Synthesis of 6,7-Dihydrobenzo[4,5]cyclohept-[1,2-*b*]indol-12(5*H*)-one and Related Compounds

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The synthetic routes of 6,7-dihydrobenzo[4,5]cyclohept[1,2-*b*]indol-12(5*H*)-one **5** from either 1-methyl or 1-sulfonylindole-2-carboxaldenyde **1** or ethyl 1,2-dimethylindole-3-carboxylate **6** are reported. The structure of the ketone **5a** was confirmed by X-ray crystallography. Several indole derivatives have been prepared with potential antitumor activity.

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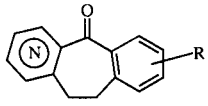
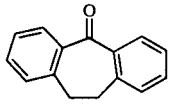
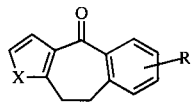
From previous works, it was known that the key intermediate tricyclic ketones **I**, **II**, **III** having two aromatic rings (pyridine, benzene or pyrrole rings) fused to a central seven-membered ring provide a variety of derivatives displaying therapeutic activities (antihistaminic, antiinflammatory, antipsychotic) [1-6].



I



II



III

X = S, NH

In this present report, we describe the synthesis of a new type of indole compounds with a tetracyclic skeleton from indole ketone **5a**. To the best of our knowledge, only two reports on an analogous ring system have been found in the literature [7,8]. We have already published a synthetic route with a Heck annulation to obtain some cyclized derivatives [9]. Some of the new compounds prepared in our laboratory from **5a** might be further derivatised for antitumor testing.

The fused indole ring system **5a** was synthesized by two routes starting from 1-methylindole-2-carboxaldehyde **1a** or ethyl 1,2-dimethylindole-3-carboxylate **6**. Compound **5b** was prepared from l-phenylsulfonylindole-2-carboxaldehyde **1b**. The first synthetic method is illustrated in Scheme 1. The preparation of the starting compounds **1a-b** has been described [10]. A Wittig reaction of **1a** with the ylide prepared from (2-carbomethoxybenzyl)-triphenylphosphonium bromide and lithium diisopropylamide gave an *E/Z* mixture (8:2) of alkene **2a** in good yield. For **1b**, only the *E* isomer **2b** was isolated (see Experimental).

Compounds **2** were hydrogenated over 10% Pd/C to afford **3** (93-98% yield). Saponification of ester **3** gave the corresponding acid **4** (90-98% yield). Finally, ketones **5a** and **5b** were obtained by intramolecular cyclization of the acids **4**, using a large excess of polyphosphoric acid, in fair yield (62-73%). Hydrolysis of the phenylsulfonyl group was observed during the cyclization of **4b** to give the non protected ketone **5b**.

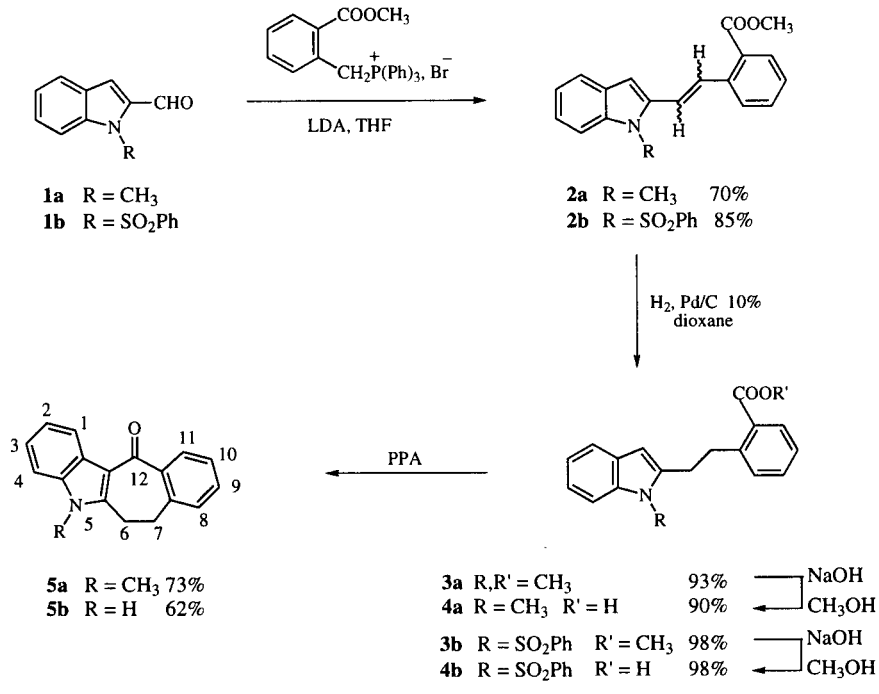
An alternative route in three steps to obtain **5a** is described in Scheme 2. The initial reaction was a lithiation of the methyl position of **6** with lithium diisopropylamide at -78° [11,12] in THF followed by a quenching of the carbanion obtained, by benzyl bromide to give compound **7** in 86% yield.

Saponification of the ester **7** gave the acid **8**. Final cyclization of **8** with trifluoroacetic anhydride and boron trifluoride diethyl etherate in dichloroethane was performed to give **5a** in 70% yield. Recrystallization from methylene chloride provided single crystals suitable for X-ray crystallographic analysis, which finally established the exact structure of **5a** [13]. Crystal data and selected torsion angles are reported in Tables 1 and 2. The numbering system used for the structure of **5a** from the X-ray crystallography is different to ours as shown in Figure 1 (H atoms are omitted in the figure for the sake of clarity).

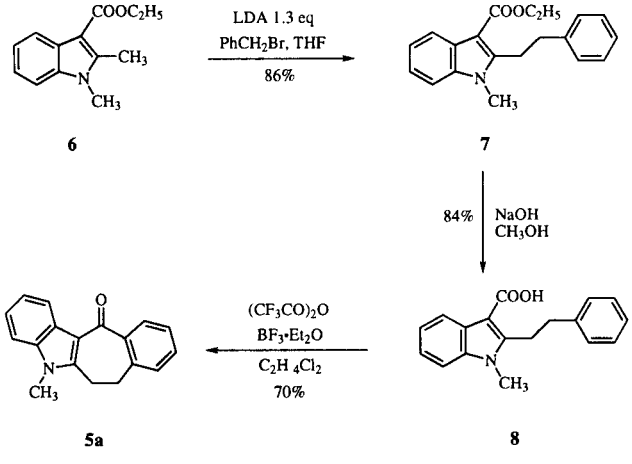
The study of the reactivity of the ketone model **5a** has been undertaken. The Wittig reaction of **5a** with (carbethoxymethylene)triphenylphosphorane at the reflux temperature of toluene or the Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate, sodium hydride in DMF at 90° failed, the starting material was recovered. The same attempts on unsaturated ketone **11** were unsuccessful also.

Treatment of **5a** with an excess of methyl or ethylmagnesium chloride in THF gave the compounds **9** and **10** in 90% and 70% yields respectively. The unsaturated ketone **11** was prepared in good yield (70%) from compound **5a** by bromination-dehydrobromination using standard meth-

Scheme 1



Scheme 2



odology (*N*-bromosuccinimide and triethylamine). Compound **11** was reduced with an excess of sodium borohydride in refluxing ethanol/dichloromethane solution to afford compound **12** (Scheme 3).

Due to the double bond between carbons 6 and 7, compounds **11** and **12** have a planar structure and can be considered as putative DNA binding agents.

From compound **9**, several others derivatives have been elaborated (Scheme 4). A catalytic hydrogenation of the exo double bond led to saturated compound **13** in good yield. The conversion of **13** to the desired compound **14** was achieved in 80% yield following the procedure

Table 1

Crystallographic Data for **5a**

empirical formula	$C_{18}H_{15}NO$
formula weight	261.31
crystal dimension	0.1 x 0.1 x 0.2 mm
temperature	293(2) K
crystal system	monoclinic
space group	$P2_1/a$
a	a = 11.205(6) Å α = 90°
b	b = 10.700(4) Å β = 111.87° (3)
c	c = 12.074(2) Å γ = 90°
V	1343.4(9) Å^3
Z	4
D (calculated)	1.292 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	552
Theta range for data collection	1.82 to 30.01°
Index ranges	-5<=h<=14, -3<=k<=15, 0<=l<=16
Reflections collected	4097
independent reflections	3895 [R(int) = 0.0522]
refinement method	full-matrix least-squares on F^2
data/restraints/parameters	3845/0/228
goodness-of-fit on F^2	1.001
final R indices [I>2σ (I)]	R1 = 0.0571, wR2 = 0.1415
R indices (all data)	R1 = 0.1114, wR2 = 0.1850
extinction coefficient	0.059 (6)
largest diff. peak and hole	0.211 and 0.381 e.Å^{-3}

shown in Scheme 2. On the other hand, hydroboration of **9** with boron hydride, THF followed by oxidation gave the corresponding alcohol **15**. Model *O*-alkylation of **15** was performed in the presence of sodium hydride and iodomethane in DMF at 80°, the desired compound **16** was isolated in good yield (76%).

Table 2

Selected Torsion Angles (degrees) for **5a***

C(8)-N-C(1)-C(2)	180.0	C(17)-C(7)- C(8)-C(9)	-7.9
C(8)-N-C(1)-C(6)	0.0	C(6)-C(7)-C(17)-O	-14.8
C(18)-N-C(1)-C(2)	0.0	C(6)-C(7)-C(17)-C(16)	158.8
C(18)-N-C(1)-C(6)	180.0	C(8)-C(7)-C(17)-O	169.8
C(1)-N-C(8)-C(7)	0.8	C(8)-C(7)-C(17)-C(16)	-16.6
C(1)-N-C(8)-C(9)	-176.5	N-C(8)-C(9)-C(10)	155.1
C(18)-N-C(8)-C(7)	-179.1	C(7)-C(8)-C(9)-C(10)	-21.6
C(18)-N-C(8)-C(9)	3.5	C(8)-C(9)-C(10)-C(11)	70.4
N-C(1)-C(2)-C(3)	180.0	C(9)-C(10)-C(11)-C(12)	112.9
C(6)-C(l)-C(2)-C(3)	0.0	C(9)-C(10)-C(11)-C(16)	-67.2
N-C(1)-C(6)-C(5)	-178.6	C(10)-C(11)-C(12)-C(13)	180.0
N-C(1)-C(6)-C(7)	0.0	C(16)-C(11)-C(12)-C(13)	0.0
C(2)-C(1)-C(6)-C(5)	1.2	C(10)-C(11)-C(16)-C(15)	-179.0
C(2)-C(1)-C(6)-C(7)	180.0	C(10)-C(11)-C(16)-C(17)	2.4
C(1)-C(2)-C(3)-C(4)	0.0	C(12)-C(11)-C(16)-C(15)	0.9
C(2)-C(3)-C(4)-C(5)	0.0	C(12)-C(11)-C(16)-C(17)	-177.7
C(3)-C(4)-C(5)-C(6)	1.0	C(11)-C(12)-C(13)-C(14)	-1.7
C(4)-C(5)-C(6)-C(1)	-1.5	C(12)-C(13)-C(14)-C(15)	0.9
C(4)-C(5)-C(6)-C(7)	180.0	C(13)-C(14)-C(15)-C(16)	0.0
C(1)-C(6)-C(7)-C(8)	0.0	C(14)-C(15)-C(16)-C(11)	-1.7
C(1)-C(6)-C(7)-C(17)	-175.7	C(14)-C(15)-C(16)-C(17)	177.0
C(5)-C(6)-C(7)-C(8)	178.7	C(11)-C(16)-C(17)-O	-147.7
C(5)-C(6)-C(7)-C(17)	2.4	C(11)-C(16)-C(17)-C(7)	38.6
C(6)-C(7)-C(8)-N	-0.8	C(15)-C(16)-C(17)-O	33.7
C(6)-C(7)-C(8)-C(9)	176.1	C(15)-C(16)-C(17)-C(7)	-140.0
C(17)-C(7)-C(8)-N	175.1		

[a] * Numbering system from Figure 1.

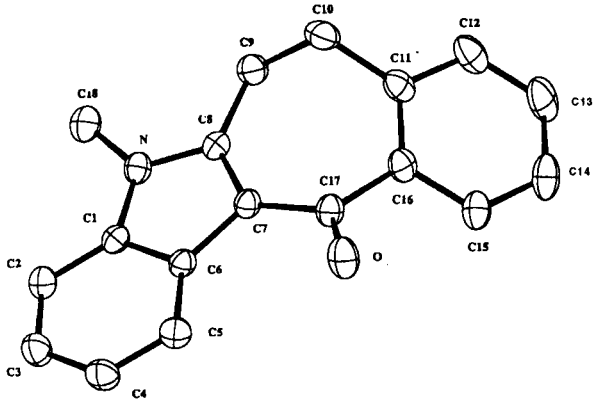
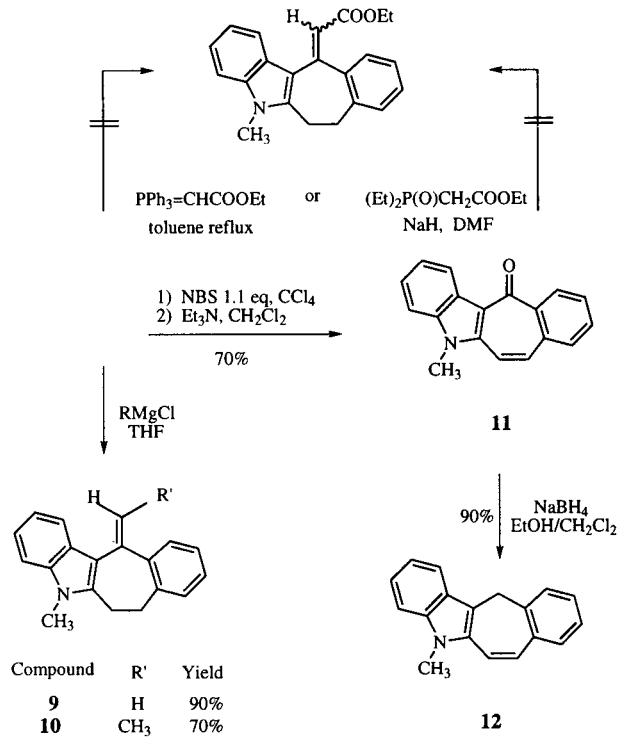


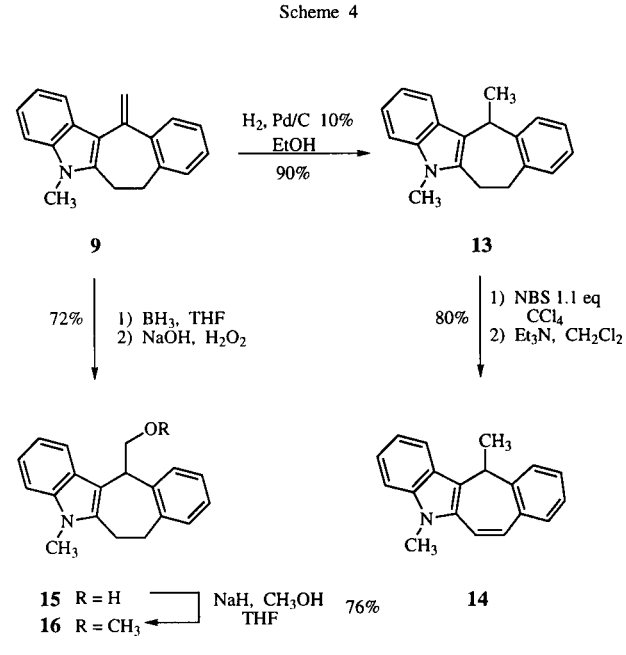
Figure 1.

Having explored the reactivity of the ketone **5a**, we are now investigating the reactions **5a** and **11** with various Grignard reagents in order to introduce functionalized arms in position 12, which may give rise to useful pharmacological properties.

Scheme 3



Scheme 4



EXPERIMENTAL

Melting points were determined with a Büchi SMP-20 apparatus and are uncorrected. The nmr spectra were recorded at 300°K in deuteriochloroform or DMSO-d_6 on a Bruker Avance DPX 250 (250.13 MHz for ^{1}H and 62.90 MHz for ^{13}C) or Bruker AM 300WG (300.13 MHz for ^{1}H). Chemical shifts are expressed in parts per million downfield from TMS. Mass spectra were recorded on Nermag-R-10-10C using chemical ionization. Reactions were monitored by thin layer chromatography using Merck silica gel 60F_{254} visualized by uv. Column chromatography was performed using Merck silica gel 60 (0.063-0.200 mm).

2-[2-(1-Methyl-1*H*-indol-2-yl)vinyl]benzoic Acid Methyl Ester (**2a**).

To a suspension of (2-carbomethoxybenzyl)triphenylphosphonium bromide (7.27 g, 14.8 mmoles) in anhydrous THF (120 ml), 3*M* lithium diisopropylamide in heptane (4.93 ml, 14.8 mmoles) was added dropwise at -78°. After 30 minutes, a solution of **1a** (1.66 g, 10.4 mmoles) in THF (20 ml) was added dropwise with vigorous stirring at -78°. The mixture was stirred one hour at -78°, then one hour at room temperature and THF was distilled off at reduced pressure. The residue was partitioned between ethyl acetate (30 ml) and 10% hydrochloric acid (30 ml), the aqueous phase separated and extracted with ethyl acetate (2 x 30 ml). The organic layer was dried and evaporated *in vacuo*. The crude oil was purified by column chromatography using petroleum ether/methylene chloride 6:4 as the eluting solvent to afford 2.12 g (70% yield) of **2a** as a yellow oil (*E/Z* mixture 8:2). Crystallization from methylene chloride-hexane gave only the *E* isomer as a yellow crystal, mp 107-109°; ir (potassium bromide): ν 1716 (CO) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 3.82 (s, 3H, $COOCH_3$), 3.92 (s, 3H, N-CH_3), 6.85 (s, 1H, =CH), 7.08 (d, 1H, J = 16.2 Hz, CH=CH), 7.05-7.36 (m, 4H, Ar-H), 7.53 (t, 1H, J = 8.0 Hz, Ar-H), 7.58 (d, 1H, J = 8.0 Hz, Ar-H), 7.74 (d, 1H, J = 8.0 Hz, Ar-H), 7.95 (dd, 1H, J = 8.0 and 1.5 Hz, Ar-H), 8.02 (d, 1H, J = 16.2 Hz, CH=CH); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 30.1, 52.3, 100.2, 109.1, 119.8, 119.9, 120.5, 121.9, 126.7, 127.3, 127.9, 128.5, 129.2, 130.8, 132.2, 138.3, 138.8, 167.8; ms: m/z 292 $(M+1)^+$.

Anal. Calcd. for $C_{19}H_{17}NO_2$ (291.35): C, 78.33; H, 5.88; N, 4.81. Found: C, 78.55; H, 5.97; N, 4.69.

2-[2-(1-Phenylsulfonyl-1*H*-indol-2-yl)vinyl]benzoic Acid Methyl Ester (**2b**).

With the same methodology but using **1b** as starting material, **2b** (only *E* isomer) was prepared in 85% yield, mp 145-146° (recrystallization from methylene chloride-hexane); ir (potassium bromide): ν 1716 (CO) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 3.91 (s, 3H, $COOCH_3$), 6.00 (s, 1H, =CH), 6.57 (d, 1H, J = 8.0 Hz, CH=CH), 7.02-7.60 (m, 10H, Ar-H and CH=CH), 7.89 (d, 2H, J = 8.7 Hz, Ar-H), 7.99 (d, 1H, J = 8.1 Hz, Ar-H), 8.26 (d, 1H, J = 8.8 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 52.1, 112.5, 114.8, 119.2, 120.7, 123.7, 124.8, 126.7, 127.3, 129.1, 129.2, 129.6, 130.1, 130.6, 131.9, 133.5, 133.8, 136.3, 136.7, 139.0, 139.1, 167.2; ms: m/z 418 $(M+1)^+$.

Anal. Calcd. for $C_{24}H_{19}NO_4S$ (417.49): C, 69.05; H, 4.59; N, 3.36. Found: C, 68.86; H, 4.41; N, 3.50.

2-[2-(1-Methyl-1*H*-indol-2-yl)ethyl]benzoic Acid Methyl Ester (**3a**).

A mixture of **2a** (1.05 g, 3.6 mmoles) and 10% Pd/C (110 mg) in dioxane (20 ml) was shaken in a Parr apparatus under 40 psi of hydrogen at room temperature for 2 hours. The catalyst was removed by filtration, and evaporation of the solvent gave the desired compound as a colorless oil which was crystallized from methanol to give 965 mg (91% yield) of **3a**, mp 158-160°; ir (potassium bromide): ν 1717 (CO) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 3.06 (t, 2H, J = 8.1 Hz, CH_2-CH_2), 3.37 (t, 2H, J = 8.1 Hz, CH_2-CH_2), 3.65 (s, 3H, $COOCH_3$), 3.82 (s, 3H, N-CH_3), 6.28 (s, 1H, =CH), 7.03-7.44 (m, 6H, Ar-H), 7.53 (d, 1H, J = 8.0 Hz, Ar-H), 7.91 (dd, 1H, J = 8.0 and 1.5 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 29.0, 29.4, 34.3, 52.0, 99.0, 108.8, 119.2, 119.8, 120.5, 126.3, 127.9, 129.5, 130.7, 131.2, 132.2, 137.3, 140.6, 143.1, 167.8; ms: m/z 294 $(M+1)^+$.

Anal. Calcd. for $C_{19}H_{19}NO_2$ (293.37): C, 77.79; H, 6.53; N, 4.77. Found: C, 77.96; H, 6.48; N, 4.61.

2-[2-(1-Phenylsulphonyl-1*H*-indol-2-yl)ethyl]benzoic Acid Methyl Ester (**3b**).

Using the same procedure, **3b** was prepared in 98% yield, mp 134-136° (recrystallization from methanol); ir (potassium bromide): ν 1716 (CO) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 3.26-3.45 (m, 4H, CH_2-CH_2), 3.86 (s, 3H, $COOCH_3$), 6.42 (s, 1H, =CH), 7.16-7.53 (m, 9H, Ar-H), 7.73 (d, 2H, J = 8.0 Hz, Ar-H), 7.91 (dd, 1H, J = 8.0 and 1.5 Hz, Ar-H), 8.17 (bd, 1H, J = 8.0 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 31.0, 34.2, 52.0, 109.7, 114.8, 120.3, 123.6, 124.0, 126.2, 126.3, 126.3, 129.2, 129.9, 130.8, 131.2, 132.2, 133.6, 139.0, 143.0, 167.9; ms: m/z 420 $(M+1)^+$.

Anal. Calcd. for $C_{24}H_{21}NO_4S$ (419.50): C, 68.72; H, 5.05; N, 3.34. Found: C, 68.58; H, 4.94; N, 3.52.

2-[2-(1-Methyl-1*H*-indol-2-yl)ethyl]benzoic Acid (**4a**).

A solution of ester **3a** (732 mg, 2.5 mmoles) in ethanol 95% (15 ml) and sodium hydroxide (500 mg, 12.5 mmoles) was stirred at reflux for 16 hours. The solvent was removed *in vacuo*, water (20 ml) was added to the residue and the *p*H was adjusted to 1 by careful addition of 10% hydrochloric acid. After extraction with methylene chloride (2 x 20 ml), the organic layer was dried and evaporated. The residue was separated by column chromatography (petroleum ether/methylene chloride 6:4) to give 648 mg (93% yield) of **4a**, mp 151° (recrystallization from methylene chloride-hexane); ir (potassium bromide): ν 3300-2600 (OH), 1693 (CO) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 3.26-3.45 (m, 4H, CH_2-CH_2), 3.86 (s, 3H, $COOCH_3$), 6.34 (s, 1H, =CH), 7.16-7.53 (m, 4H, Ar-H), 7.73 (d, 2H, J = 8.0 Hz, Ar-H), 7.91 (d, 1H, J = 8.0 Hz, Ar-H), 8.18 (d, 1H, J = 8.0 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 29.0, 29.3, 34.7, 99.1, 108.9, 119.3, 119.8, 120.6, 124.0, 126.6, 127.9, 127.9, 131.6, 131.9, 137.3, 140.6, 144.3, 172.4; ms: m/z 280 $(M+1)^+$.

Anal. Calcd. for $C_{18}H_{17}NO_2$ (279.34): C, 77.40; H, 6.13; N, 5.01. Found: C, 77.63; H, 6.01; N, 5.15.

2-[2-(1-Phenylsulfonyl-1*H*-indol-2-yl)ethyl]benzoic Acid (**4b**).

Using the same methodology, **4b** was prepared in 98% yield, mp 138-140° (recrystallization from methylene chloride-hexane); ir (potassium bromide): ν 3300-2600 (OH), 1693 (CO) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 3.32-3.39 (m, 2H, CH_2-CH_2), 3.45-3.52 (m, 2H, CH_2-CH_2), 6.39 (s, 1H, =CH), 7.15-7.62 (m, 9H, Ar-H), 7.72 (d, 2H, J = 8.0 Hz, Ar-H), 8.08 (dd, 1H, J = 8.0 and 1.5 Hz, Ar-H), 8.17 (bd, 1H, J = 8.0 Hz, Ar- H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 30.9, 34.4, 109.7, 114.9, 120.3, 123.6, 124.0, 126.2, 126.5, 127.9, 129.2, 129.9, 131.6, 131.8, 133.3, 133.6, 137.2, 138.9, 141.4, 144.1, 172.2; ms: m/z 406 $(M+1)^+$.

Anal. Calcd. for $C_{23}H_{19}NO_4S$ (405.48): C, 68.13; H, 4.72; N, 3.45. Found: C, 68.25; H, 4.87; N, 3.29.

5-Methyl-6,7-dihydrobenzo[4,5]cyclohept[1,2-*b*]indol-12(5*H*)-one (**5a**).

Method A.

Finely powdered **4a** (300 mg, 1.07 mmoles) was added to polyphosphoric acid (2 g) with stirring at 90°. After the addition was complete, the mixture was stirred at 110° for 2 hours. After cooling, ice was added, then the mixture was neutralized with saturated sodium hydrogenocarbonate, and extracted with methylene chloride (2 x 15 ml). The combined organic layers were dried over magnesium sulfate and evaporated. The crude residue was purified by column chromatography (eluent methylene chloride) to give 205 mg (73% yield) of **5a**, mp 200-202° (recrystallization from methanol); ir (potassium bromide): ν 1612 (CO) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 3.12-3.18 (m, 2H, CH_2-CH_2), 3.24-3.29 (m, 2H, CH_2-CH_2), 3.69 (s, 3H, N-CH_3), 7.24-7.41 (m, 6H, Ar-H), 7.98-8.01 (m, 1H, Ar-H), 8.65 (dd, 1H, J = 8.0 Hz and 1.5 Hz, Ar-H). ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 27.0, 30.0, 33.5, 108.9, 122.8, 122.9, 123.1, 127.2, 127.6, 128.8, 129.7, 131.0, 136.9, 137.8, 140.8, 149.1, 188.1; ms: m/z 262 $(M+1)^+$.

Anal. Calcd. for $C_{18}H_{15}NO$ (261.33): C, 82.73; H, 5.79; N, 5.36. Found: C, 82.69; H, 5.85; N, 5.20.

Method B.

To a solution of **8** (1.48 g, 5.3 mmoles) in dichloroethane (20 ml) was added trifluoroacetic anhydride (1.87 ml, 13.2 mmoles), and the mixture was stirred at room temperature for 1 hour, then boron trifluoride etherate (0.66 ml, 5.3 mmoles) was added. The reaction was carried out at 25° for 5 hours. After cooling, water (20 ml) was added and the mixture was neutralized with 10% aqueous sodium hydroxide, then extracted with ethyl acetate (3 x 15 ml). The organic layer was dried then evaporated. The crude residue was purified by column chromatography (eluent methylene chloride) to give 1.01 g (73% yield) of **5a**.

6,7-Dihydrobenzo[4,5]cyclohept[1,2-*b*]indol-12(5*H*)-one (**5b**).

Using Method A, **5b** was prepared in 62% yield, mp 283-285° (recrystallization from methylene chloride-hexane); ir (potassium bromide): ν 3300 (NH), 1611 (CO) cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6): δ 3.19 (s, 4H, CH_2-CH_2), 7.15-7.20 (m, 2H, Ar-H), 7.36-7.46 (m, 4H, Ar-H), 7.92 (dd, 1H, J = 8.0 and 1.5 Hz, Ar-H), 8.36-8.39 (m, 1H, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 27.6, 33.3, 111.1, 113.5, 121.6, 121.7, 122.6, 126.7, 127.9, 129.4, 131.0, 135.2, 138.9, 139.7, 150.0, 186.4; ms: m/z 248 $(M+1)^+$.

Anal. Calcd. for $C_{17}H_{13}NO$ (247.30): C, 82.57; H, 5.30; N, 5.66. Found: C, 82.60; H, 5.15; N, 5.60.

1-Methyl-2-phenylethylindole-3-carboxylic Acid Ethyl Ester (**7**).

To a solution of **6** (434 mg, 2 mmoles) in anhydrous THF (10 ml), 3*M* lithium diisopropylamide in heptane (0.87 ml, 2.6 mmoles) was added dropwise at -78°. After 30 minutes, a solution of benzyl bromide (0.36 ml, 3 mmoles) diluted in THF (10 ml) was added dropwise with vigorous stirring at -78°. The mixture was stirred one hour at -78°, then one hour at room temperature and THF distilled off at reduced pressure. The residue was partitioned between ethyl acetate (20 ml) and water (20 ml), the aqueous phase separated, acidified to *p*H = 1 with 10% hydrochloric acid, and extracted with ethyl acetate (2 x 15 ml). The assembled organic layers were dried and evaporated *in vacuo*. The crude oil was purified by column chromatography using petroleum ether/ethyl acetate 9:1 as the eluting solvent to afford 518 mg (84% yield) of **7**, mp 68-70° (recrystallization from methylene chloride-hexane); ir (potassium bromide): ν 1689 (CO) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 1.48 (t, 3H, J = 7.4 Hz, CH_3), 3.00 (t, 2H, J = 7.4 Hz, CH_2-CH_2), 3.43 (s, 3H, N-CH_3), 3.49 (t, 2H, J = 7.4 Hz, CH_2-CH_2), 4.44 (q, 1H, J = 7.4 Hz, CH_2), 7.16-7.29 (m, 8H, Ar-H), 8.17-8.20 (m, 1H, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 14.7, 28.1, 29.3, 35.7, 59.4, 103.6, 109.3, 121.6, 121.8, 122.1, 126.3, 126.6, 128.5, 136.5, 141.1, 148.4, 165.8; ms: m/z 308 $(M+1)^+$.

Anal. Calcd. for $C_{20}H_{21}NO_2$ (307.40): C, 78.15; H, 6.89; N, 4.56. Found: C, 78.00; H, 6.80; N, 4.60.

1-Methyl-2-phenylethylindole-3-carboxylic Acid (**8**).

A solution of ester **7** (2.4 g, 7.8 mmoles) and sodium hydroxide (1.56 g, 39.1 mmoles) in methanol (50 ml) was stirred at reflux for 2 days. The solvent was removed *in vacuo*, water (30 ml) was added to the residue and the solution was acidified with 10% hydrochloric acid. After extraction with methylene chloride (2 x 20 ml), the organic layer was dried and evaporated. The crude residue was purified by column chromatography (eluent petroleum ether/methylene chloride 6:4) to give 1.83 g (84% yield) of **8**, mp 179-180° (recrystallization from methylene chloride-hexane); ir (potassium bromide): ν 3300-2600 (OH), 1642 (CO) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 3.05 (t, 2H, J = 7.7 Hz, CH_2-CH_2), 3.44 (s, 3H, N-CH_3), 3.53 (t, 2H, J = 7.7 Hz, CH_2-CH_2), 7.17-7.30 (m, 8H, Ar-H), 8.25-8.30 (d, 1H, J = 8.0 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 28.2, 29.4, 35.7, 102.9, 109.4, 121.8, 122.1, 122.3, 126.3, 127.1, 128.6, 128.6, 136.6, 141.0, 149.8, 171.1; ms: m/z 280 $(M+1)^+$.

Anal. Calcd. for $C_{18}H_{17}NO_2$ (279.34): C, 77.40; H, 6.13; N, 5.01. Found: 77.30; H, 6.00; N, 5.00.

5-Methyl-12-methylene-5*H*-6,7-dihydrobenzo[4,5]cyclohept-[1,2-*b*]indole (**9**).

To a solution of **5a** (1.0 g, 3.80 mmoles) in dry THF (15 ml) at 0° under an argon atmosphere was added dropwise commercially available methyl magnesium chloride (2.55 ml, 7.66 mmoles). After 1 hour, 2 more equivalents of Grignard reagent were added. The reaction was stirred at room temperature for 2 hours. The mixture was quenched with water (15 ml) and extracted with ethyl acetate (3 x 15 ml). Organic layer was dried and evaporated. The crude oil was purified by column chromatography using petroleum ether/methylene chloride 2:8 as the eluting solvent to afford 886 mg (90% yield) of **9**, mp 171-172° (recrystallization from methylene chloride-methanol); ^1H nmr (300 MHz, deuteriochloroform): δ 3.04-3.08 (m, 2H, CH_2-CH_2), 3.19-3.23 (m, 2H, CH_2-CH_2), 3.58 (s, 3H, N-CH_3), 5.48 (d, 1H, J = 1.8 Hz, =CH_2), 5.73 (d, 1H, J = 1.8 Hz, =CH_2), 7.11-7.24 (m, 6H, Ar-H), 7.38-7.41 (m, 1H, Ar-H), 7.87-7.90 (m, 1H, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 27.3, 29.2, 31.7, 108.6, 111.6, 114.0, 119.5, 119.7, 121.3, 126.0, 126.7, 127.2, 127.3, 128.1, 136.3, 136.9, 137.8, 143.3, 145.4; ms: m/z 260 $(M+1)^+$.

Anal. Calcd. for $C_{19}H_{17}N$ (259.35): C, 87.99; H, 6.61; N, 5.40. Found: C, 87.80; H, 6.65; N, 5.50.

5-Methyl-12-ethylidene-5*H*-6,7-dihydrobenzo[4,5]cyclohept-[1,2-*b*]indole (**10**).

With the same methodology but using ethyl magnesium chloride as reagent, compound **10** was prepared in 70% yield, mp 195° (recrystallization from methylene chloride-methanol); ^1H nmr

(300 MHz, deuteriochloroform): δ 1.90 (d, 3H, J = 7.4 Hz, CH_3), 2.80-3.50 (m, 4H, CH_2-CH_2), 3.57 (s, 3H, N-CH_3), 6.21 (q, 1H, J = 7.4 Hz, =$CH(CH_3)$), 7.10-7.30 (m, 7H, Ar-H), 7.82 (d, 1H, J = 8.0 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 15.3, 27.4, 29.1, 31.3, 108.4, 119.1, 119.2, 121.0, 123.6, 125.8, 125.9, 126.1, 126.8, 128.3, 128.4, 134.5, 136.6, 138.7, 142.2; ms: m/z 274 $(M+l)^+$.

Anal. Calcd. for $C_{20}H_{19}N$ (273.38): C, 87.87; H, 7.01; N, 5.12. Found: C, 87.98; H, 7.17; N, 5.02.

5-Methylbenzo[4,5]cyclohept[1,2-*b*]indol-12(5*H*)-one (**11**).

To a solution of ketone **5a** (650 mg, 2.5 mmoles) in dry carbon tetrachloride (30 ml) at 60° was added *N*-bromosuccinimide (443 mg, 2.5 mmoles). The mixture was stirred one hour at the same temperature. After cooling and evaporation of the solvent, the residue was taken up in methylene chloride/water (40 ml v/v) and extracted. The organic phase was dried and evaporated. The residual oil was dissolved in triethylamine (15 ml) and methylene chloride (5 ml) and the reaction mixture was refluxed overnight. The reaction mixture was concentrated and the crude oil was partitioned between methylene chloride (10 ml) and 10% hydrochloric acid (10 ml). After extraction, the organic phase was dried over magnesium sulfate then evaporated. The product was purified by column chromatography using methylene chloride as eluting solvent to give 453 mg (70% yield) of **11**, mp 175-176° (recrystallization from methylene chloride-methanol); ir (potassium bromide): ν 1622 (CO) cm^{-1}, ^{1}H nmr (300 MHz, deuteriochloroform): δ 3.81 (s, 3H, N-CH_3), 7.14 (d, 1H, J = 11.8 Hz, CH=CH), 7.26 (d, 1H, J = 11.8 Hz, CH=CH), 7.30-7.45 (m, 6H, Ar-H), 7.62-7.73 (m, 1H, Ar-H), 8.94-9.00 (m, 1H, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 29.8, 109.1, 116.5, 122.7, 124.5, 125.3, 125.8, 127.3, 129.6, 131.0, 134.0, 134.2, 134.7, 138.0, 138.2, 140.6, 182.1; ms: m/z 260 $(M+l)^+$.

Anal. Calcd. for $C_{18}H_{13}NO$ (259.31): C, 83.38; H, 5.05; N, 5.40. Found: C, 83.52; H, 4.90; N, 5.53.

5-Methyl-5*H*,12*H*-benzo[4,5]cyclohept[1,2-*b*]indole (**12**).

A solution of **11** (477 mg, 1.84 mmoles) and sodium borohydride (139 mg, 3.68 mmoles) in dichloromethane (10 ml) and ethanol (10 ml) was heated at reflux. Two more equivalents of sodium borohydride were added to the mixture at 2, 4 and 6 hours of reaction. Consumption of the starting material was monitored by tlc. After cooling, water was added and the mixture was extracted with methylene chloride (2 x 10 ml). Organic phase was dried over magnesium sulfate, then evaporated. The crude residue was purified by column chromatography using petroleum ether/methylene chloride 2:8 as eluting solvent to give 420 mg (90% yield) of **12**, mp 104-105° (recrystallization from methylene chloride-methanol); ^{1}H nmr (300 MHz, deuteriochloroform): δ 3.72 (s, 3H, N-CH_3), 3.88 (s, 2H, CH_2), 6.95 (d, 1H, J = 11.8 Hz, CH=CH), 7.14 (d, 1H, J = 11.8 Hz, CH=CH), 7.10-7.33 (m, 7H, Ar-H), 7.73 (d, 1H, J = 8.0 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 29.7, 30.7, 109.1, 113.5, 118.4, 118.9, 119.2, 122.0, 125.6, 125.7, 128.4, 129.0, 129.2, 131.9, 133.8, 135.6, 137.7, 138.6; ms: m/z 246 $(M+1)^+$.

Anal. Calcd. for $C_{18}H_{15}N$ (245.33): C, 88.13; H, 6.16; N, 5.71. Found: C, 87.96; H, 6.03; N, 5.89.

5,12-Dimethyl-5*H*,12*H*-6,7-dihydrobenzo[4,5]cyclohept[1,2-*b*]-indole (**13**).

A mixture of **9** (250 mg, 1 mmole) and 10% Pd/C (25 mg) in dioxane (10 ml) was shaken in a Parr apparatus under 40 psi of hydrogen at room temperature for 2 hours. The catalyst was removed by filtration, and evaporation of the dioxane gave 235 mg (90% yield) of **13**, mp 158-160° (recrystallization from methylene chloride-methanol); ^{1}H nmr (300 MHz, deuteriochloroform): δ 1.68 (d, 3H, J = 7.4 Hz, CH_3), 2.87 (td, 1H, J = 4.0 and 15.0 Hz, CH_2-CH_2), 3.01 (dt, 1H, J = 4.0 and 15.0 Hz, CH_2-CH_2), 3.20 (dt, 1H, J = 4.0 and 15.0 Hz, CH_2-CH_2), 3.59 (s, 3H, N-CH_3), 3.64 (td, 1H, J = 4.0 and 14.0 Hz, CH_2-CH_2), 4.44 (q, 1H, J = 7.4 Hz, CH), 7.09-7.27 (m, 7H, Ar-H), 7.62 (bd, 1H, J = 8.0 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 24.3, 26.7, 29.2, 32.0, 38.3, 108.4, 113.7, 117.4, 118.7, 120.8, 126.5, 126.7, 127.4, 129.0, 130.0, 135.1, 136.2, 139.6, 145.6; ms: m/z 262 $(M+1)^+$.

Anal. Calcd. for $C_{19}H_{19}N$ (261.37): C, 87.31; H, 7.33; N, 5.36. Found: C, 87.60; H, 7.56; N, 5.43.

5,12-Dimethyl-5*H*,12*H*-benzo[4,5]cyclohept[1,2-*b*]indole (**14**).

Using the methology described to obtain **11**, compound **14** was isolated with a 80% yield; mp 109-110° (recrystallization from methylene chloride-methanol); ^{1}H nmr (300 MHz, deuteriochloroform): δ 1.27 (bd, 3H, J = 6.2 Hz, CH_3), 3.78 (s, 3H, N-CH_3), 4.45-4.65 (bs, 1H, CH), 6.95 (d, 1H, J = 11.8 Hz, CH=CH), 7.07 (d, 1H, J = 11.8 Hz, CH=CH), 7.14-7.42 (m, 7H, Ar-H), 7.80 (d, 1H, J = 8.0 Hz, Ar-H). ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 18.3, 29.5, 37.2, 109.1, 117.9, 119.1, 122.3, 125.7, 129.5, 131.3, 132.4, 134.1, 138.4, 142.5; ms: m/z 260 $(M+1)^+$.

Anal. Calcd. for $C_{19}H_{17}N$ (259.35): C, 87.99; H, 6.61; N, 5.40. Found: C, 88.21; H, 6.44; N, 5.27.

12-Hydroxymethyl-5-methyl-5*H*,12*H*-6,7-dihydrobenzo[4,5]-cyclohept[1,2-*b*]indole (**15**).

To a solution of **9** (259 mg, 1 mmole) in dry THF (10 ml), was added 1*M* boron hydride, THF (1 ml, 1 mmole). The solution was stirred for 3 hours at room temperature. Excess of reagent was hydrolyzed with water, then 3*M* sodium hydroxide (3 ml) followed by 35% hydrogen peroxide (3 ml) were added. The final solution was stirred for 15 minutes at reflux. After cooling and neutralization with 10% hydrochloric acid, the solution was extracted with ethyl acetate (2 x 10 ml). The organic phase was dried over magnesium sulfate and evaporated. The crude compound was purified by column chromatography (eluent methylene chloride) to afford 200 mg (72% yield) of **15**, mp 163° (recrystallization from methanol); ir (potassium bromide): ν 3334 (OH), 1025 (C-O) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 2.87 (td, 1H, J = 4.0 and 15.0 Hz, CH_2-CH_2), 3.00 (dt, 1H, J = 4.0 and 15.0 Hz, CH_2-CH_2), 3.19 (dt, 1H, J = 4.0 and 15.0 Hz, CH_2-CH_2), 3.57 (td, 1H, J = 4.0 and 15.0 Hz, CH_2-CH_2), 3.61 (s, 3H, N-CH_3), 4.06 (t, 2H, J = 8.0 Hz, CH_2-O), 4.50 (t, 1H, J = 8.0 Hz, CH), 7.10-7.33 (m, 7H, Ar-H), 7.70 (bd, 1H, J = 8.1 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 26.5, 29.2, 32.1, 47.1, 67.5, 108.2, 108.5, 117.8, 119.2, 121.2, 126.7, 127.4, 128.2, 130.4, 130.9, 136.2, 136.5, 140.0, 140.5; ms: m/z 278 $(M+1)^+$.

Anal. Calcd. for $C_{19}H_{19}NO$ (277.37): C, 82.28; H, 6.90; N, 5.05. Found: C, 81.95; H, 6.68; N, 4.91.

12-Methoxymethyl-5-methyl-5*H*,12*H*-6,7-dihydrobenzo[4,5]-cyclohept[1,2-*b*]indole (**16**).

To a solution of **15** (100 mg, 0.36 mmole) in dry DMF (5 ml),

was added sodium hydride (24 mg, 1.04 mmoles) at room temperature. The solution was stirred for 30 minutes, then iodomethane (150 mg, 1.08 mmoles) diluted in dry DMF (2 ml) was added. The final solution was stirred for one hour. After evaporation of the solvent, the residue was partitioned between water (5 ml) and dichloromethane (5 ml) and the mixture was extracted. The organic phase was dried over magnesium sulfate and evaporated. The crude compound was purified by column chromatography (eluent methylene chloride) to afford 80 mg (76% yield) of **16**, mp 154-155° (recrystallization from methanol); ir (potassium bromide): ν 1113 (C-O) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 2.89 (td, 1H, J = 4.0 and 14.0 Hz, CH_2-CH_2), 3.02 (dt, 1H, J = 4.0 and 14.0 Hz, CH_2-CH_2), 3.21 (dt, 1H, J = 4.0 and 14.0 Hz, CH_2-CH_2), 3.36 (s, 3H, OCH_3), 3.62 (s, 3H, N-CH_3), 3.64 (td, 1H, J = 4.0 and 14.0 Hz, CH_2-CH_2), 3.87 (dd, 1H, J = 5.6 and 9.4 Hz, CH_2-O), 3.96 (t, 1H, J = 9.4 Hz, CH_2-O), 4.60 (dd, 1H, J = 5.6 and 9.4 Hz, CH), 7.10-7.33 (m, 7H, Ar-H), 7.71 (bd, 1H, J = 8.0 Hz, Ar-H); ^{13}C nmr (62.90 MHz, deuteriochloroform): δ 26.6, 29.2, 31.9, 44.5, 59.0, 108.4, 109.1, 117.6, 118.9, 121.0, 126.5, 127.0, 127.9, 130.0, 130.8, 136.2, 136.3, 139.6, 141.7; ms: m/z 292 $(M+1)^+$.

Anal. Calcd. for $C_{20}H_{21}NO$ (291.40): C, 82.44; H, 7.26; N, 4.81. Found: C, 82.19; H, 7.36; N, 4.70.

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[13] A prismatic crystal of **5a**, obtained from a methylene chloride solution, with the approximate size 0.1 x 0.1 x 0.2 mm was employed. The crystal was mounted on a Philips PW-1100 four-circle diffractometer. Unit-cell parameters were determined from automatic centering of 25 reflexions ($8 < \theta < 12°$) and refined by least-squares method. Intensities were collected with graphite monochromatized MoK_α radiation, using $\omega/2\theta$ scan-technique. 4097 reflections were measured in the range $1.82 < \theta < 30.01$. 3895 of which were non-equivalent by symmetry (Rint(on I) = 0.052). 2381 reflections were assumed as observed applying the condition $I>2\theta$ (I). Three reflections were measured every two hours as orientation and intensity control, significant intensity decay was not observed. Lorentz-polarisation but no absorption corrections were made. The structure was solved by Patterson synthesis, using SHELXS computer program and refined by full-matrix least-squares method with SHELX93 computer program, using 3845 reflections. The extinction coefficient was 0.059(6). 15 hydrogen atoms were located from a difference synthesis and refined with an overall isotropic temperature factor.