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Article

Synthesis and Configuration Determination of Styrylquinolines as Leukotriene D_4 Antagonist Precursors

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Differently substituted styrylquinoline derivatives (6-9) were synthesized by condensation of quinaldine (1) and corresponding substituted benzaldehydes (2-5). Their relative configuration at C11-C12 and coupling patterns were determined by NMR techniques.

Key words : *styrylquinoline derivatives, nOe, configuration.*

Since the discovery of slow reacting substance of anaphylaxis (SRS-A), which is known as a mixture of leukotrienes, a number of investigations have been focused to identify the roles of leukotrienes and to develope their antagonists. Especially recent studies have implicated leukotriene D_4 in asthma.[1)] A number of leukotriene D_4 antagonists have been reported, most of which bear close structural similarities, including hydroxyacetophenone types[2)] and quinoline types.[3,4)] Our continuing interest in the development of potent leukotriene D_4 antagonists has led us to synthesize a series of substituted styrylquinoline derivatives (**6-9**) as leukotriene antagonist precursors.[5,6)] However, it was not easy to identify the configuration of olefin double bond at C11-C12, since the complication of double bond protons with aromatic protons was inevitable. In this study, synthesis of styrylquinoline derivatives (**6-9**) and their configuration determination are reported.

Experimental

General methods. Infrared spectra were recorded on a Perkin Elmer Paragon 2000 FT-IR spectrometer. NMR spectra were obtained on a Bruker DPX 400 (9.4 T) instrument in $CDCl_3$ and DMSO-d_6. Analytical thin-layer chromatography was performed by using precoated silica gel 60 F_{254} plates and the silica gel used for flash column chromatography was supplied from Merck (230~400 mesh, 60Å). InsightII/Discover (msi) was used for Molecular Dynamics calculations.

Synthesis of 4-[2-(2-Quinolinyl)-(E)-ethenyl]benzaldehyde (6). Three grams (22 mmol) of 1,4-benzenedicarboxaldehyde (**2**) and 2.1 g (15 mmol) of quinaldine (**1**) were dissolved in 30 mL of xylene and stirred for 10 min at room temperature. To this clear solution, 4.15 mL (40 mmol) of acetic anhydride was added and refluxed for 8 h. The reaction mixture was cooled down to room temperature and 50 mL of petroleum ether was added to the reaction mixture to precipitate. The solid was filtered off and resulting filtrate was concentrated under vacuum. The residue was purified by flash column chromatography to give desired product **6** in 48.9% yield (1.91 g); m.p. 111~112°C; IR(KBr disk) ν_{max} 1697, 1601, 1504, 1212, 969, 823, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49~7.51 (m, 2H), 7.54 (dd, 1H) 7.56~7.80 (m, 5H), 7.89~7.90 (dd, 2H), 8.09 (d, 1H), 8.14 (d, 1H), 10.01 (s, 1H); ^{13}C NMR (100 MHz) δ 119.6,126.6, 127.58, 127.64 (double intensity), 129.37, 129.8, 129.95 (double intensity), 130.2, 132.2, 132.8, 135.9, 136.6, 142.5, 148.3, 155.1, 191.6.

Synthesis of 2-[2-(2-Quinolinyl)-(E)-ethenyl]phenoxy acetate (7). Two and a half grams (20 mmol) of 2-hydroxybenzaldehyde (**3**) and 2.8 mL (20 mmol) of quinaldine (**1**) were dissolved in 7 mL of acetic anhydride and the reaction mixture was heated at 130°C for 12 h. To the cooled reaction mixture, 70 ml of ice water was added and consequently extracted with ethyl acetate (3×50 ml). The combined organic layers were dried under $MgSO_4$. After filtration, resulting filtrate was condensed under vacuum. The residue was purified by flash column chromatography (ethyl acetate; hexane 1:1) to give 4.2 g of desired product **7** (71%); m.p. 88~89°C; IR (KBr disk) ν_{max} 1751, 1597, 1202, 1183, 963, 812, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 6.99 (dd, 1H, 8 Hz, 1 Hz), 7.12 (t, 1H, 7.4 Hz) 7.19 (t, 1H, 7.5 Hz), 7.25 (d, 1H, 15.5 Hz), 7.33 (dt, 1H, 7 Hz, 1 Hz) 7.44 (d, 1H, 8.6 Hz), 7.51~7.69 (m, 4H), 7.91 (d, 1H, 12.4 Hz), 7.95 (d, 1H, 10.5 Hz);

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^{13}C NMR (100 MHz) δ 21.5, 119.8, 123.3, 126.72, 126.75, 127.37, 127.85, 127.94 (double intensity), 129.58, 129.73, 129.80, 130.2, 131.6, 136.8, 148.6, 149.1, 156.0, 169.7.

Synthesis of 3-[2-(2-Quinolinyl)-(E)-ethenyl]phenoxy acetate (8) and 4-[2-(2-Quinolinyl)-(E)-ethenyl]phenoxy acetate (9). The same procedures were used as described in synthesis of compound **7**, but taken from 3-hydroxybenzaldehyde (**4**) and 4-hydroxybenzaldehyde (**5**) to give corresponding product **8** (59%) and **9** (43%).

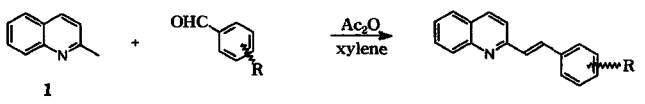
Product 8. m.p. 68°C; IR (KBr disk) ν_{max} 1763, 1594, 1577, 1367, 1206, 825, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H), 7.05 (dd, 2H, 6.7 Hz), 7.35~7.46 (m, 5H) 7.52 (m, 2H, 8.0 Hz), 7.59 (t, 1H, 7 Hz), 7.64 (d, 1H, 8.1 Hz) 8.06 (dd, 1H, 9.5 Hz, 6 Hz); ^{13}C NMR (100 MHz) δ 21.5, 119.6, 120.5, 122.1, 125.2, 126.7, 127.8, 128.1, 129.4, 130.1, 130.2, 130.5, 133.9, 136.9, 138.5, 148.5, 151.5, 155.0, 169.8.

Product 9. m.p. 121~122°C; IR (KBr disk) ν_{max} 1748, 1591, 1506, 1371, 1205, 976, 832, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H), 7.10 (d, 2H, 6.7 Hz), 7.31 (d, 1H, 16.4 Hz) 7.45 (t, 1H, 8.0 Hz), 7.56-7.71 (m, 6H), 8.05 (t, 2H, 8.0 Hz) ; ^{13}C NMR (100 MHz) δ 21.6, 119.7, 122.4 (double intensity), 126.6, 127.8, 127.9 (double intensity), 128.6, 129.6, 129.62, 130.1, 133.7, 134.7, 136.8, 148.7, 151.3, 156.2, 169.7.

Results and Discussion

As described in Scheme 1, the styryl aldehyde **6** was obtained by condensation of 2-methylquinoline[7] with 1,4-benzenedicarboxaldehyde in refluxing xylene in the presence of acetic anhydride.[8] Condensation of 2-methylquinoline with appropriate hydroxybenzaldehyde (**3-5**) in acetic anhydride at evaporated temperature (130°C) afforded corresponding styryl acetates (**7-9**) in 43% to 71% yield after purification.

In this work, 2D-nOe experiments were applied for the determination of configurations. In order to get slow correlation time, DMSO-d_6 was used as a solvent instead of $CDCl_3$. Proton assignments should precede the work of configurations. However, proton signals of quinoline moiety are ranged between 7 ppm and 8 ppm, hence it was difficult to have proton peaks to be assigned without the assistance of 2D NMR experiments. The numbering of the compound **6** was shown in Fig. 1. The first column and the second column of Table 1 showed the chemical shifts of ^{13}C-NMR and multiplicities obtained by DEPT



1

2 R = CHO
3 R = 2-OH
4 R = 3-OH
5 R = 4-OH

6 R = CHO
7 R = 2-OAc
8 R = 3-OAc
9 R = 4-OAc

Scheme 1. The synthesis of compounds 6, 7, 8, and 9.

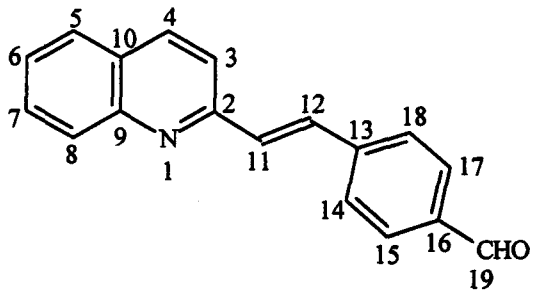


Fig. 1. The structure and numbering of the compound 6.

Table 1. The NMR data and assignments of the compound 6.

δ_c	CH_n DEPT	δ_H of directly attached protons, HMQC	assignments
120.7	d	7.91	3
127.0	d	7.58	7
127.7	s		10
128.2	d	7.95	14, 18
128.3	d	7.94	5
129.3	d	8.03	8
130.4	d	7.77	6
130.5	d	7.95	15, 17
132.4	d	7.65/7.70	4
133.2	d	7.90/7.94	12
136.3	s		16
137.2	d	8.40	11
142.6	s		13
148.1	s		9
155.5	s		2
192.9	d	10.02	19

experiments, respectively. The peaks of 128.2 and 130.5 ppm showed the intensities assigned to C14 and C18, and C15 and C17, respectively. The third column of Table 1 listed the chemical shifts of ^{1}H-NMR determined by HMQC.[9] The peak of 192.9 ppm/10.02 ppm (^{13}C/^{1}H) should be assigned to aldehyde group. Among five quaternary carbons, 127.7 ppm belonged to C10, 155.5 ppm, C2, and 148.1 ppm, C9. In HMQC (Fig. 2), 7.95 ppm of ^{1}H was correlated to C14 and C18 as well as C15 and C 17. Since 7.95 ppm of ^{1}H in HMBC[10] was long-ranged correlated to 142.6 ppm and 136.3 ppm of ^{13}C, these were C13 and C16, respectively (Fig. 3). In HMBC, ^{1}H signal at 8.40 ppm was long-ranged correlated to three carbon signals at 155.5 ppm, 148.1 ppm and 128.2 ppm, which were assigned to C2, C9 and C14, respectively so that the proton peak at 8.40 ppm was assigned to H11. As a result, ^{13}C peak at 137.2 ppm was C11 based on HMQC. 7.91 ppm of H3 was correlated to 7.65 ppm and 7.70 ppm which were attached to ^{13}C at 132.4 ppm, so that the ^{13}C should be C4 (Fig. 4). In addition, 8.40 ppm of H11 was correlated to 7.90 ppm which was attached to ^{13}C at 133.2 ppm, so that the ^{13}C should be C12. The most difficult parts for assignments were C5, C6, C7 and C8, because their ^{13}C peaks were ranged between 127 ppm and 130 ppm as well as their ^{1}H peaks were ranged between 7.5 ppm and 8.0 ppm. This problem was solved with the help of the interpretation of COSY.[11]

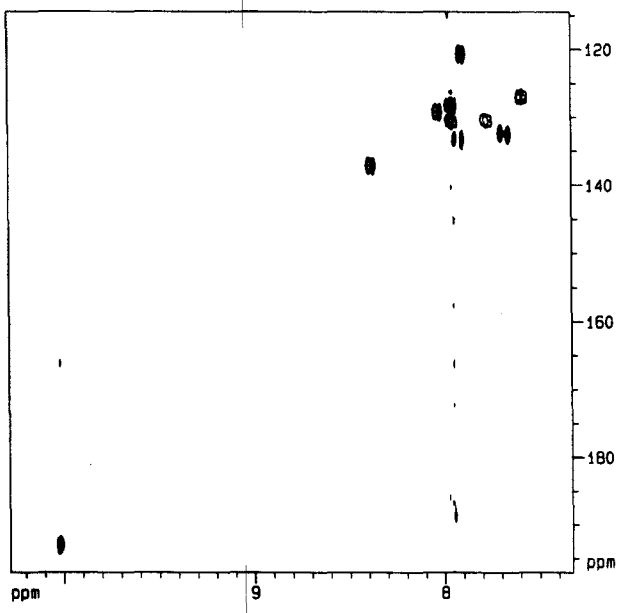


Fig. 2. The Heteronuclear Multiple Quantum Coherence (HMQC) spectrum of the compound 6 dissolved in DMSO-d_6; 2K(t_2) x 256(t_1).

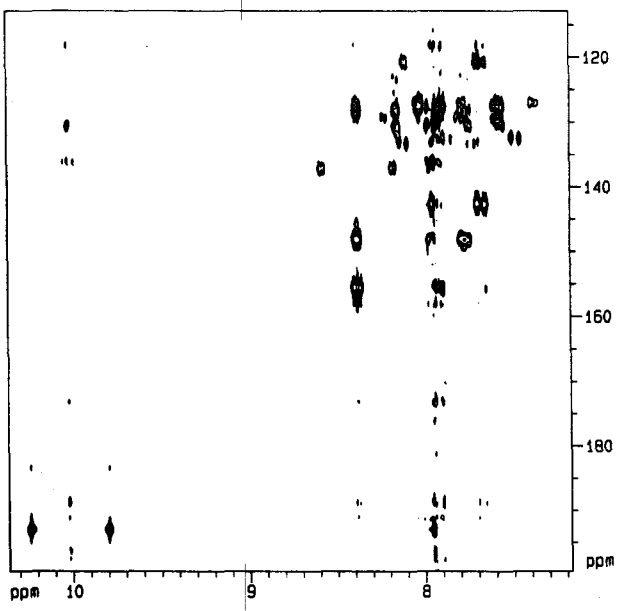


Fig. 3. The Heteronuclear Multiple Bonded Coherence (HMBC) spectrum of the compound 6 dissolved in DMSO-d_6; 2K(t_2) x 256(t_1), long ranged coupling delay=45 msec.

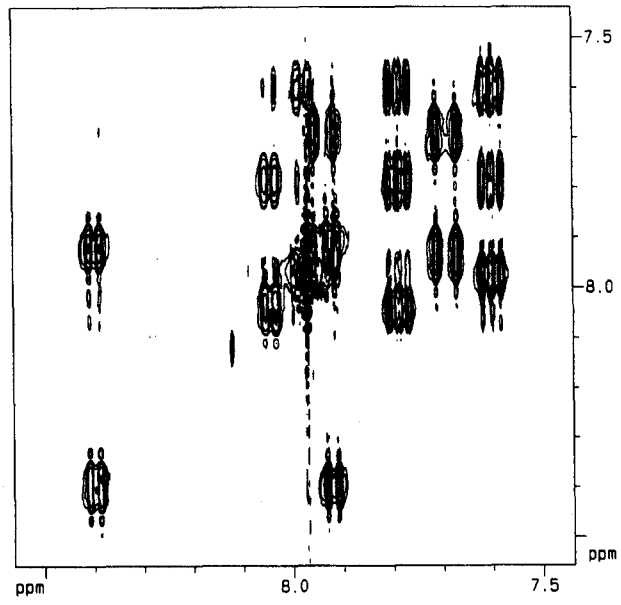


Fig. 4. The Correlated Spectroscopy (COSY) spectrum of the compound 6 dissolved in DMSO-d_6; 2K(t_2) x 256(t_1).

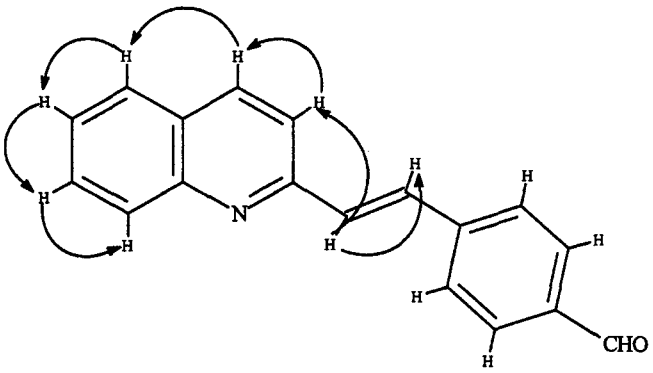


Fig. 5. The proton-correlations of the compound 6 obtained from COSY.

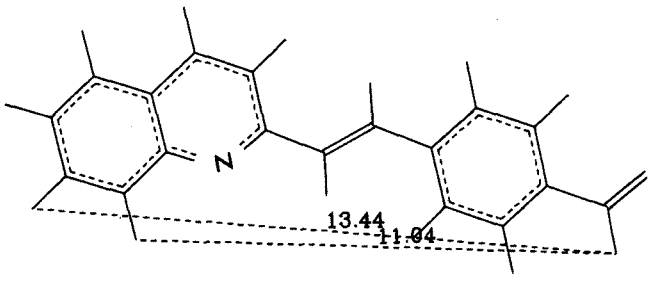


Fig. 6. The trans conformer of the compound 6 obtained from molecular dynamics calculation; Discover(msi), experimental time=100 psec.

The correlations and the partial structure obtained from COSY were shown in Fig. 5. As a result, the total assignments of the compound **6** were listed in the last column of Table 1.

In order to confirm the configuration of the compound **6**, NOESY experiment[12] and Computer Aided Molecular Modeling (CAMM) calculation were carried out. The trans conformer with the low energy obtained from Molecular Dynamic (MD) was shown in Fig. 6. In this conformer, the distance between H19 and H8, and that between H19 and H7 were 11.04Å and 13.44Å, respectively. Their ^{1}H chemical shifts were 10.02 ppm (H19), 8.03 ppm (H8) and 7.58 ppm (H7). Likewise, the cis conformer with the low energy obtained from MD was shown in Fig. 7. The distance between H19 and H8, and that between H19 and H7 were 3.71Å and 4.49Å, respectively. If the compound **6** had a cis configuration, nOe's between H19 and H8, and H19 and H7 should be able to observe in the NOESY spectrum. As shown in Fig. 8, however, no nOe peaks

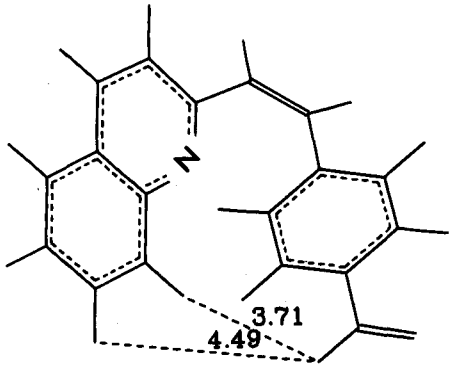


Fig. 7. The cis conformer of the compound 6 obtained from Molecular Dynamics calculation; Discover(msi), experimental time=100 psec.

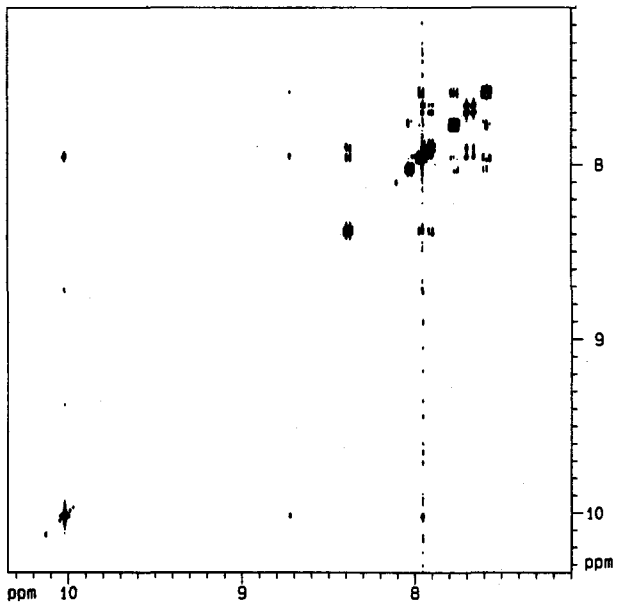


Fig. 8. The Nuclear Overhauser and Exchange Spectroscopy (NOESY) spectrum of the compound 6 dissolved in DMSO-d_6; 2K(t_2) x 256(t_1), mixing time=1 sec.

were observed. Therefore, it could be said that the compound **6** had a trans configuration. In the cases of compounds **7**, **8**, and **9**, aldehyde group of the compound **6** was substituted with acetyl group. The only difference among the three compounds was the position in the phenyl ring. The NOESY experiments and MD calculations of compounds **7**, **8**, and **9** were carried out (supplementary materials). Like the compound **6**, it was determined that these three isomers had a trans configuration.

In conclusion, styrylquinoline derivatives synthesized by condensation of quinaldine and corresponding substituted benzaldehydes, **6**, **7**, **8**, and **9**, had a *trans* configuration.

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