Synthesis of 2,3,3a,8a-Tetrahydroindeno[2,1-*b*]pyrrole Derivatives

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A new entry into the 2,3,3a,8a-tetrahydroindeno[2,1-*b*]pyrrole system, **1**, has been investigated. 2,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-1-methylindeno[2,1-*b*]pyrrole-2,8-dione, **3**, formed from the reaction of ninhydrin and *N*-methylacetamide has been subjected to catalytic hydrogenation, hydride reduction, and chlorination reactions to afford a variety of substituted derivatives of **1**.

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In previous reports (1a), we have described the synthesis and pharmacological activities of a number of conformationally restricted phenethylamine analogs in order to obtain information about the structure-activity requirements for centrally acting drugs. Our interest has recently focused on the 2,3,3a,8a-tetrahydroindeno[2,1-*b*]pyrrole system **1** since this heterocycle may be regarded as containing the elements of a rigid phenethylamine unit within its structure held in a rigid molecular framework. We now report some initial results of a synthetic route to 2,3,3a,8a-tetrahyroindeno[2,1-*b*]pyrrole derivatives, developed in our laboratory, which may be of general synthetic utility.

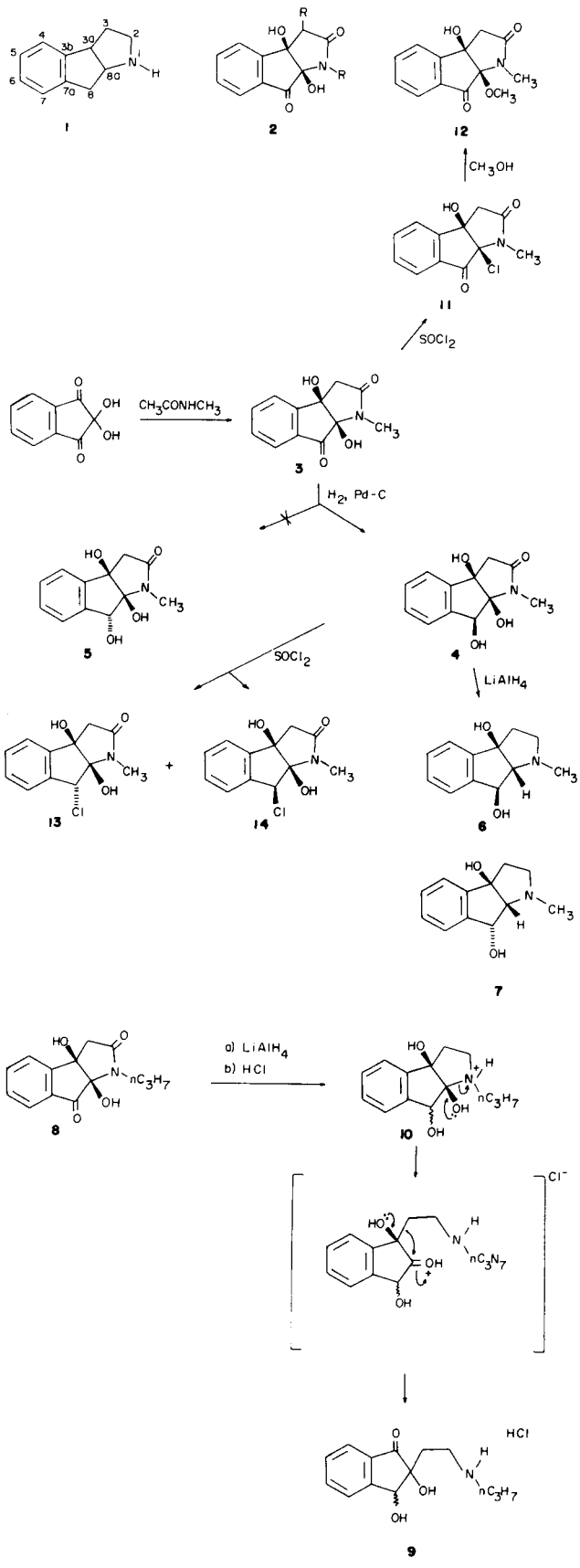
Relatively few general synthetic routes to 2,3,3a,8a-tetrahydroindeno[2,1-*b*]pyrrole derivatives have been described in the chemical literature (2). We have previously reported a preliminary communication (3) describing the reaction of ninhydrin with *N*-alkylacetamides in refluxing benzene to afford the corresponding *N*-alkyl-2,3,-3a,8a-tetrahydro-3a,8a-dihydroxyindeno[2,1*b*]pyrrole-2,8-dione **2**. The ease of synthesis of the above compounds, the capacity for varying the substituents at N-1 or C-3 by utilizing the appropriate *N*-alkylacetamide and the ready access to indane-1,2,3-triones bearing aromatic substituents (4), prompted us to examine the utility of compounds of structure **2** in the preparation 2,3,3a,8a-tetrahydroindeno[2,1-*b*]pyrrole derivatives. In our initial studies, we examined a number of reductive methods of defunctionalizing **3** and have investigated the reaction of **3** and **4** with thionyl chloride. Compound **3** was prepared from the reaction of *N*-methylacetamide with ninhydrin (3). Catalytic hydrogenation of **3** with a Pd-C catalyst both at atmospheric pressure and at pressures ranging from 50 to 300 atmospheres, afforded on almost quantitative yield of 2,3,3a,8a-tetrahydro-3,8,8a-trihydroxy-1-methylindeno-[2,1-*b*]pyrrole-2-one **4**. Examination of the pmr and cmr spectrum (see Table 1 and Experimental Section) of this product showed it to be isomerically pure, none of the alternative isomeric ketone reduction product **5** was detected in the reaction mixture. The trihydroxy compound could not be exhaustively reduced further to dehydroxylated products, even after employing a variety of reduction conditions. Lithium aluminum hydride reduction of **4** afforded a modest yield (53%) of 2,3,3a,8a-tetrahydro-3a,8-dihydroxy-1-methylindeno[2,1-*b*]pyrrole **6**. The stereochemistry at C-8 in this compound was determined from its pmr spectrum, which exhibited singlets at δ 4.92 and δ 4.73 for the C-8 and C-8a protons respectively, indicating that $J_{8,8a} \cong 0$ Hz. The dihedral angle for these protons must therefore approach 90°. Drieding model examination of the isomeric structures **6** and **7** showed that a transoid geometry for C-8 and C-8a protons was consistent with the pmr spectroscopic data, thus indicating the

Table 1

Carbon-13 Chemical Shifts (1a) of 2,3,3a,8a-Tetrahydroindeno[2,1-*b*]pyrrole Derivatives

Compound (b)	C-2	C-3	C-3a	C-8	C-8a	N-CH_3
3	169.17 s	39.06 t	78.64 s	201.86 s	91.96 s	24.37 q
4	171.82 s	38.94 t	83.14 s	79.11 d	96.02 s	24.90 q
6	55.63 t	32.21 t	91.19 s	78.53 d	79.04 d	40.88 q
12	169.82 s	39.45 t	78.83 s	201.47 s	95.60 s	24.63 q
13 (c)	170.54 s	40.61 t	82.80 s	66.97 d	95.89 s	24.46 q
14 (c)	170.56 s	40.63 t	83.31 s	67.40 d	95.46 s	24.48 q

(a) The abbreviations, s (singlet), d (doublet), t (triplet) and q (quartet) are used. (b) Spectra were recorded at 310°K in DMSO-d_6 using TMS as internal reference. (c) These structural assignments may be interchangeable.



former isomer as the structure of the lithium aluminum hydride reduction product. This also establishes **4** as the product obtained from catalytic hydrogenation of **3**. Attempted exhaustive hydrogenation of **6** with a variety of catalysts and conditions led to recovery of starting material in all cases. Lithium aluminum hydride reduction of **3** could not be carried out with ease, because of the very poor solubility of this compound in both diethyl ether and tetrahydrofuran. However, the *N*-*n*-propyl derivative **8**, which was prepared by the reaction of *N*-*n*-propylacetamide with ninhydrin (3), was sparingly soluble in both the above solvents. Lithium aluminum hydride reduction of **8** was carried out utilizing a Soxhlet extraction apparatus and afforded 41% of a product tentatively identified as 2,3-dihydroxy-2-(*n*-propylaminoethyl)indan-1-one **9**. This cleavage product may have arisen from initial formation of **10** followed by an acid catalyzed pinacol-type rearrangement during the work-up procedure, to give **9**. However, on repeating the reduction and carrying out the work-up procedure in the absence of aqueous acid, a multicomponent mixture was obtained from which no pure product could be isolated.

Reaction of **3** with thionyl chloride in pyridine at room temperature afforded an unstable monochloro derivative **11** which could be converted rapidly and quantitatively into the monomethoxy derivative **12** by treatment with methanol. The cmr spectra of **12** and other 2,3,3a,8a-tetrahydroindeno[2,1-*b*]pyrrole derivatives are given in Table 1. The assignment of **12** for the structure of the monomethoxy compound is based upon the chemical shift of the C-8a carbon which moves from 91.96 ppm in the spectrum of the parent compound **3** to 95.60 ppm in the spectrum of the monomethoxy derivative (see Table 1); the relative shifts of other carbons in the two spectra are virtually unchanged. Reaction of **4** with thionyl chloride in pyridine at room temperature produced a vigorous exothermic reaction which yielded an intractable tar on work-up. Carrying out the reaction at 0-4° resulted in the formation of two major products which could be separated by preparative thin layer chromatography. These compounds were identified as the isomeric monochloro derivatives **13** and **14** from their pmr and cmr spectroscopic properties (see Table 1).

These initial studies suggest that *N*-alkyl-2,3,3a,8a-tetrahydro-3a,8a-dihydroxyindeno[2,1-*b*]pyrrole-2,8-diones formed from the reaction of ninhydrin with the appropriate *N*-alkylacetamide may be useful intermediates in the synthesis of a variety of substituted 2,3,3a,8a-tetrahydroindeno[2,1-*b*]pyrrole derivatives.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Perkin-Elmer R24 spectrometer and ^{13}C-nmr were recorded on a Bruker WP80 spectrometer using

tetramethylsilane as internal reference. Mass spectra were obtained on a A. E. I. MS12 spectrometer operating at a probe temperature of 200° and an ionization voltage of 70 eV. Infrared spectra were recorded on a Perkin-Elmer 237 gating spectrophotometer. Catalytic hydrogenations were carried out at atmospheric pressure on a Gallenkampf all glass hydrogenator, and at high presssure on a Baskerville electromagnetically agitated autoclave. All melting points are uncorrected and were taken on a Reichert hot-stage microscope. Evaporations were carried out under reduced pressure on a rotary evaporator. Yields of solids refer to products obtained prior to recrystallization, unless otherwise stated.

2,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-1-methylindeno[2,1-*b*]pyrrole-2,8-dione (**3**).

A solution of ninhydrin (8.9 g, 0.05 mole) and *N*-methylacetamide (3.65 g, 0.05 mole) in benzene (150 ml) was heated under reflux in a Dean and Stark apparatus for 48 hours, during which time a white crystalline precipitate was deposited. The mixture was filtered, the resulting solid washed with dry ether and dried *in vacuo* over phosphorus pentoxide, to afford **3** as white prisms, yield 9.32 g (80.0%), mp 226-228°; ir (liquid paraffin): ν 1730 (ketone C=O), 1665 (amido C=O) cm^{-1}; ^{1}H-nmr (deuteriopyridine): δ 9.01 (broad s, 2H, exchangeable with deuterium oxide, two OH), 8.10-7.29 (m, 4H, aromatic), 3.05 (s, 3H, N-CH_3), 3.30 and 3.05 (d of d, 2H, J = 18 Hz, geminal C-3 protons); ms: m/e (%) 223 (M^+, 90), 204 (24), 190 (48), 176 (30), 174 (16), 163 (100), 162 (50), 146 (25), 130 (19), 117 (25), 105 (50), 77 (33).

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.00. Found: C, 62.11; H, 4.92; N, 5.95.

2,2,3a,8a-Tetrahydro-3a,8a-dihydroxy-1-propylindeno[2,1-*b*]pyrrole-2,8-dione (**8**).

A solution of ninhydrin (8.90 g, 0.02 mole) and *N*-*n*-propylacetamide (5.50 g, 0.05 mole) in benzene (150 ml) was heated under reflux for 72 hours in a Dean and Stark apparatus and then treated as described for the preparation of **3**, to afford 8.35 g (64.1%) of **8** as a white powder, mp 165-168°; ir (liquid paraffin): ν 1725 (ketone C=O), 1670 (amido C=O) cm^{-1}; ^{1}H-nmr (deuteriopyridine): δ 8.53 (broad s, 2H, exchangeable with deuterium oxide, two OH), 7.81-7.10 (m, 4H, aromatic), 3.64 (t, 2H, NCH_2CH_2), 3.34 and 2.95 (d of d, 2H, J = 18 Hz, geminal C-3 protons), 1.70 (m, 2H, N-CH_2CH_2), 0.80 (t, 3H, CH_3); ms: m/e (%) 261 (M^+, 100), 202 (20), 191 (53), 177 (32), 176 (73), 175 (71), 146 (23), 130 (40), 105 (75), 104 (45), 77 (64), 76 (36).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.60; H, 5.74; N, 5.31.

2,3,3a,8a-Tetrahydro-3a,8,8a-trihydroxy-1-methylindeno[2,1-*b*]pyrrol-2-one (**4**).

A stirred solution of **3** (0.75 g, 0.0032 mole) in a mixture of absolute ethanol (60 ml) and concentrated hydrochloric acid (1 ml) containing 5% palladium-on-charcoal catalyst (1 g) was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen ceased (approximately 3 hours). The mixture was then filtered, the filtrate evaporated to low volume and then chilled to 4°. The resulting crystalline deposit was filtered off, washed with a little cold ethanol and then recrystallized from 95% ethanol to afford 0.70 g (92.5%) of **4** as white prisms, mp 169-171°; ir (liquid paraffin): ν 1640 (amido C=O) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.60-7.21 (m, 4H, aromatic), 6.12 (s, 1H, exchangeable with deuterium oxide, C-8a OH), 5.72 (d, 1H, J = 6 Hz, exchangeable with deuterium oxide, C-8 OH), 5.32 (s, 1H, exchangeable with deuterium oxide, C-3a OH), 4.81 (d, 1H, J = 6 Hz, collapses to s on exchange with deuterium oxide, C-8 proton), 2.75 (s, 3H, N-CH_3), 2.45 (d of d, 2H, J = 18 Hz, C-3 protons); ms: m/e (%) 235 (M^+, 9), 217 (49), 176 (21), 160 (100), 134 (31), 131 (12), 118 (10), 105 (45), 100 (30).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.37; H, 5.29; N, 5.86.

2,3,3a,8a-Tetrahydro-3a,8-dihydroxy-1-methylindeno[2,1-*b*]pyrrole Hydrochloride (**6**).

A Soxhlet extractor thimble was charged with a finely divided sample of **4** (2.3 g, 0.01 mole) and to the reservoir of the Soxhlet apparatus was added lithium aluminum hydride (3.8 g, 0.1 mole) suspended in dry ether (100 ml). The mixture was heated under reflux for 48 hours, after which time all of the powder in the thimble had disappeared. The excess lithium aluminum hydride was destroyed by careful addition of water and then anhydrous magnesium sulfate (10 g). The resulting mixture was filtered and dry hydrogen chloride gas bubbled through the filtrate to give a copious greenish-white precipitate, which was filtered off and recrystallized from absolute ethanol to afford 1.36 g (57.0%) of **6** hydrochloride as white crystals, mp 218-220°; ir (liquid paraffin): ν 3,400, 3,120 (two -OH's) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.72-7.22 (m, 4H, aromatic), 6.26 (s, 1H, exchangeable with deuterium oxide, C-3a OH), 6.09 (d, 1H, J = 5 Hz, exchangeable with deuterium oxide, C-8 OH), 4.92 (d, 1H, J = 5 Hz, collapses to s on exchange with deuterium oxide, C-8 proton), 4.73 (s, 1H, C-8a proton), 3.61-3.15 (m, 2H, -CH_2-N^+), 3.05 (s, 3H, $^+$N-CH_3), 2.50-1.81 (m, 2H, CH_2-CH_2-N^+); ms: m/e (%) 205 (M^+ of free base, 49), 189 (58), 188 (50), 172 (21), 160 (100), 146 (76), 145 (52), 144 (49), 131 (38), 116 (40), 90 (29).

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.80. Found: C, 59.90; H, 6.59; N, 6.01.

Attempted Reductive Dehydration of **4** and **6**.

A stirred solution of **4** or **6** (0.5 g, 0.0021 mole) in glacial acetic acid (20 ml) containing platinum black catalyst (0.5 g) was hydrogenated at 100 atmospheres of hydrogen gas for 6 hours. The resulting solution was filtered, evaporated to dryness *in vacuo* and the residue recrystallized from 95% ethanol. Spectroscopic examination showed that in each case, the product isolated was mainly recovered starting material. The use of methanol/hydrochloric acid or acetic acid/perchloric acid as solvent, or palladium black or palladium-on-charcoal as the catalyst, still resulted in almost quantitative return of starting material from these reactions, even at hydrogen pressures in excess of 200 atmospheres.

Formation of 2,3-dihydroxy-2-(*n*-propylaminoethyl)indan-1-one Hydrochloride (**9**) from Lithium Aluminum Hydride Reduction of **8**.

Reduction of **8** (2.6 g, 0.01 mole) with lithium aluminum hydride (3.8 g, 0.1 mole) in dry ether (100 ml) and treatment of the filtered reaction mixture with dry hydrochloric acid gas in a similar manner to that described for the preparation of **6** (see above), afforded an off-white precipitate which was recrystallized from ethanol-ether to afford 1.3 g (44.3%) of **9** hydrochloride as white prisms, mp 189-194°; uv (ethanol): λ max (log ϵ) 206.5 (4.31), 247.5 (4.03), 288-293 (3.28) nm; ir (liquid paraffin): ν 3,300, 3250, 3120 (-OH's), 1710 (ketone C=O) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 9.97 (brd s, 2H, replaceable with deuterium oxide, $\rangle NH_2$), 7.90-7.35 (m, 4H, aromatic), 6.41 (broad s, 1H, replaceable with deuterium oxide, OH), 6.08 (broad s, 1H, replaceable with deuterium oxide, OH), 5.05 (s, 1H, C-3 proton), 3.08 (m, 2H, CH_2-N^+), 2.81 (t, 2H, CH_2-N^+), 2.13 and 1.69 (overlapping m's, 4H, two CH_2's), 0.90 (t, 3H, CH_3); ms: m/e (%) 249 (M^+ of free base, 6), 220 (22), 177 (13), 162 (25), 161 (16), 160 (31), 71 (100).

Anal. Calcd. for $C_{14}H_{20}NO_3Cl \cdot \frac{1}{2}H_2O$: C, 57.04; H, 7.18; N, 4.75. Found: C, 57.41; H, 7.40; N, 4.95.

8a-Chloro-2,3,3a,8a-tetrahydro-3a-hydroxy-1-methylindeno[2,1-*b*]pyrrole-2,8-dione (**11**).

Compound **3** (2.3 g, 0.01 mole) was dissolved in pyridine (12 ml) at 25°, thionyl chloride (1.4 g, 0.012 mole) added and the mixture stirred at room temperature overnight. The resulting mixture was evaporated to dryness under reduced pressure and the residue continuously extracted with dry tetrahydrofuran using a Soxhlet extractor. The tetrahydrofuran extract was cooled to 4° for 12 hours. Filtration of the resulting crystalline deposit afforded 1.03 g (41.2%) of **11** as an off-white powder, mp 202-208°, which was unstable in air; ir (liquid paraffin): ν 3265 (-OH), 1720 (ketone C=O), 1650 (amido C-O) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.95-7.59 (m, 4H, aromatic), 2.75 (s, 3H, NCH_3), 2.36-2.51 (d of d, 2H, J = 18 Hz, geminal C-3 protons), 2.54 (s, 1H, exchangeable with deuterium oxide, OH).

Satisfactory elemental analysis figures for this compound could not be obtained.

2,3,3a,8a-Tetrahydro-3a-hydroxy-8a-methoxy-1-methylindeno[2,1-*b*]-pyrrole-2,8-dione (**12**).

Freshly prepared **11** (1.25 g, 5 mmoles) was dissolved in superdry methanol (10 ml) and the solution refluxed for 8 hours. The mixture was then evaporated to dryness under reduced pressure and the residue recrystallized from aqueous ethanol to give 1.18 g (95.9%) of **12** as white crystals, mp 189-205°; ir (liquid paraffin): ν 1725 (ketone C=O), 1685-1675 (amido C=O) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.89-7.32 (m, 4H, aromatic), 4.50 (broad s, 1H, exchangeable with deuterium oxide, OH), 3.35 (s, 3H, -OCH_3), 3.12-2.48 (d of d, 2H, centered at 2.70 and 2.65, J = 18 Hz, geminal C-3 protons), 2.71 (s, 3H, N-CH_3); ms: m/e (%) 247 (m^+, 81), 219 (22), 190 (32), 177 (49), 162 (100), 148 (25), 117 (30), 105 (28).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.54; H, 5.51; N, 6.01.

8-Chloro-2,3,3a,8a-tetrahydro-3a,8a-dihydroxy-1-methylindeno[2,1-*b*]-pyrrol-2-one (**13**) and (**14**).

Compound **4** (2.35 g, 0.01 mole) was dissolved in pyridine (15 ml) cooled to between 0-4° in an ice bath and thionyl chloride (1.4 g, 0.012 mole) added. The mixture was stirred at room temperature for 3 hours and then quenched with ice-water (25 ml). The resulting gummy precipitate was filtered off at the pump to give 1.63 g (64.4%) of a hygroscopic, brown semi-solid. This sample was chromatographed on Eastman Chromagram silica gel sheet containing fluorescent indicator using chloroform-methanol (1:3 v/v) as solvent, and showed to spots at R_f 0.75 (major) and 0.67 (minor) when viewed under uv light at 254 nm. An ^{1}H-nmr examination of this product indicated it to be a 2:1 mixture of the isomers **13** and **14**. Chromatographic separation of the above isomers was carried out on preparative silica gel GF254 (type 60, Merck) thin layer plates. The major band corresponding to R_f 0.75 was obtained as a homogenous clear, light brown gum which could not be crystallized; ^{1}H-nmr (DMSO-d_6): δ 7.75-7.20 (m, 4H, aromatic), 6.11-5.45 (broad s, 2H, exchangeable with deuterium oxide, two OH), 5.27 (s, 1H, C-8 proton), 2.60 (s, 3H, N-CH_3), 2.62-2.32 (d of d, 2H, J = 18 Hz, geminal C-3 protons).

Anal. Calcd. for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.95; H, 5.02; N, 5.53.

The minor band (R_f 0.67) could not be obtained in a homogenous state and was isolated as a brown gum. The ^{1}H-nmr spectrum showed the sample to be contaminated with a small amount (8-12%) of the R_f 0.75 isomer; ^{1}H-nmr (DMSO-d_6): δ 7.83-7.18 (m, 4H, aromatic), 5.72-5.51 (broad s, 2H, exchangeable with deuterium oxide, two OH), 5.35 (s, 1H, C-8 proton), 2.72 (s, 3H, N-CH_3), 2.61-2.30 (d of d, 2H, J = 18 Hz, geminal C-3 protons).

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