Synthesis of an Antileishmanial Alkaloid Isolated from *Galipea longiflora* and of Related Compounds

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Synthesis of an antileishmanial alkaloid and related compounds by using various epoxide-forming reactions is described.

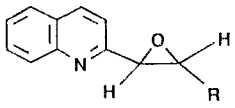
Keywords antileishmanial derivative; stereoselective epoxidation; quinolinic compound

The visceral antileishmanial activity of chimanine D **1a** was recently reported,[1] but the synthesis of this compound or related ones, except for **2a**,[2] has not been described in the literature. It was therefore of interest to synthesize compounds of this kind in order to carry out further biological studies. We first synthesized chimanine D, in racemic form (rans **1a**). The obtained compound has the same NMR spectra as the natural alkaloid and was identical with it. We then prepared the *cis* stereoisomer **1b** and several analogous compounds phenylated **2a** or carbethoxylated **3a** and **4a**. Epoxides can be produced by various kinds of reactions, especially *via* the action of peracids or peroxides[3,4] on a double bond. In our case, the quinolinic nitrogen is a limiting factor owing to formation of an insoluble N-oxide, even under the conditions used successfully in the case of other quinoline derivatives (use of monoperoxyphthalic acid).[5] We used three different methods to obtain the various epoxides in the best possible yields: 1—3 elimination from 1,2-boromohydrins; condensation of sulfur ylides with a carbonyl compound; Darzens reaction.

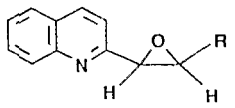
In order to synthesize the epoxides **1a** and **2a**, we used the reaction described by Florio *et al.*,[6] *i.e.*, decomposition of bromohydrins **4** and **5** in alkaline medium. It is not necessary to isolate the intermediate bromohydrins. Alkaline treatment *in situ* leads to the epoxides **1a** and **2a**, with small quantities of the dibromo derivatives **8** and **9**, undoubtedly formed during the reaction by addition of bromine to the double bond.

The *cis* isomer **1b** was obtained by reaction of a sulfur ylide generated from a triethylsulfonium ion on quinoline-2-carboxaldehyde under the conditions described by Brochet *et al.*[7] Changes in the experimental conditions lead to the isolation of epoxide **1b** together with epoxide **1a**. We weakly hydrated the reaction medium, because according to Borredon *et al.*,[8] water acts as a phase transfer agent and initiates the reaction. We used a large excess of potassium hydroxide pellets,[8] and triethylsulfonium tetrafluoroborate instead of triethylsulfonium iodide, because it is less light-sensitive and has a more active counter ion in phase transfer reactions. A similar process has been described, using carbethoxymethylthiolanium bromide,[8] to prepare glycidic epoxides. In our case, no product could be obtained by this method.

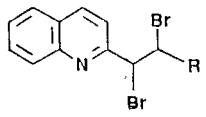
The Darzens reaction is the most general method to synthesize glycidic esters. Treatment of the quinoline-2-carboxaldehyde with ethyl 2-chloroacetate and sodamide or sodium hydroxide gave quinoline-2-methanol as a sole



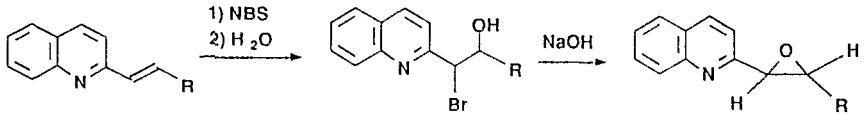
1a : R = CH_3
2a : R = C_6H_5
3a : R = $COOC_2H_5$
4a : R = $COOCH_2COOC_2H_5$



1b : R = CH_3



8 : R = CH_3 (22%)
9 : R = C_6H_5 (4%)



6 : R = CH_3
7 : R = C_6H_5

4 : R = CH_3
5 : R = C_6H_5

1a : R = CH_3 (44%)
2a : R = C_6H_5 (45%)

Chart 1

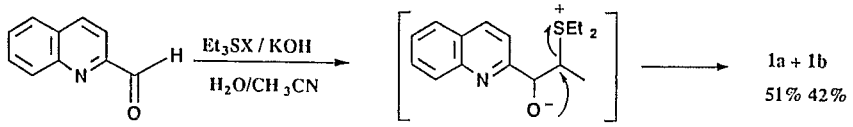


Chart 2

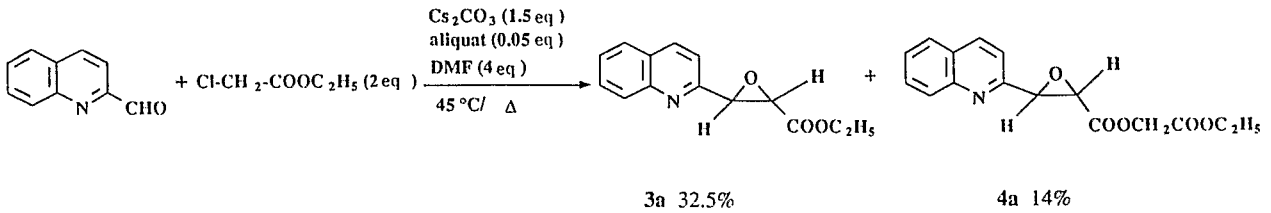


Chart 3

product *via* a Cannizzaro-like oxidation-reduction reaction. To avoid this, we used the phase transfer complex conditions described by Gladiali and Soccolini,[9] but obtained only a 25% yield. We improved this to 47% yield and obtained a better selectivity by using cesium carbonate instead of potassium carbonate and by slowly adding this base and the halide to the mixture. Only the *trans* stereoisomer **3a** was obtained as determined by NMR. The structure of derivative **4a** was verified by ^{1}H-NMR, ^{13}C-NMR and mass spectra. Its formation can be explained by a transesterification between **3a** and ethyl-2-hydroxyacetate formed from ethyl-2-chloroacetate during the isolation of the product.

In conclusion, the use of the above methodologies leads stereoselectively to *trans* epoxides **1a**—**4a**. The *cis* expoxide **1b** is not obtained stereoselectively, but is formed in a better yield than can be obtained with the other methods generally used to obtain *cis* epoxides.

Experimental

Thin layer chromatography was performed on Kieselgel 60 F Merck or Riedel-De Haen. Flash chromatography was done with Merck 9385 40—63 mm or Riedel-De Haen 31607 silica gel. Melting points were determined on Köfler apparatus. Mass spectra were obtained on a V.G 70-70 apparatus and elemental analysis was done on a Perkin Elmer 240 apparatus. ^{1}H-NMR spectra were recorded on a Bruker AC 200 P (200 MHz), in deuterated chloroform, with tetramethylsilane (TMS) used as an internal reference. Chemical shifts were expressed in ppm and coupling constants in Hz.

***trans*-1-(2-Quinolyl)-2-methyloxirane (1a)** *N*-Bromosuccinimide (0.42 g, 2.35 mmol) was added portionwise to a solution of **6** (330 mg, 1.96 mmol) in 12 ml of dioxane and 5 ml of water and the mixture was stirred for 9 h at room temperature. The mixture was poured into water and extracted with diethylether. The organic layer was dried over sodium sulfate and evaporated. The residue was taken up in 10 ml of isopropanol, a few drops of phenolphthalein were added, and the solution was neutralized with a solution of sodium hydroxide (1 M). The solution was diluted with 10 ml of water and the precipitate was extracted three times with ether. The organic layer was dried over sodium sulfate and evaporated, then the residue was chromatographed on silica gel with hexane–ethyl acetate (9 : 1) to give the *trans* epoxide **1a** as a syrup (160 mg, 44%) with a by-product **8** (80 mg, 22%).

1a: ^{1}H-NMR ($CDCl_3$) δ: 1.4 (3H, d, J=5.1 Hz), 3.1 (1H, qd, J_1=1.9 Hz, J_2=5.1 Hz), 3.8 (1H, d, J=1.9 Hz), 7.1 (1H, d), 7.4 (1H, m), 7.5—7.6 (2H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.98; N, 7.56. Found: C, 77.69; H, 5.88; N, 7.49.

8: ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, d, J=6.5 Hz), 5.0 (1H, qd, J_1=10.5 Hz, J_2=6.5 Hz), 5.3 (1H, d, J=10.5 Hz), 7.5 (2H, M), 7.7—7.9 (2H, M), 8.1—8.2 (2H, M).

***trans*-1-(2-Quinolyl)-2-phenyloxirane (2a)** From 1.04 g of **7** (4.5 mmol), the same procedure afforded **2a** (510 mg, 45%), mp 64 °C and the by-product **9** (70 mg, 4%).

2a: ^{1}H-NMR ($CDCl_3$) δ: 4.0 (1H, d, J=1.85 Hz), 4.2 (1H, d, J=1.85 Hz), 7.1—7.4 (7H, m), 7.5—7.7 (2H, m), 8.0 (2H, d). *Anal.* Calcd for $C_{17}H_{13}NO$: C, 82.56; H, 5.30; N, 5.66. Found: C, 82.60; H, 5.45; N, 5.67.

9: ^{1}H-NMR ($CDCl_3$) δ: 5.8 (1H, d, J=11.5 Hz), 6.0 (1H, d, J=11.5 Hz), 7.3—7.9 (7H, m), 8.1—8.3 (2H, m). *Anal.* Calcd for $C_{17}H_{13}Br_2N$: C, 52.21; H, 3.35; N, 3.58. Found: C, 52.74; H, 3.68; N, 3.44.

***trans*-1-(2-Quinolyl)-2-methyloxirane 1a and *cis*-1-(2-Quinolyl)-2-methyloxirane (1b)** A mixture of triethylsulfonium iodide (1.61 g, 6.54 mmol), potassium hydroxide pellets (2.6 g, 7 eq), 13 ml of acetonitrile and 0.1 ml of water was warmed at 60 °C for 15 min in the absence of light. A solution of of quinoline-2-carboxaldehyde (1.03 g, 1 eq) in 13 ml of acetonitrile was then added and the mixture was stirred at 60 °C for 6 h. The mixture was filtered and the solid was extracted with acetonitrile, then with dichloromethane. The organic layers were dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel with hexane–ethyl acetate (8 : 2). The first eluted product was the *trans* epoxide **1a** as a syrup (260 mg, 22%) and the second product was the *cis* epoxide **1b** (230 mg, 19%), syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.0 (3H, d, J=5.6 Hz), 3.3 (1H, qd, J_1=4.5 Hz, J_2=5.6 Hz), 4.2 (1H, d, J=4.5 Hz), 7.2—7.4 (2H, m), 7.5—7.6 (2H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.98, N, 7.56. Found: C, 77.61; H, 6.13; N, 7.60.

When triethylsulfonium tetrafluoroborate was used instead of the iodide, the reaction was completed after 1.5 h and the yields were 51% for **1a** and 42% for **1b**.

***trans*-Ethyl-3-(2-quinolyl)gycidate 3a and *trans*-Carbethoxymethyl-3-(2-quinolyl)gycidate (4a)** Aliquat (80 mg, 0.2 mmol) and ethyl chloroacetate (0.6 ml, 4.8 mmol) were added to a solution of quinoline-2-carboxaldehyde (628 mg, 4 mmol) in anhydrous dimethylformamide (DMF, 3 ml) under argon. Under stirring, 400 mg of cesium carbonate was added and the mixture was warmed to 45—50 °C. Every 15 min, new portions of 400 mg of cesium carbonate were added until 1.6 g (*ca.* 5 mmol). The mixture was stirred for 2 h and 0.2 ml of ethyl chloroacetate and 200 mg of cesium carbonate were added again. After 4 h, the mixture was poured into 5 ml of water and extracted with ether. The ethereal extracts were washed with water, dried (sodium sulfate) and evaporated. Reaction products were isolated by chromatography on silica gel with petroleum ether–ethyl acetate (8 : 2) to give the quinoline-2-carboxaldehyde (300 mg, 48%), **3a** as a syrup (316 mg, 32.5%) and **4a** (137 mg, 14%) as a syrup.

3a: ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, t), 3.7 (1H, d, J=1.6 Hz), 4.28 (2H, ddq), 4.4 (1H, d, J=1.6 Hz), 7.3 (1H, d), 7.55 (1H, dt), 7.75 (2H, m), 8.05 (1H, d), 8.15 (1H, d). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76. Found: C, 68.94; H, 5.58; N, 5.61.

4a: ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, t), 3.9 (1H, d, J=1.7 Hz), 4.25 (2H, q), 4.5 (1H, d, J=1.7 Hz), 4.8 (2H, dd, J=15 Hz), 7.3 (1H, d), 7.55 (1H, dt), 7.6—7.9 (2H, m), 8.05 (1H, d), 8.15 (1H, d). MS: MH^+ (NH_3): 302; EI-MS *m/z*: 256, 198, 170, 158, 142, 128, 115.

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References and Notes

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