Chemical Transformations of Abundant Natural Products. 3.[1a] Modifications of Eremanthin Leading to Other Naturally Occurring Guaianolides[1b]

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Several selective modifications of eremanthin (1) were achieved. Reaction of the epoxide **2** with equimolar amounts of BF_3·Et_2O gave mainly the aldehyde **4**. On the other hand, treatment of **2** with HCl gave a mixture of chlorohydrins **5** (55%) and **6** (45%). Dehydration of **5**, followed by dechlorination of the resulting product **7**, gave **8**. This latter compound was shown to be identical with dehydrocostus lactone. In addition, reaction of **1** with excess BF_3·Et_2O yielded isoeremanthin (**9**), which upon treatment with *N*-bromosuccinimide in dioxane–water gave the dibromo ether **10**.

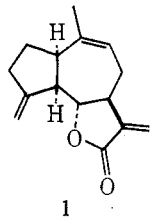
The interesting biological properties of sesquiterpene lactones[2] and the possibility that they could represent a lead in the search for new tumor inhibitors has stimulated many research groups to develop total syntheses for some of the most promising members of this group of compounds.[3]

In this Center the search for plant-derived inhibitors against infection by cercariae of *Schistosoma mansoni* led to the isolation and characterization of eremanthin (**1**) from *Eremanthus elaeagnus*.[4,5] The relative abundance of this latter compound made it possible to start a program of chemical modifications of **1** as an alternative route to the synthetic approach for the obtention of other biologically active derivatives. In addition, selective transformations of **1** could also provide an entry to the partial synthesis of less abundant, and sometimes not well characterized, naturally occurring lactones.

In this paper we report the synthesis of several derivatives of **1**, including dehydrocostus lactone.

Results and Discussion

We have briefly reported that treatment of the epoxide **2** with excess BF_3·Et_2O gives the aldehyde **3**.[5] We have now found that isomerization of the exocyclic double bond at the five-membered ring can be prevented by using equimolar amounts of BF_3·Et_2O. In this manner compound **4** could be obtained selectively.



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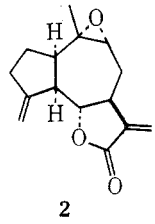

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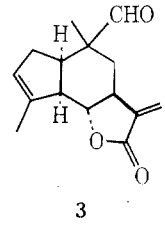

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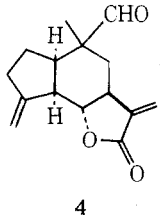

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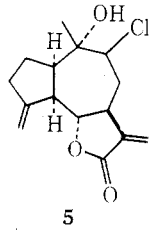

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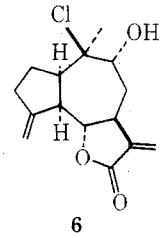

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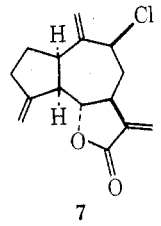
Ring contraction to give **4** without double bond migration could be easily determined by ^1H NMR spectroscopy. A sharp singlet at δ 9.45 could be attributed to the aldehyde function, consistent with the presence of a three-proton singlet at δ 1.13 assigned to the quaternary C_{10}–CH_3. Two typical broad singlets at δ 5.03 and 5.17 assured the presence of the exocyclic nonconjugated double bond whereas the unmistakable doublets at δ 5.44 and 6.10 (J = 3.5 Hz) demonstrated the presence of the conjugated α-methylene group. These features were also corroborated by the IR spectrum which showed characteristic bands at 2740 and 1724 cm^{-1} attributed to the aldehyde function. A strong band at 890 cm^{-1} further supported the exocyclic nonconjugated double bond. The molecular formula was supported by the mass spectrum which showed besides the parent peak at m/e 246 fragments at m/e 218 ($M^+ - 28$) and m/e 217 ($M^+ - 29$) characteristic of the aldehyde group.

On the other hand when **2** was treated with HCl in THF at room temperature, two chlorohydrins could be isolated. These were identified as **5** (55%) and **6** (45%). Both isomers showed spectral properties in complete agreement with the proposed structures. In particular, the ^1H NMR spectrum of **5** showed the C_{10}–CH_3 at δ 1.12 while H-9 appeared as a double doublet centered at δ ~4.10. The corresponding signals in **6** appeared at δ 1.69 and 4.09. Further comparison between the ^1H NMR spectrum of **5** and **6** showed their H-6 at δ 4.22 and 4.70, respectively. This difference in chemical shift in H-6 is attributed to field effects caused by a β-oriented electronegative substituent at C_{10} and has been found to be of great value in determining the stereochemistry of addition reactions at the 9,10 double bond.[6] Additional support for the trans nature of the halohydrins **5** and **6** was obtained by transforming a mixture of them into **2** by reaction with Na_2CO_3 in MeOH.

The facile conversion of **2** into **5** provided an entry toward the syntheses of other naturally occurring guaianolides. Thus, treatment of **5** with a mixture of thionyl chloride and pyridine[7] at −8 °C gave 85% yield of **7**. The structure of **7** was strongly



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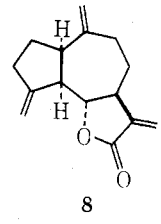

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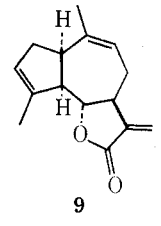

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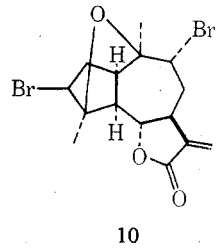

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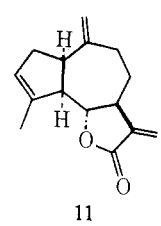

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supported by physical methods. In the IR spectrum a band at ~890 cm^{-1} appeared much stronger than the corresponding band in any of the previously discussed compounds. The ^1H NMR spectrum clearly indicated the dehydration reaction as proposed. Thus, the methyl group at δ 1.12 disappeared and a new pair of well-separated signals associated with the newly formed exocyclic methylene group appeared at δ 5.08 and 5.60. Dechlorination of **7** by treatment with Zn in MeOH gave **8** in about 80% yield. The absence of C_9–Cl was easily determined by inspection of the ^1H NMR spectrum which showed the signals associated to the C_{10}=CH_2 group at δ 4.83 and 4.91, 0.25 and 0.69 ppm upfield from the corresponding signals in **7**.

The structure of **8** as depicted is the same as that proposed for dehydrocostus lactone.[8] Comparison of our data with those for this latter compound[8,9] (optical rotation and ^1H NMR spectrum) confirms that both compounds are identical.[10] Since the sequence of reactions leading to **8** from **1** would hardly result in epimerization at the chiral centers, the absolute configuration at C_1, C_5, C_6, and C_7 in dehydrocostus lactone would thus be established as being identical to those found for **1**.[5]

It was shown at the beginning that ring contraction of **2** with 4,14 double-bond isomerization depended on using an excess of BF_3·Et_2O. This finding suggested that **1** and **8** could be isomerized to their corresponding $\Delta^{3,4}$ isomers. In fact, when **1** was allowed to react with excess of BF_3·Et_2O in dry benzene ar room temperature, a smooth conversion to isoeremanthin (**9**) took place.[11,12] Spectral data strongly support the double-bond migration as indicated. In the IR spectrum, the characteristic exocyclic double-bond absorption at ~890 cm^{-1} was absent whereas the band at ~811 cm^{-1}, typical of trisubstituted double bond, increased in intensity. The absorptions at 1754 and 1661 cm^{-1} typical of the α-methylene-γ-lactone group were intact. The mass spectrum of **9** was almost identical to that of **1** and the molecular ion at *m/e* 230 supported its molecular formula. In the ^1H NMR spectrum the signals at δ 5.08 and 5.25, attributed to the exocyclic double bond at C_4 in **1**, were substituted by a new methyl at δ 1.95 long-range coupled with an additional vinylic proton located at δ 5.50. That isomerization of **1** to **9** did not result in change of the configuration at C_1 or C_5 was firmly demonstrated by the formation of the dibromo ether **10** when **9** was allowed to react with NBS in a mixture of dioxane–H_2O. Here again, the structure of **10** was easily determined by ^1H NMR spectroscopy. The ether linkage between C_4 and C_{10} determined both methyl groups to appear at δ 1.59 whereas the signals corresponding to H-3 and H-9 appeared at δ 4.10 and 4.24, respectively.

The utilization of **9** in the partial synthesis of eregoyazin and eregoyazidin, two new guaianolides isolated from *Eremanthus goyazensis*, is described in a following paper.

Initial evaluation of the cercaricidal activities of some of the compounds under study showed that **9** is the most active of the derivatives of **1** so far studied.[13]

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were run as KBr pellets on a Perkin-Elmer 137-B spectrophotometer. ^1H NMR spectra of $CDCl_3$ solutions using Me_4Si as internal standard were recorded on a Varian XL-100 instrument. Mass spectra were obtained at 70 eV on a Varian-Mat CH-5 spectrometer. Silica gel GF_{254}, PF_{254}, and Kieselgel 60 were used for TLC, preparative TLC, and column chromatography, respectively. Microanalyses were performed by Alfred Bernhardt, West Germany.

Reaction of Eremanthin 9,10-α-Epoxide (2) with BF_3·Et_2O. Epoxide **2** (0.100 g, 0.408 mmol) was dissolved in benzene (6 mL) and the solution was frozen at −5 °C. Recently distilled BF_3·Et_2O (0.1 mL, 0.408 mmol) was added and the mixture was allowed to reach 10 °C slowly (~3 h). The mixture was then diluted with EtOAc (25 mL), washed with 5% aqueous $NaHCO_3$ (3 × 20 mL) and H_2O (3 × 20 ml), and concentrated in vacuo to give an oily residue which was purified by preparative TLC using hexane–EtOAc (7:3) as eluent. The main product (R_f 0.32) was eluted giving 0.050 g (50%) of **4**: mp 102–104 °C; IR 2740, 1754, 1724, 1667, 890 cm^{-1}; ^1H NMR δ 1.13 (s, 3, C_{10}–CH_3), 3.56 (t, 1, J = 10 Hz, H-6), 5.03 and 5.17 (narrow m, 1 each, C_4=CH_2), 5.44 and 6.10 (d, 1 each, J = 3.5 Hz, C_{11}=CH_2), 9.45 (s, 1, C_{10}–CHO); mass spectrum *m/e* (rel intensity) 246 (M^+, 15), 228 (10), 218 (30), 217 (17), 80 (100). Anal. Calcd for $C_{15}H_{18}O_3$: M^+, 246.1255. Found: M^+, 246.1293. A small amount of **3**[5] (R_f 0.38, <10%) could also be detected on the preparative TLC.

Reaction of Eremanthin 9,10-α-Epoxide (2) with HCl. Epoxide **2** (1.878 g, 7.634 mmol) was dissolved in THF (10 mL) and the solution was stirred and cooled at ~0 °C. Concentrated HCl was then added (37%, 0.7 mL, 8 mmol) and the stirring was continued for 30 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue (2.0 g, 88%) was purified by column chromatography using a gradient of CH_2Cl_2 in hexane as eluant to give 1.031 g (48%) of **5** and 0.852 g (39.7%) of **6**. **5**: mp 152–154 °C; IR 3540, 1755, 1650, 1250, 890 cm^{-1}; ^1H NMR δ 1.12 (s, 3, C_{10}–CH_3), 4.10 (dd, 1, J = 5 and 12 Hz, H-9), 4.22 (t, 1, J = 9.5 Hz, H-6), 5.00 and 5.16 (narrow m, 1 each, C_4=CH_2), 5.60 and 6.30 (d, 1 each, J = 3 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 284 (M^+, 2), 282 (M^+, 6), 266 (2), 264 (6), 229 (14), 131 (16), 107 (30), 93 (33), 81 (37), 43 (100). Anal. Calcd for $C_{15}H_{19}{}^{35}ClO_3$: M^+, 282.1022. Found: M^+, 282.0996. **6**: mp 142–144 °C; IR 3450, 1760, 1660, 1265, 885 cm^{-1}; ^1H NMR δ 1.69 (s, 3, C_{10}–CH_3), 4.09 (broad t, 1, H-9), 4.70 (t, 1, J = 9 Hz, H-6), 4.95 and 5.15 (narrow m, 1 each, C_4=CH_2), 5.50 and 6.22 (d, 1 each, J = 3 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 284 (M^+, 5), 282 (M^+, 15), 246 (5), 230 (14), 133 (24), 107 (64), 51 (58), 80 (64), 53 (100). Anal. Calcd for $C_{15}H_{19}{}^{35}ClO_3$: M^+, 282.1022. Found: M^+, 282.0949. A mixture of **5** and **6** (0.04 g) was dissolved in MeOH (5 mL) and Na_2CO_3 (~0.050 g) was added. After ~10 h at room temperature with vigorous stirring, the product was isolated and shown to be identical (TLC, ^1H NMR) with **2**.

Reaction of 9-β-chloro-10-α-hydroxyl Eremanthin (5) with $SOCl_2$/Pyridine. A solution of compound **5** (1.072 g, 3.78 mmol) in pyridine (~1 ml) was cooled to ~8 °C and a mixture of $SOCl_2$/pyridine (6 mL of a mixture prepared by mixing 9.5 mL of pyridine and 0.5 mL of $SOCl_2$) was added. After 5 min, CH_2Cl_2 (~50 mL) was added and the resulting mixture was washed with water (3 × 30 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a residue (~1.030 g) which was purified by column chromatography to give 0.842 g (85%) of **7**: mp 128–130 °C; IR 1755, 1645, 1242, 890 cm^{-1}; ^1H NMR δ 3.97 (t, 1, J = 9.5 Hz, H-6), 4.44 (dd, 1, J = 4.5 and 12 Hz, H-9), 5.08 and 5.60 (broad s, 1 each, C_{10}=CH_2), 5.10 and 5.27 (narrow m, 1 each, C_4=CH_2), 5.56 and 6.28 (d, 1 each, J = 3.5 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 266 (M^+, 6), 264 (M^+, 21), 230 (16), 229 (16), 149 (25), 105 (31), 91 (76), 80 (100), 53 (70), 39 (73). Anal. Calcd for $C_{15}H_{17}{}^{35}ClO_2$: M^+, 264.0917. Found: M^+, 264.0896.

Reaction of 7 with Zn. Compound **7** (0.8 g, 3.03 mmol) was dissolved in MeOH (15 mL) containing AcOH (0.1 mL) and Zn dust was added (2.0 g). The mixture was vigorously stirred at room temperature for 72 h. It was then filtered and the precipitate was washed with AcOEt (25 mL). The solvent was removed in vacuo and the residue (0.625 g) was purified by column chromatography to give 0.56 g (80%) of **8** as an oil which did not crystallize: $[\alpha]^{30}D$ −12.2 (*c*, 0.33, $CHCl_3$); IR (film) 1760, 1640, 1250, 890 cm^{-1}; ^1H NMR δ 3.96 (t, 1, J = 9 Hz, H-6), 4.83 and 4.91 (broad s, 1 each, J = 3 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 230 (M^+, 48), 150 (50), 105 (65), 81 (53), 80 (100), 77 (66), 53 (57), 44 (75), 41 (78), 39 (85). Anal. Calcd for $C_{15}H_{18}O_2$: M^+, 230.1306. Found: M^+, 230.1342

Reaction of Eremanthin (1) with BF_3·Et_2O. Synthesis of Isoeremanthin (9). A solution of **1** (0.50 g, 0.218 mmol) was dissolved in benzene (4 mL) and recently distilled BF_3·Et_2O (0.1 mL, 0.408 mmol) was added. The mixture was stirred for 4 h at room temperature, diluted with AcOEt (20 mL), washed with 5% aqueous $NaHCO_3$ (2 × 20 mL) and H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC to give 0.026 g (52%) of **9**: mp 71–73 °C; IR 1754, 1661, 811 cm^{-1}; ^1H NMR δ 1.81 (broad s, 3, C_{10}–CH_3) 1.95 (broad s, 3, C_4–CH_3), 4.03 (dd, 1, J = 9 and 11 Hz, H-6), 5.50 (m, 2, H-3 + H-9), 5.48 and 6.17 (d, 1 each, J = 3.5 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 230 (M^+, 16), 215 (3), 150 (100), 122 (22), 119 (20), 91 (30), 80 (25). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.30; H, 7.80. Found: C, 78.12; H, 7.65. We have repeated this reaction many times in up to 5 g scale obtaining yields ranging from 65 to 80%. When the reaction is run in more than 0.5 g scale better yields

have been obtained using a 4-mol excess of $BF_3 \cdot Et_2O$ and allowing the reaction to proceed for ~30 h at room temperature.

Reaction of 9 with *N*-Bromosuccinimide. A solution of **9** (0.09 g, 0.38 mmol) in dioxane–H_2O (8/2) was frozen at −30 °C and NBS (0.14 g, 0.76 mmol) was added. The reaction was then allowed to reach room temperature (4 h) and the mixture was diluted with AcOEt and washed with H_2O (2 × 50 mL), the resulting organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by preparative TLC to give 0.014 g (9.1%) of **10:** IR 1754, 1653 cm^{-1}; ^1H NMR δ 1.59 (s, 6, C_{10}–CH_3 + C_4–CH_3), 4.01 to 4.10 (m, 2, H-3 + H-6), 4.24 (t, 1, J = 3 Hz, H-9), 5.49 and 6.18 (d, 1 each, J = 3.5 Hz, C_{11}=CH_2); mass spectrum m/e (rel intensity) 404 (M^+, 1) 406 (M^+, 2), 408 (M^+, 1), 387 (1), 389 (3), 391 (1), 325 (6), 327 (8), 57 (100). Anal. Calcd for $C_{15}H_{18}{}^{79}BrO_3$: M^+ − Br, 325.0439. Found: M^+ − Br, 325.0483. Anal. Calcd for $C_{15}H_{18}{}^{81}BrO_3$: M^+ − Br, 327.0419. Found: M^+ − Br, 327.0492.

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Registry No.—**1,** 37936-58-6; **2,** 38963-61-0; **4,** 63832-99-5; **5,** 63833-00-1; **6,** 63833-01-2; **7,** 63833-02-3; **8,** 477-43-0; **9,** 63569-76-6; **10,** 63833-03-4.

References and Notes

(1) (a) Part 2 is *Tetrahedron Lett.*, 4535 (1975); (b) Taken in part from the M. S. Theses of Marcos Garcia, NPPN-UFRJ, 1975, and Lélio A. Maçaira, NPPN-UFRJ, in preparation.
(2) For a recent review covering some of the most important biological activities shown by sesquiterpene lactones, see: E. Rodriguez, G. H. N. Towers, and J. C. Mitchell, *Phytochemistry,* **15,** 1573 (1976).
(3) (a) For a review of α-methylenelactone syntheses, see (a) P. A. Grieco, *Synthesis,* 67 (1975); (b) S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *J. Am. Chem. Soc.,* **98,** 3028 (1976); (c) P. A. Grieco, J. A. Noguez, and Y. Masaki, *J. Org. Chem.,* **42,** 495 (1977); (d) P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, M. Nishizawa, A. Rosowsky, S. Oppenheim, and H. Lazarus, *J. Med. Chem.,* **20,** 71 (1977), and references cited therein.
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(6) In addition, we have found that for a given pair of α- and β-oriented electronegative groups at C_4 and/or C_{10}, only the β-oriented isomer causes a marked downfield shift for H-6. These include: hydroxyl groups, epoxides, halohydrins, and dibromides. M. Garcia, F. Welbaneide L. Machado, L. A. Maçaira, and J. A. Rabi, unpublished observations. The following paper in this series includes δ values of H-6 for a number of bromo derivatives showing the utility of this effect in determining the stereochemistry of bromine addition to **9**.
(7) A. Corbella, P. Gariboldi, G. Jommi, and G. Ferrari, *Phytochemistry,* **13,** 459 (1974).
(8) S. B. Mathur, S. V. Hiremath, G. H. Kulkarni, G. R. Kelkar, S. C. Bhattacharyya, D. Simonovic, and A. S. Rao, *Tetrahedron,* **21,** 3575 (1965).
(9) M. Romanuk, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.,* **21,** 894 (1976); *Chem. Abstr.,* **50,** 9344f (1956).
(10) There are a few minor differences between our rotation and NMR data and those reported for dehydrocostus lactone in ref 8 and 9. However, direct comparison of our TLC, IR, and ^1H NMR data with those obtained on an authentic sample of dehydrocostus lactone kindly supplied by Dr. S. C. Bhattacharyya (Bombay) establishes that the two samples are identical.
(11) Isoeremanthin (**9**) seems to be a powerful allergen having caused allergic contact dermatitis in some workers of this laboratory.
(12) In a similar manner **8** has been isomerized to **11** which has been converted to a compound showing similar properties with estafiatin [J. Romo, and F. Sanchez-Viesca, *Tetrahedron,* **19,** 1285 (1963)]. Estafiatin possess a 1,5-cis-fused gualane skeleton. J. Romo, private communication.
(13) J. C. Holanda, M. Garcia, and J. A. Rabi, unpublished observations.

Syntheses of Nitrogen-Containing Heterocyclic Compounds. 26.[1] Reaction of Benzo[*f* or *h*]quinolines and Their *N*-Oxides with Methylsulfinyl Carbanion

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Benzo[*h*]quinoline (**1**) and its methyl derivatives were synthesized by the modified Skraup reaction of 1-naphthylamines with glycerol, crotonaldehyde, or methyl vinyl ketone, in the presence of Sulfo-mix, ferrous sulfate, and boric acid. 1 or benzo[*f*]quinoline (**8**) was treated with dimethyl sulfoxide in the presence of sodium hydride at 70 °C to give methylated products. When benzo[*h* or *f*]quinoline *N*-oxide (**6** or **11**) was treated with methylsulfinyl carbanion in the usual procedure, a new reaction took place to produce phenanthrene (**7**) in excellent yield, whereas in the presence of potassium *tert*-butoxide only the methylated product was obtained. Reaction conditions of **6** with methylsulfinyl carbanion or deuterated methylsulfinyl carbanion and substituent effects were examined.

Reaction of quinolines, isoquinolines,[2] and their *N*-oxides[3] with methylsulfinyl carbanion has already been reported, and the products were all methylated compounds. We have also carried out methylation of 1,*X*-naphthyridines (*X* = 5, 6, 7, and 8) with methylsulfinyl carbanion.[4] In the present work, reaction of benzo[*h*]quinoline and its *N*-oxide with methylsulfinyl carbanion was carried out in order to examine the difference, if any, in reactivity between the parent ring and the *N*-oxide. We have found that the *N*-oxide and methylsulfinyl carbanion undergo an entirely different reaction.

Results and Discussion

To identify the methylated derivatives expected from methylation of benzo[*h*]quinoline, syntheses of the starting benzo[*h*]quinoline and its methylated derivatives were carried out by a modified Skraup reaction.[5] Glycerol, crotonaldehyde, and methyl vinyl ketone were reacted with 1-naphthylamine, in the presence of Sulfo-mix,[6] ferrous sulfate, and boric acid; and benzo[*h*]quinoline[7] (**1**), 2-methylbenzo[*h*]quinoline[8] (**2**), and 4-methylbenzo[*h*]quinoline[9] (**3**) were obtained in a respective yield of 50, 36, and 36%. 6-Methylbenzo[*h*]quinoline[10] (**4**) was obtained in a low yield of 15% by the application of glycerol to 4-methyl-1-naphthylamine[11] by the modified Skraup reaction. Compound **1** has been obtained by the usual Skraup reaction in 45% yield. There are several methods for the synthesis of **2,** such as the Doebner–Miller reaction of 1-naphthylamine[8a] and from acetylene and ethanol.[8b] Compound **3** has been synthesized using 1-naphthylamine and 1,3-dichloro-2,3-butene[9a] or 1-naphthylamine and ethyl acetoacetate.[9b] These synthetic methods for **2** and **3** are all complicated, and our procedure provides a better method.

The compounds synthesized were identified by mixture melting point determination with the samples obtained by the method in the literature[7,8a,9a,10] for **1**–**4,** by comparison of IR