A NEW EVIDENCE FOR THE PRESENCE OF A SPIROINDOLENIUM SPECIES IN THE PICTET-SPENGLER REACTION†

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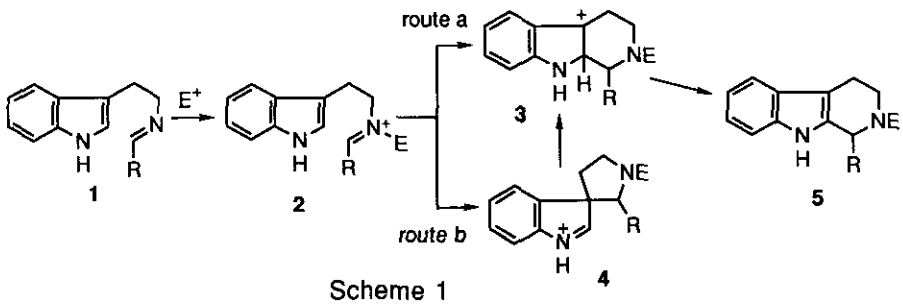
Abstract- The Pictet-Spengler reaction of the imine (**9**) with chloro (-)-diisopinocamphenylborane yielded optically active spiroindolines (**14**) and (**15**), providing a new evidence for the presence of a spiroindolenium intermediate.

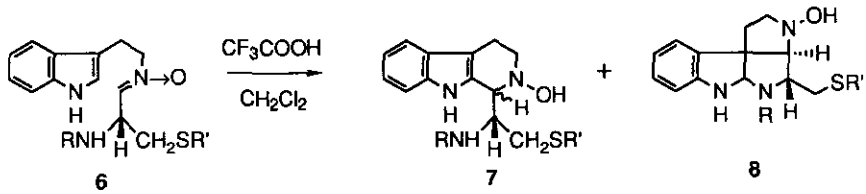
The Pictet-Spengler reaction has been developed for the synthesis of tetrahydro-β-carbolines and has often been applied to the synthesis of indole alkaloids.[1] In the course of our research on the synthesis of biologically active alkaloids, we have recently reported the syntheses of two types of β-carboline alkaloids, fumitremorgin B[2] and eudistomins,[3] in which we have also employed the Pictet-Spengler reaction as a key step.

Concerning the mechanism of the Pictet-Spengler reaction of tryptamine and tryptophan derivatives, two possible pathways have been proposed, which involve either direct attack at the indole 2-position (route a), or attack at the 3-position of indole ring to form spiroindolenium intermediate followed by migration (route b).

†Dedicated to Professor Emeritus Masatomo Hamana on the occasion of his seventy-fifth birthday.



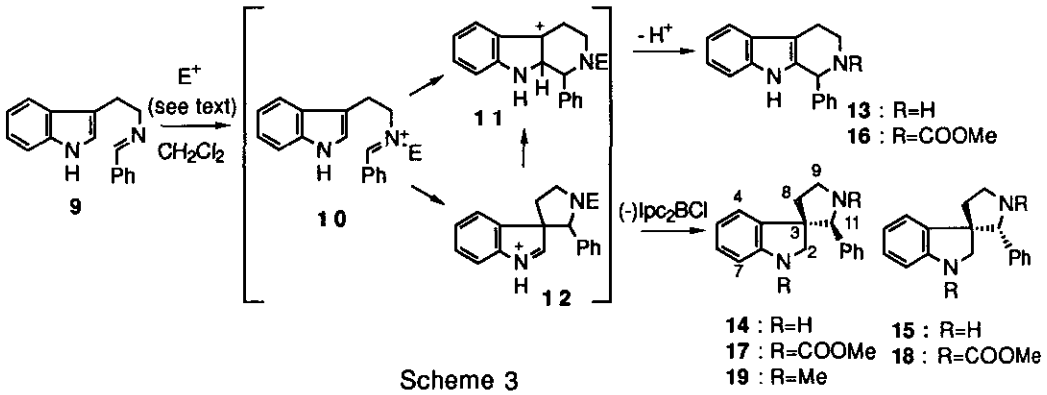
Scheme 1



Scheme 2

(Scheme 1) A substantial amount of evidence in support of the spiroindolenine mechanism has been reported.[4] For example, Ghosal and Banerjee have trapped a spiroindolenium as its trimer.[5] Jackson and Smith demonstrated the facile acid catalyzed migration of 2-hydroxyspiroindolines to tetrahydro-β-carbolines.[6] And several groups have shown the involvement of spiroindolenium intermediates using nmr technique on the reaction of related system.[7] More recently, we have isolated tetracyclic compounds (**8**) by the Pictet-Spengler reaction of nitrons (**6**) which demonstrated the involvement of a spiroindolenine species in the Pictet-Spengler reaction.[8] (Scheme 2) However, electrophilic attack at the indole 2-position is known to compete with attack at the 3-position.[9] In addition, from the view point of Baldwin rule,[10] attack at the indole 3-position would involve 'disfavored' 5-*endo*-trig ring-closure, whereas direct attack at the 2-position could proceed through the 'favoured' 6-*endo*-trig pathway.

We now wish to report a new evidence with regard to the intermediate (**4**) which was obtained by an attempted asymmetric Pictet-Spengler reaction of tryptamine. Protic acids such as hydrochloric acid, sulfuric acid, and trifluoroacetic acid[11] have been used as a catalyst of Pictet-Spengler reaction, while little was known on the use of other electrophiles such as Lewis acids.[12] Therefore, we first carried out the Pictet-Spengler reaction using various electrophiles other than protic acids, which



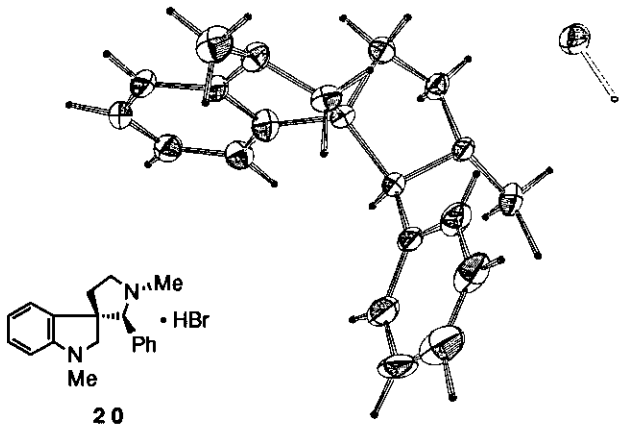
Scheme 3

Table. Pictet-Spengler Reaction of **9** with Electrophiles

Entry	E^+ (mol eq.)	Conditions temp(°C)	time(h)	Result **13**(%)
1	TMSCl(4.4)	0	1	97
		room temperature	88	
2	TMSI(2.1) pyridine(4.4)	room temperature	8.5	83
3	Me_2BBr(1.1)	-78	1.5	87
		room temperature	37	
4	TMSI(2.1)	room temperature	0.5	55
5	*N*-TMS-imidazole(2.6)	room temperature	9.5	0
6	TMSOTf(2.8) Et_3N(4.8)	room temperature	9.5	0
7	TMSCl(4.4) pyridine(4)	room temperature	28.5	28
8	BF_3•OEt_2(3.0)	room temperature	6days	7
9	CF_3COOH(3.1)	room temperature	34	64

would activate the *C=N double bond of* **1** *in order to form the corresponding iminium* ion **2**. We first carried out the Pictet-Spengler reaction of the imine (**9**), prepared from tryptamine and benzaldehyde, with 4.4 mol eq. of Me_3SiCl in CH_2Cl_2 at 0°C for 1 h then at room temperature for 88 h (Entry 1). (Scheme 3) The β-carboline (**13**)[6,13] was obtained in 97% yield.[14] Similar high yields of **13** were obtained with Me_3SiI-pyridine and Me_2BBr (Entries 2 and 3). However, the reaction did not proceed to give **13** when *N*-TMS-imidazole and TMSOTf-Et_3N were used as an electrophile. (Entries 5 and 6) The results were summarized in the Table. In keeping with our interest in chiral control in the Pictet-Spengler reaction for the

enantiospecific synthesis of tetrahydro-β-carbolines, our effort was focused on the asymmetric Pictet-Spengler reaction using chiral boron compounds as a chiral electrophile. In contrast to the above result, when **9** was treated with chloro (-)-diisopinocamphenylborane, (-)-Ipc_2BCl, in CH_2Cl_2 at room temperature for 63 h, to our surprize, we obtained two new optically active compounds (**14**; 64%, $[\alpha]_D^{19}$ -139.3°) and (**15**; 26%, $[\alpha]_D^{20}$ +131.7°) along with the normal Pictet-Spengler product (**13**; 2%). From spectroscopic data, the structures of the diastereomers (**14**) and (**15**) were assigned as shown in Scheme 3. Namely, both **14** and **15** showed same molecular ion peak(m/z 250). The ultraviolet (uv) spectra of both **14** and **15** showed the presence of the aniline chromophore(**14**: 245.5, 298 nm, **15**: 243, 299 nm). ^{13}C-Nmr spectra of **14** and **15** exhibited the presence of sp^3 quaternary carbons at δ 56.19 ppm and δ 57.13 ppm, respectively. And the presence of an isolated CH_2 unit was confirmed by the ^1H-nmr spectrum. For further confirmation of the structures, the mixture of **13**, **14**, and **15** was converted to the corresponding methoxycarbonyl derivatives by treating with excess ClCOOMe to give the dimethoxycarbonyl derivative (**17**) as a white powder(61% from tryptamine) along with **16**(3%) and **18**(21%). The methoxycarbonyl groups in **17** were reduced to the methyl groups with $LiAlH_4$ in refluxing dioxane, giving **19** in 89% yield. The X-ray analysis of its hydrobromide (**20**), mp 243.5-236.0°C, revealed the structure as shown in the Figure, though the absolute configuration still remains to be solved. The formation of **14** and **15** can be explained as follows. Ipc_2BCl may first attack at the imine group of **9** as an electrophile to activate the C=N bond followed by intramolecular attack at the 3-position to form the spiroindolenine (**12**). As Ipc_2BCl has been known as a reducing agent,[15] the imimiun group in **12** was immidiately reduced to the spiroindolines (**14** and **15**) before rearrangement to **11**. Although the isolation of **14** and **15** dose not prove that the spiroindolenine was the sole intermediate of the Pictet-Spengler reaction to the β-carboline[8b], our result provides an evidence for the presence of an spiroindolenine in the reaction course. Similar successful isolation of the spiroindoline (**22**) has been reported by Williams and Unger in the reaction of tryptophan methyl ester with excess formaldehyde



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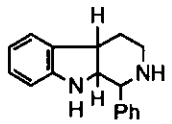

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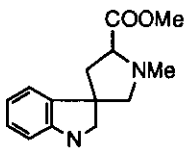

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Figure

under reductive conditions (H_2-Pd/C).[16] However, the corresponding spiroindoline was not obtained in the similar reaction of tryptamine.[16] On the other hand, our previous results[8b] suggested direct cyclization at the indole 2-position (route a in Scheme 1) at low temperature (-78°C) in the Pictet-Spengler reaction of nitrons (**6**). Therefore, we treated **9** with (-)-Ipc_2BCl at low temperature (-15 - -30°C). However, we could not obtain the indoline (**21**), which would be formed by the reduction of the intermediate (**11**), and instead **14** and **15** were obtained in 48 and 13% yields, respectively.

Our effort on the asymmetric Pictet-Spengler reactions is in progress, and will be reported in due course.

EXPERIMENTAL

Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point apparatus and are uncorrected. Uv spectra were recorded on a Hitachi 323 spectrophotometer and refer to a solution in 95% EtOH (λ in nm). Infrared (ir) spectra were obtained with a Hitachi 260-10 spectrophotometer. Unless otherwise noted, ir spectra (ν in cm^{-1}) refer to KBr disks. Mass spectra (ms) were recorded on a Hitachi M-60, a RMU-7, or a JEOL HX-110 mass spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H- and ^{13}C-nmr) spectra were recorded on JEOL JNM-

GSX-400, JNM-GSX-500, and JNM-GSX-500α apparatus. Nmr spectra were measured in $CDCl_3$ and chemical shifts were recorded in δ values (ppm) relative to internal Me_4Si standard. Optical rotations were recorded with a JASCO DIP-140 polarimeter. Microanalyses were performed on a Perkin-Elmer 240 C, H, and N analyzer. Silica gel column chromatography was performed on Fuji-Davison BW-200 or BW-300 silica gel.

1-Phenyl-1,2,3,4-tetrahydro-β-carboline 13

(Typical procedure, Entry 1 in Table) To a solution of N_b-benzylidenetryptamine (**9**) (prepared from tryptamine (240 mg, 1.50 mmol) and benzaldehyde (0.24 ml, 1.60 mmol)) in CH_2Cl_2 (10 ml), Me_3SiCl (0.42 ml, 3.31 mmol) was added under ice-cooling and the whole was stirred at 0°C for 1 h, then stirred at room temperature under an argon atmosphere. After 41 h, further Me_3SiCl (0.42 ml, 3.31 mmol) was added and the mixture was stirred for further 47 h at room temperature. The reaction mixture was diluted with CH_2Cl_2, and washed with aq. 10% NaOH and brine, dried over Na_2SO_4. Evaporation of the solvent gave a residue (381 mg), which was chromatographed on silica gel (BW-200, 16 g, AcOEt:hexane=40:1) to give **13** (362 mg, 97%). **13**: light yellow prisms. mp 166.0-167.0°C(AcOEt-hexane; lit.,168-169°C[6]; 167-168°C[13]), λ_{max} 226, 275, 283, 290 nm; ν_{max} 3400, 3250, 1455, 750 cm^{-1}; δ_H 1.73(1H, br, N_b-H), 2.88(1H, dddd, J=1.7, 3.9, 4.7, 15.4 Hz, 4-H_a), 2.92(1H, dddd, J=1.9, 5.4, 9.0, 15.4 Hz, 4-H_b), 3.14(1H, ddd, J=4.7, 9.1, 12.5 Hz, 3-H_a), 3.38(1H, ddd, J=3.9, 5.4, 12.7 Hz, 3-H_b), 5.16(1H, br t, 1-H), 7.12(2H, m, Aromatic H), 7.21(1H, m, Aromatic H), 7.30-7.38(5H, m, Aromatic H), 7.50-7.56(2H, m, Aromatic H and N_a-H); m/z(%) 249(M^++1, 18.43), 248(M^+, 100), 218(82.91), 171(48.77).

Reaction of N_b-benzylidenetryptamine with chloro (-)diisopino-camphenylborane - Formation of 2,3-dihydroindole-3-spiro-3'-(2'-phenylpyrrolidine 14 and 15 -

A solution of (-)-Ipc_2BCl (8409 mg, 26.22 mmol) in CH_2Cl_2 (25 ml) was added to a solution of N_b-benzylidenetryptamine (**9**) (prepared from tryptamine (801 mg, 5.00

mmol) and benzaldehyde (0.62 ml, 6.10 mmol)) in CH_2Cl_2 (25 ml) and the resulting solution was stirred for 63 h at room temperature. Aq. 15% NaOH (30 ml) was added and the mixture was stirred for further 15 min, and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4. Evaporation of the solvent gave a residue (7.78 g), which was purified by chromatograpy on silica gel (BW-200, 80 g, AcOEt:MeOH:Et_3N=1:0:0 - 10:1:0 - 20:2:1) to give **13** (27 mg, 2%), **14** (799 mg, 64%), and **15** (327 mg, 26%). **13**: yellow prisms. mp 194.0-195.0°C (AcOEt-n-hexane),[17] $[\alpha]_D^{18}$ 0.0°(c 0.23, $CHCl_3$). **14**: pale brown oil. $[\alpha]_D^{19}$ -139.3°(c 1.22, $CHCl_3$); λ_{max} 245.5, 298 nm; ν_{max}(neat) 3450^{br}, 3350^{br}, 1605, 1490, 1460, 750, 705 cm^{-1}; δ_H 2.00-2.76(2H, br, NH x 2), 2.16(1H, m, 8-H_a), 2.38(1H, ddd, J=6.60, 8.06, 13.00 Hz, 8-H_b), 3.09(1H, dd, J=2.75, 9.71 Hz, 2-H_a), 3.30(2H, m, 9-H_2), 3.39(1H, dd, J=2.93, 9.70 Hz, 2-H_b), 4.30(1H, s, 11-H), 6.52(1H, d, J=7.88, 7-H), 6.82(1H, dt, J=2.75, 7.33 Hz, 5-H), 7.06(1H, dt, J=1.10, 7.70 Hz, 6-H), 7.08-7.12(2H, m, Ph), 7.18-7.25(3H, m, Ph), 7.27(1H, dd, J=1.10, 7.32 Hz, 4-H); δ_C 40.00(t, 8), 44.23(t, 9), 55.66(t, 2), 56.19(s, 3), 70.95(d, 11), 110.02(d, 7), 118.82(d, 5), 122.70(d, 4), 126.83, 126.97, 127.74, and 127.92(each d, 6 and 2'-6'), 134.25(s, 3a), 140.47(s, 1'), 151.71(s, 7a); m/z(%) 251(M^++1, 1.72), 250(M^+, 9.64), 131(100); HR-FABms calcd for $C_{17}H_{18}N_2$+H(M^++H) 251.1550; found 251.1545. **15**: pale brown prisms. mp 92.5-94.0°C(MeOH); $[\alpha]_D^{20}$ +131.7°(c 0.54, $CHCl_3$); λ_{max} 243, 299 nm; ν_{max} 3270^{br}, 1615, 1490, 1465, 760, 745, 710 cm^{-1}; δ_H 2.00(1H, ddd, J=3.48, 8.24, 12.94 Hz, 8-H_a), 2.37(1H, td, J=8.61, 12.82 Hz, 8-H_b), 2.82(2H, br, NH x 2), 3.25(1H, td, J=8.24, 10.26 Hz, 9-H_a), 3.49(1H, ddd, J=3.48, 8.97, 10.26 Hz, 9-H_b), 3.55(1H, d, J=9.16 Hz, 2-H_a), 3.70(1H, d, J=8.97 Hz, 2-H_b), 4.25(1H, s, 11-H), 6.43-6.51 and 6.91(3H and 1H, m, 4-7), 6.98-7.02(2H, m, Ph), 7.10-7.14(3H, m, Ph); δ_C 37.27(t, 8), 44.56(t, 9), 57.14(s, 3), 59.62(t, 2), 70.74(d, 11), 109.27(d, 7), 118.03(d, 5), 124.91, 126.73, 127.30, 127.40, and 127.55(each d, 4, 6, and 2'-6'), 131.88(s, 3a), 141.78(s, 1'), 151.46(s, 7a); m/z(%) 251(M^++1, 1.82), 250(M^+, 8.85), 131(100); Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.50; H, 7.31; N, 11.24.

The optical purities of **14** and **15** were determined by hplc analysis using a chiral column, DAICEL CHIRACEL OD (^{i}PrOH:hexane=50:50, 0.5 ml/min) and were 77%ee and 95%ee, respectively.

The similar reaction (starting from tryptamine (801 mg, 5.00 mmol) and benzaldehyde (0.62 ml, 6.10 mmol)) at -15 - -30°C for 163 h gave **14** (604 mg, 48%) and **15** (166 mg, 13%)

Preparation of 1-methoxycarbonyl-2,3-dihydroindole-3-spiro-3'-(1'-methoxycarbonyl-2'-phenylpyrrolidine) 17 and 18

A solution of (-)-Ipc$_2$BCl (7640 mg, 23.82 mmol) in CH_2Cl_2 (15 ml) was added to a solution of N_b-benzylidenetryptamine (**9**) (prepared from tryptamine (767 mg, 4.79 mmol) and benzaldehyde (0.77 ml, 7.58 mmol)) in CH_2Cl_2 (30 ml) and the whole was stirred for 48 h at room temperature. Workup as above gave a residue (7.24 g), which was chromatographed on silica gel briefly (BW-300, 108 g, AcOEt:hexane=1:2 - AcOEt - AcOEt:MeOH=5:1) to give a mixture of **13**, **14**, and **15** (1.19 g). The mixture of **13**, **14**, and **15** was dissolved in CH_2Cl_2 (50 ml) and cooled with ice-bath. 20%K_2CO_3 (20 ml) and ClCOOMe (1.25 ml, 16.18 mmol) were added to the mixture and the whole was stirred for 60 min under ice-cooling. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue (1609 mg), which was chromatographed on silica gel (BW-300, 60 g, AcOEt:hexane=1:10 - 1:3) to give **16** (51 mg, 3%), **17** (1063 mg, 61%), and **18** (370 mg, 21%). **16**: $[\alpha]_D^{22}$ +0.8°(c 0.51, $CHCl_3$); λ_{max} 225, 275, 283, 291 nm. **17**[18]: white powder. mp 157.5-159.0°C(MeOH); $[\alpha]_D^{22}$ -30.0°(c 0.58, $CHCl_3$); λ_{max} 245, 283, 290 nm, ν_{max} 1720, 1700 cm^{-1}; m/z(%) 367(M^++1, 6.06), 366(M^+, 24.78), 178(100); Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.71; H, 6.07; N, 7.74. **18**[18]: pale yellow amorphous solid. $[\alpha]_D^{23}$ +150.9°(c 0.75, $CHCl_3$); λ_{max} 245, 283, 290 nm, m/z(%) 367(M^++1, 5.27), 366(M^+, 21.40), 178(94.38), 91(100); HRms calcd for $C_{21}H_{22}N_2O_4$, 366.1581; found, 366.1580.

Preparation of 1-methyl-2,3-dihydroindole-3-spiro-3'-(1'-methyl-2'-phenylpyrrolidine) 19 by $LiAlH_4$ reduction of 17

To a refluxing suspension of $LiAlH_4$ (995 mg, 26.22 mmol) in dioxane (30 ml), **17** (837 mg, 2.28 mmol) in dioxane (30 ml) was added and the whole was refluxed for 2.5 h. After cooling to 0°C, H_2O (1 ml), aq. 15% NaOH (1 ml), and H_2O (3 ml) were added dropwise in this order, and the whole was stirred for further 20 min. The mixture was filtered and the solvent was evaporated to give residue, which was chromatographed on silica gel (BW-200, 12 g, AcOEt:hexane=1:10 - 1:5) to give **19** (569 mg, 89%). **19**: light yellow oil. $[\alpha]_D^{23}$ -84.2°(c 0.57, $CHCl_3$); λ_{max} 260, 310 nm; ν_{max}(neat) 2950, 2780, 1610, 1450, 740, 700 cm^{-1}; δ_H 2.12(1H, ddd, J=8.25, 9.07, 12.92 Hz, 8-H_a), 2.25(1H, ddd, J=2.75, 8.52, 12.92 Hz, 8-H_b), 2.29(3H, s, NCH_3), 2.36(3H, s, NCH_3), 2.56(1H, dd, J=9.35, 17.87 Hz, 9-H_a), 2.89(1H, d, J=9.35 Hz, 2-H_a), 3.04(1H, d, J=9.07 Hz, 2-H_b), 3.31(1H, ddd, J=2.75, 8.25, 9.35 Hz, 9-H_b), 3.39(1H, s, 11-H), 6.28(1H, d, J=7.69 Hz, 7-H), 6.73(1H, dt, J=0.82, 7.42 Hz, 5-H), 7.05-7.10 and 7.16-7.25(total 7H, m, 4, 6, and Ph); m/z(%) 279(M^++1, 1.92), 278(M^+, 9.55), 134(100); HRms calcd for $C_{19}H_{22}N_2$(M^+): 278.1785; found 278.1783. HBr salt **20**: pale green prisms. mp 234.5-236.0°C(MeOH-Et_2O), Anal. Calcd for $C_{19}H_{23}N_2Br$: C, 63.51; H, 6.45; N, 7.80. Found: C, 63.31; H, 6.47; N, 7.74. Crystal Data for **20**: $C_{19}H_{23}N_2Br$, orthorhombic, space group: $P2_12_12_1$, a=7.330(9) Å, b=24.962(30) Å, c=9.569(8) Å, α=90.0°, β=90.0°, γ=90.0°. Cell volume: 1754.08Å^3, Z=4, D_{calcd}=1.363gcm^{-3}. Lattice constants and intensity data were measured using graphite-monochromated CuKα(λ=1.54178) radiation on a Rigaku AFC-5 diffractometer. A total of 1487 unique reflections with $F_o>3\sigma Fo$ were obtained using $\omega\leq30°\leq\omega$-2θ scanning method with a 2θ scan speed of 4° min^{-1} to 3°<2θ<120°. The structure was solved by the UNICS-III system MULTAN 80 (Library of Computer Center of Tokyo University, T. Sakurai and K. Kobayashi, *Rep. Inst. Phys. and Chem. Res.*, **55**, 69 (1979)) based on direct methods and refined to a final R value of 0.042.

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18. ^{1}H- and ^{13}C-nmr show broadning peaks due to the presence of rotational isomers and are unable to assign.

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