73, d, *J*=3.1 Hz, 1H; 7.22, 1H, d, *J*=3.1 Hz; 7.34-7.54, m, 3H, ArH; 7.89, d, *J*=7.9 Hz, 1H. ^{13}C NMR ($CDCl_3$): δ 32.55, 100.77, 109.08, 119.15, 120.73, 121.35, 128.42, 128.66, and 136.62.

Synthesis of 3-(*p*-Chlorobenzoyl)-1-methylindole (5). *p*-Chloro-*N*,*N*-dimethyl-benzamide (1.44g, 7.84 mmol) was stirred and warmed at 60 °C, phosphoryl chloride (0.88 mL, 9.44 mmol) was added and the mixture was stirred for five minutes. *N*-Methylindole (**4**) (7.85 mmol) was added and the mixture was heated at 80 °C for two hours. 10% Aqueous sodium hydroxide was added to the mixture and the product was extracted with dichloromethane. The combined extract was washed with saturated brine solution, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified using gravity column chromatography with dichloromethane eluant to yield the new ketone (**5**) as a white solid (1.41g, 67%), m. p. 144-145 °C. $\nu_{max.}$ (Nujol) 1610, 1580, 1505, 1450, 1365, 1260, 1225, 1150, 1120, 1080, 1060, 1030, 1000, 965, 870, 840, 770, 745, 720, 690 cm^{-1}. $\lambda_{max.}$ (MeOH) 254 (ε 21,600), 322 nm (ε 19,400). ^{1}H NMR ($CDCl_3$): δ 3.85, s, 3H; 7.33-7.78, m, 7H; 7.51, s, 1H; 8.36-8.42, m, 1H. ^{13}C NMR ($CDCl_3$): δ 33.62, 109.69, 115.49, 122.72, 122.87, 123.83, 127.14, 128.57, 130.11, 137.31, 137.61, 139.27, 189.39. Mass spectrum (EI): *m/z* 272 (M+1, ^{37}Cl, 2%), 271 (M, ^{37}Cl, 10), 270 (M+1, ^{35}Cl, 5), 269 (M, ^{35}Cl, 30), 268 (3), 234 (5), 158 (100), 139 (5), 130 (15), 111(10).

Synthesis of 3-(1-Hydroxy-p-chlorobenzyl)-1-methylindole (3). 3-(*p*-Chloro-benzoyl)-1-methylindole (**5**) (2.60 mmol) was added and followed by addition of absolute ethanol (20 mL). The mixture was refluxed for two hours, and after cooling the solvent was evaporated under reduced pressure to dryness. The residue was suspended in 10% aqueous sodium hydroxide and the resulting white precipitate was filtered off, washed with water and dried to afford the new alcohol (**3**) as a white solid (0.70g, 99%), m. p. 109-110 °C (Found C, 69.2; H, 5.3; N, 5.0. $C_{16}H_{14}NOCl.1/4H_2O$ requires C, 69.6; H, 5.3; N, 5.1%). $\nu_{max.}$ (Nujol) 3300, 1580, 1540, 1450, 1370, 1320, 1300, 1230, 1190, 1140, 1120, 1080, 1050, 1010, 980, 810, 730 cm^{-1}. $\lambda_{max.}$ (MeOH) 223 (ε 58,800), 285 nm (ε 7,400). ^{1}H NMR ($CDCl_3$): δ 3.73, s, 3H; 6.11, d, *J*=4.1 Hz, 1H; 6.79, s, 1H; 7.11, t, 1H; 7.23-7.34, 4H, m; 7.44, d, *J*=8.2 Hz, 2H; 7.57, d, *J*=7.7 Hz, 1H. ^{13}C NMR ($CDCl_3$): δ 32.73, 69.44, 109.47, 117.93, 119.57, 119.59, 122.14, 126.12, 127.44, 127.83, 128.36, 132.94, 137.44, and 142.22. Mass spectrum (EI): *m/z* 274 (M+1, ^{37}Cl, 5%), 273 (M, ^{37}Cl, 20), 272 (M+1, ^{35}Cl, 10), 271 (M, ^{35}Cl, 65), 270 (5), 254 (55), 160 (35), 141 (10), 139 (25), 132 (100), 130 (20), 117 (35), 111 (15), 103 (10), 77 (30).

Condensation of 3-(1-Hydroxy-*p*-chlorobenzyl)-1-methylindole (3). 3-(1-Hydroxy-*p*-chlorobenzyl)-1-methylindole (**3**) (0.74 mmol) in dichloromethane was treated with a small amount of *p*-toluene sulfonic acid monohydrate, and stirred for one hour at room temperature.

The solvent was removed under reduced pressure and the crude product was purified using gravity column chromatography with dichloromethane/light petroleum (1/1) eluent to afford di-(1-methylindol-3-yl)-(*p*-chlorophenyl)methane **(6)** as a white solid (71%), m. p. 204-205 °C (Found C, 77.7; H, 5.7; N, 7.1. $C_{25}H_{21}N_2Cl$ requires C, 78.0;.6; H, 5.5; N, 7.3%). $\nu_{max.}$ (Nujol) 1640, 1600, 1580, 1460, 1420, 1380, 1320, 1220, 1200, 1150, 1120, 1080, 1010, 920, 860, 830, 800, 730, 700 cm^{-1}. $\lambda_{max.}$ (CH_2Cl_2) 231 (ε 66,600), 293 nm (ε 16,300). ^1H NMR ($CDCl_3$): δ 3.71, s, 6H; 5.91, s, 1H; 6.56, s, 2H; 7.05, t, 2H; 7.23-7.35, m, 8H; 7.41, d, *J*=7.7 Hz, 2H. ^{13}C NMR ($CDCl_3$): δ 32.66, 39.55, 109.15, 117.77, 118.78, 119.93, 121.59, 127.30, 128.32, 130.06, 131.68, 137.45, and 143.04. Mass spectrum (EI): *m/z* 387 (M+1, ^{37}Cl, 10%), 386 (M, ^{37}Cl, 30), 385 (M+1, ^{35}Cl, 20), 384 (M, ^{35}Cl, 95), 383 (30), 274 (20), 273 (100), 257 (20), 253 (30), 230 (10), 144 (10), 130 (15), 115 (10).

3. Results and Discussions

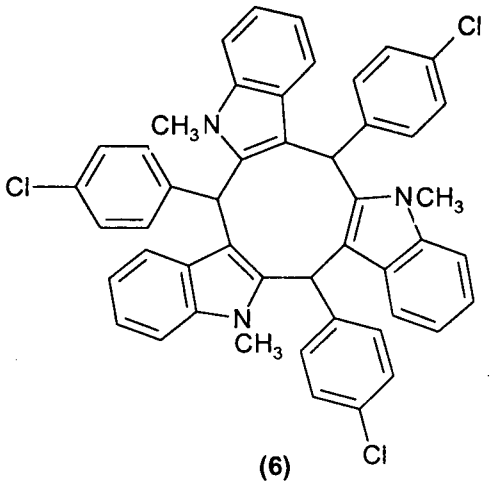
N-Methylindole **(4)** was synthesized by indole alkylation following Heaney and Ley's method[6]. Structure determination of the product was carried out by comparing its boiling point with the literature data, and by NMR spectroscopy. The boiling point of the product was close to that found in literature data and its NMR spectra matched with the structure of *N*-methylindole **(4)**. The ^1H NMR spectrum (in $CDCl_3$) showed a singlet at 3.91 ppm corresponding to the *N*-methyl group protons; two doublets at 6.73 and 7.22 ppm to H3 and H2 respectively, and the remaining aromatic protons gave signals in the region 7.34-7.89 ppm. The structure **(4)** was supported by the ^{13}C NMR spectrum (in $CDCl_3$) which exhibited a signal at 32.55 ppm for the *N*-methyl group carbon, four tertiary carbons signals at 100.77, 109.08, 119.15, 120.73, 121.35 and 128.66 ppm, and two signals at 128.42 and 136.62 ppm for two quaternary carbons. As a result, *N*-methylindole **(4)** was obtained in 87 % yield by indole methylation.

Acylation of *N*-methylindole **(4)** was then carried out by Vislmeier-Haack formylation as described by Black *et al*[7]. to formylate 4,6-dimethoxy-3-methylindole. The structure of the product was determined by spectroscopy as 3-(*p*-chlorobenzoyl)-1-methylindole **(5)**. The ^1H NMR spectrum (in $CDCl_3$) of the carbonyl compound **(5)** exhibits two singlets at 3.85 and 7.51 ppm correspond to the *N*-methyl and H2 protons respectively, and the remaining aromatic protons gave signals in the region 7.33-7.78 (7H) and 8.36-8.42 ppm (1H). The ^{13}C NMR spectrum (in $CDCl_3$) showed a signal at 33.62 ppm for the *N*-methyl carbon, and the number of tertiary carbons had increased from six to seven, and two to six carbons for quaternary carbons.

The mass spectrum (EI) shows molecular ions at *m/z* 271 and 269 with relative abundances in 1:3 ratio indicating the presence of one chlorine atom. The peaks at *m/z* 234, 158 (the base peak) and 130 suggested loss of chlorine atom, *p*-chlorophenyl, and *p*-chlorobenzoyl radicals respectively. The new ketone **(5)** accordingly has been synthesized in 67% yield by Vilsmeier-Haack formylation of *N*-methylindole **(4)**.

Synthesis of 3-(1-hydroxy-*p*-chlrobenzyl)-1-methylindole **(3)** was carried out by sodium borohydride reduction of the new ketone **(5)**. Tetrahydrofuran was used as co-solvent to dissolve the ketone **(5)** which is insoluble in absolute ethanol. The corresponding indole alcohol **(3)** was then obtained in quantitative yield after refluxing the new ketone **(5)** for two hours. The structure of the secondary indole alcohol **(3)** was established by microanalysis and spectroscopy. The most significant feature of the ^1H NMR spectrum of the alcohol **(3)** compared to the ketone **(5)** is the presence of a new signal at 6.11 ppm corresponding to CHOH proton. It was strongly supported by the ^{13}C NMR spectrum of the alcohol **(3)** which showed a signal at 69.44 ppm for CHOH, and the signal for a carbonyl group of the ketone **(5)** at 189.39 had disappeared.

Acid catalysed condensation of the secondary indole alcohol **(3)** was then carried out following the condensation of the primary alcohols **(1a-c)**. Accodring to the previous results[1-4]. The reaction might give the corresponding new indolo-cyclotriveratrylene **(6)**. The mass spectrometric examination showed that the product has molecular ions at *m/z* 386 and 385 with relative abundances in 1:3 ratio which strongly indicated that the condensation product contains one chlorine functionality and its structure was not the trimer **(6)**.



(6)

The presence of steric hindrance of the *p*-chlorophenyl group in this case probably caused the condensation to give di-(1-methylindol-3-yl)-(*p*-chlorophenyl)methane **(7)** rather than indole cyclic trimer **(6)**. The new 3,3'-diindolyl-methane **(7)** was obtained in 71% yield, and accompanied by *p*-

chlorobenzaldehyde as by-product. The mass spectrum also shows a peak at *m/z* 273 as the base peak indicating a loss of *p*-chlorophenyl radical, while the cleavage of an indole unit gave peaks at *m/z* 253 and 130. The ^{1}H NMR spectrum of the new 3,3'-diindolylphenylmethanes (**7**) (Figure 1) exhibited two singlets at 3.71 and 5.91 ppm assignable to the *N*-methyl group and methine protons, respectively. These assignments were supported by the chemical shifts at 32.66 and 39.55 ppm in the ^{13}C NMR spectrum (Figure 2) for the *N*-methyl and methine carbons, respectively. The ^{1}H NMR spectrum also exhibited a singlet at 6.56 ppm for H2, and signals in the region 7.03-7.42 ppm for the twelve aromatic protons. The reaction mechanism for the formation of new compound (**7**) is outlined in Scheme 3.

In conclusion, 3-(1-hydroxy-*p*-chlrobenzyl)-1-methylindole (**3**) has been synthesised in three steps from indole in an overall yield of 58%. Its acid catalysed condensation afforded new 3,3'-diindolylmethane (**7**) in 71% yield.

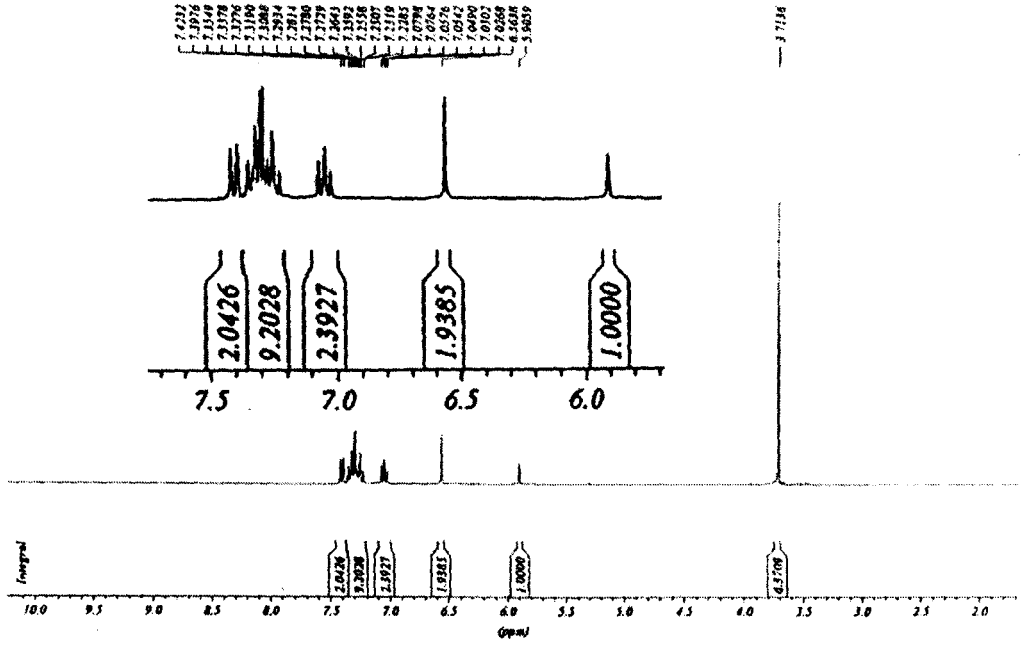


Figure 1. ^{1}H NMR spectrum of the new 3,3'diindolylmethane (**7**)

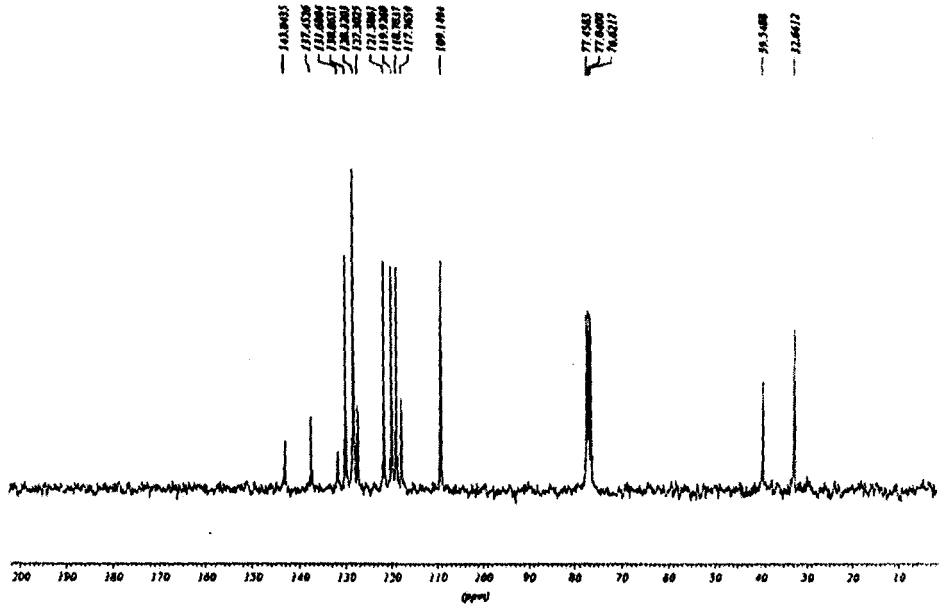
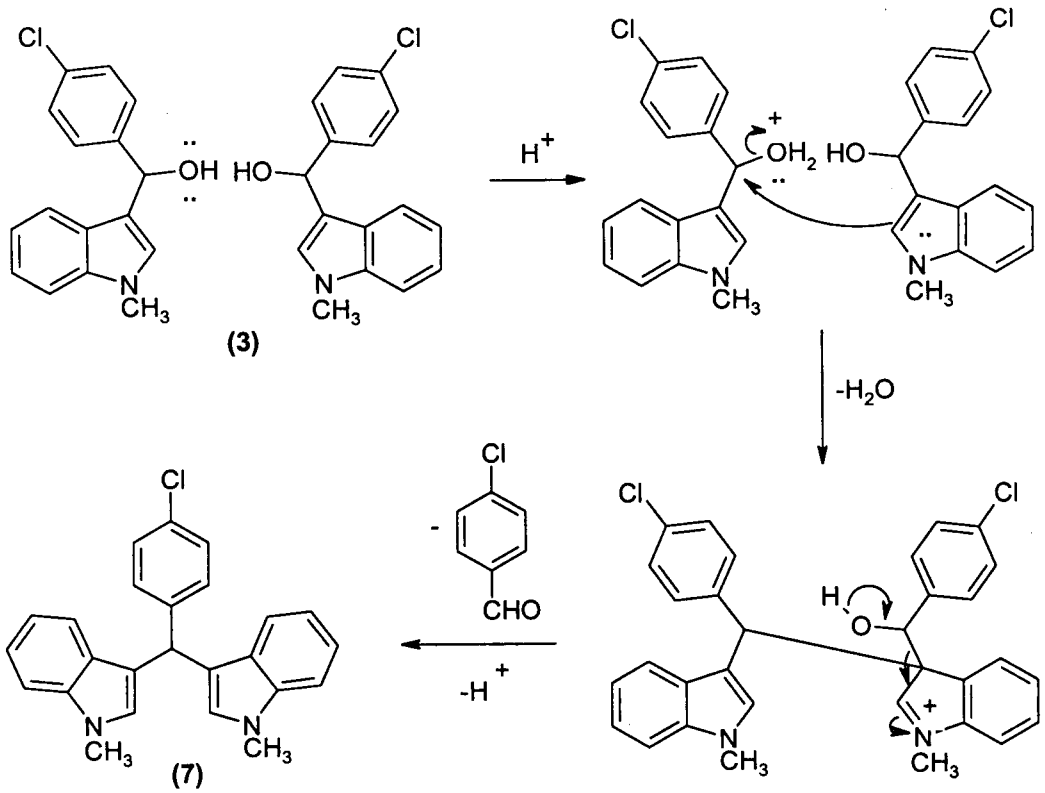


Figure 2. ^{13}C NMR spectrum of the new 3,3'diindolylmethane (**7**)



Scheme 3

Acknowledgement

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