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Reaction of Guaioxide with *N*-Bromosuccinimide and the Preparation of 4,6-Guaiadien-3-one and 1-Epi-4,6-guaiadien-3-one[1]

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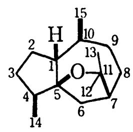
Synopsis. Treatment of guaioxide with *N*-bromosuccinimide gave 4-bromoguaioxide, which was dehydrobrominated to yield 3-dehydroguaioxide. The olefin was then converted into 8-deoxytorilolone and 8-deoxy-1-epitorilolone by the known procedures. Dehydration of these deoxy derivatives in benzene in the presence of *p*-toluenesulfonic acid gave 4,6-guaiadien-3-one and 1-epi-4,6-guaiadien-3-one, respectively.

Guaioxide (**1**; $C_{15}H_{26}O$)[2] was isolated from guaiac wood oil as a minor constituent, and also obtained by acid-catalyzed cyclization of guaiol.[2,3] Because of the absence of hydrogen on the two carbons attached to an ether oxygen atom, the sesquiterpene ether (guaioxide) is particularly inert towards common chemical reagents. By the microbial oxidation technique, hydroxyl groups were successfully introduced to the molecule. This led to the elucidation of the structure of guaioxide (**1**).[4] In this paper we wish to report on the introduction of a functional group into guaioxide by chemical method. The reaction of guaioxide (**1**) with *N*-bromosuccinimide (NBS) gave a monobromide (**2**) which in turn afforded an olefin (**3**). Conversion of **3** into two diastereomeric $\alpha,\beta:\gamma,\delta$-unsaturated ketones (**4** and **5**) is also described.

Friedelane reacts with NBS or bromine to give friedel-18-ene which may be formed *via* 18-bromofriedelane.[5] When guaioxide (**1**) was treated with 1—1.2 mol equivalent of NBS in carbon tetrachloride under reflux, a monobromide (**2**) and an olefin (**3**) were obtained in isolation yields 3—10% and 5—15%, respectively.[6] Bromide (**2**) was heated under reflux with potassium hydroxide in ethanol to give the same olefin (**3**) in 45—65% yield which was found to be identical with 3-dehydroguaioxide (**3**).[4] This shows that the bromination of **1** took place on $C_{(4)}$ to give **2**. Bromination of **1** in carbon tetrachloride with a large excess of NBS or bromine resulted in the formation of a complex mixture of reaction products, separation of which was unsuccessful.



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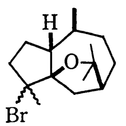

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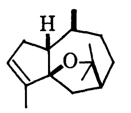

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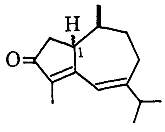

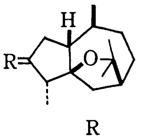

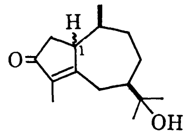

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4 1β-H **6** β-OH, α-H **8** 1β-H

5 1α-H **7** O **9** 1α-H

By the known procedures,[4] olefin (**3**) was converted *via* 3β-hydroxyliguloxide (**6**)[4,7] and 3-oxoliguloxide (**7**), into a hydroxy α,β-unsaturated ketone (**8**; 8-deoxytorilolone), which isomerized into a diastereomeric hydroxy α,β-unsaturated ketone (**9**; 8-deoxy-1-epitorilolone).[4] These hydroxy unsaturated ketones (**8** and **9**) were dehydrated to give 4,6-guaiadien-3-one (**4**) and 1-epi-4,6-guaiadien-3-one (**5**), respectively, in a quantitative yield, by refluxing with *p*-toluenesulfonic acid in benzene. When **4** was heated under reflux with methanolic potassium hydroxide, no isomerization detectable by NMR measurement took place, while more than 90% of **5** isomerized into **4** by the same treatment.[8] In the NMR spectra, the $C_{(10)}$-methyl signal of **5** appears at a fairly higher field (δ 0.73) as compared with the corresponding signal (δ 1.06) of **4**. This suggests that the $C_{(10)}$-methyl of **5** is shielded by π-electron cloud of the $\alpha,\beta:\gamma,\delta$-unsaturated ketone moiety. This is in line with the UV spectra of **4** and **5** which show that the molecular extinction coefficient (ε) at 293 nm of **5** is smaller by *ca.* 20% than that of **4**.

Experimental

IR and UV spectra were measured with a Hitachi EPI-G2 spectrometer and a Hitachi 340 spectrophotometer, respectively, ^{1}H-NMR spectra with a Varian EM-390 (90 MHz) or a Hitachi R-20B (60 MHz) spectrometer in deuteriochloroform solution containing tetramethylsilane as an internal standard, single-focus mass spectra with a Hitachi RMU-6-Tokugata mass spectrometer, and double-focus mass spectra with a JEOL D-300, with direct inlet system operating at 70 eV. Measurements of optical rotation were carried out with a JASCO polarimeter DIP-SL. CD spectra were taken on a JASCO model J-20. For column chromatography Wakogel C-200 (Wako Pure Chemical Industries) was used. Thin-layer chromatography (TLC) was carried out on Kieselgel GF_{254} (E. Merck, Darmstadt) in 0.25 mm thickness. Vapor-phase chromatographic (VPC) analyses were performed on a Shimadzu gas chromatograph model GC-6A.

Bromination of Guaioxide (1) with NBS. NBS (3.32 g; 18.7 mmol) was added to a solution of guaioxide (**1**; 4.00 g; 18.0 mmol) in carbon tetrachloride (20 ml), and the mixture was heated under reflux for 1.5 h by means of an infrared lamp. The reaction mixture was then cooled and filtered. The solvent was removed under reduced pressure to give a residue which was chromatographed on a column of silica gel. Elution with petroleum ether–benzene (4: 1) gave a *ca.* 1: 1 mixture (800 mg) of 4-bromoguaioxide (**2**) and unchanged guaioxide (**1**). Though **2** decomposed easily on contact with silica gel, a small amount of **2** was isolated from the mixture of **1** and **2** by rechromatography. 4-Bromoguaioxide (**2**): an oil, $[\alpha]_D^{22}$ +1.4° (*c* 3.25; EtOH); IR (film): 1140, 1060, 875, 800, and 740 cm^{-1}; NMR ($CDCl_3$); δ 0.85—0.95 (3H, diffused d; $C_{(10)}-CH_3$), δ 1.32, 1.34 (each 3H, s; $C_{(11)}-(CH_3)_2$), and δ 1.88 (3H, s; $C_{(4)}-CH_3$); MS: *m/e* 302 and 300 (relative abundance, each 2%; M^+), *m/e* 287 and 285 [each 20%; $(M-CH_3)^+$], *m/e* 221 [25%; $(M-Br)^+$], and 205 [100%, $(C_{14}H_{21}O)^+$]. Found: *m/e* 302.1075. Calcd for $C_{15}H_{25}O^{81}Br$: M, 302.1069. Found: *m/e* 300.1108. Calcd for $C_{15}H_{25}O^{79}Br$: M, 300.1089. The bromide showed one spot on thin-layer chromatogram. The fact that the NMR spectrum shows no other methyl signals suggests that bromide (**2**) contains no epimer on $C_{(4)}$. However, the configuration at $C_{(4)}$ of **2** remained undetermined due to its easy decomposition as previously stated.

Successive elution with the same solvents gave the starting compound (**1**; 3.1 g; 78%) and a dehydrobrominated material (**3**; 240 mg; 6.1%).

When the reaction of **1** with NBS was carried out under a nitrogen stream in order to remove the hydrogen bromide generated during the course of reaction, olefin (**3**) could be obtained in better yield (15—35%).

Dehydrobromination of 4-Bromoguaioxide (2). The bromide (**2**; 100 mg; 0.33 mmol) in an ethanolic potassium hydroxide (KOH 220 mg, EtOH 5 ml) was heated under reflux for 2.5 h and the reaction mixture was treated as usual to give a residue which was chromatographed on a column of silica gel. Elution with petroleum ether–benzene (2: 1) gave the olefin (**3**; 36 mg; 0.17 mmol; 50% yield), an oil, $[\alpha]_D^{22}$ +15.0° (*c* 1.45; EtOH); IR (film): 1660, 1640, 1130, 1040, 1010, 885, and 815 cm^{-1}; NMR ($CDCl_3$): δ 0.85—0.95 (3H, diffused d; $C_{(10)}-CH_3$), δ 1.23, 1.34 (each 3H, s; $C_{(11)}-(CH_3)_2$), δ 1.67 (3H, d, *J*=1.3 Hz; $C_{(4)}-CH_3$), and δ 5.39 (1H, q, *J*=1.3 Hz; $C_{(3)}-H$); MS: *m/e* 220 (21%; M^+), *m/e* 205 [100%; $(M-CH_3)^+$], *m/e* 202 [56%; $(M-H_2O)^+$], *m/e* 187 [26%; $(C_{14}H_{19})^+$], and *m/e* 159 [53%; $(C_{12}H_{15})^+$]. Found: *m/e* 220.1814. Calcd for $C_{15}H_{24}O$: M, 220.1827. This olefin was found to be identical with 3-dehydroguaioxide (**3**)[4] and also with the olefin obtained by the reaction of **1** with NBS.

Conversion of 3-Dehydroguaioxide (3) into 8-Deoxytorilolone (8) and 8-Deoxy-1-epitorilolone (9). According to the procedures described by Ishii *et al.*,[4] the olefin (**3**) was converted, *via* the alcohol (**6**)[4,7] and the ketone (**7**), into 8-deoxytorilolone (**8**), which was isomerized into a 1: 1 mixture of **8** and 8-deoxy-1-epitorilolone (**9**). The formation of each compound (**6**, **7**, **8**, and **9**) was confirmed by identity of their spectral data with those of authentic samples (**6**, **7**, **8**, and **9**).

Dehydration of 8-Deoxytorilolone (8). *p*-Toluenesulfonic acid (67 mg; 0.35 mmol) was added to a solution of α,β-unsaturated ketone (**8**; 56 mg; 0.23 mmol) in benzene (17 ml), and the solution was heated under reflux for 3.5 h. The reaction mixture was treated as usual to give a single product, 4,6-guaiadien-3-one (**4**; 52 mg; quantitative yield), an oil, IR (film): 1690, 1625, 1590, 1340, 1285, 1050, and 870 cm^{-1}; UV (EtOH): λ_{max} 293 nm (ε 20700); CD (*c* 6.43×10^{-4}, EtOH): $[\theta]_{365}$ $\pm$0, $[\theta]_{295}$ +18300, and $[\theta]_{240}$ $\pm$0; NMR ($CDCl_3$): δ 1.06 (3H, d, *J*=6 Hz; $C_{(10)}-CH_3$), δ 1.09 (6H, d, *J*=7 Hz; $C_{(11)}-(CH_3)_2$), δ 1.75 (3H, s; $C_{(4)}-CH_3$), and δ 6.35 (1H, br s; $C_{(6)}-H$); MS: *m/e* 218 (100%; M^+), *m/e* 203 [32%; $(M-CH_3)^+$], and *m/e* 175 [73%; $(M-C_3H_7)^+$]. Found: *m/e* 218.1662. Calcd for $C_{15}H_{22}O$: M, 218.1671.

Dehydration of 8-Deoxy-1-epitorilolone (9). By the same treatment as above, **9** was transformed quantitatively into 1-epi-4,6-guaiadien-3-one (**5**), an oil, IR (film): 1690, 1630, 1590, 1330, 1290, 1055, and 880 cm^{-1}; UV (EtOH): λ_{max} 293 nm (ε 16500); CD (*c* 9.70×10^{-5}, EtOH): $[\theta]_{380}$ $\pm$0, $[\theta]_{335}$ −6080, $[\theta]_{317}$ $\pm$0, $[\theta]_{297}$ +5050, and $[\theta]_{265}$ $\pm$0; NMR ($CDCl_3$): δ 0.73 (3H, d, *J*=6.5 Hz; $C_{(10)}-CH_3$), δ 1.11 (6H, d, *J*=6.5 Hz; $C_{(11)}-(CH_3)_2$), δ 1.73 (3H, s; $C_{(4)}-CH_3$), and δ 6.34 (1H, br. s; $C_{(6)}-H$); MS: *m/e* 218 (100%; M^+), *m/e* 203 [18%; $(M-CH_3)^+$], and *m/e* 175 [50%; $(M-C_3H_7)^+$]. Found: *m/e* 218.1649. Calcd for $C_{15}H_{22}O$: M, 218.1617.

Alkaline Treatment of the α,β: γ,δ-Unsaturated Ketones (4 and 5). 4,6-Guaiadien-3-one (**4**; 13 mg) was treated with potassium hydroxide (100 mg) in methanol (5 ml) under reflux for 2 h under a nitrogen atmosphere. The reaction product (8 mg) was obtained after the usual treatment, and found by NMR measurement to consist of only the unchanged **4**. When 1-epi-4,6-guaiadien-3-one (**5**) was subjected to the same alkaline treatment, NMR measurement showed that more than 90% of **5** isomerized into **4**. Since the retention times for **4** and **5** were too close to each other, the accurate ratio of the products could not be determined by VPC measurement (column: Dexsil-300, SP-1000, and SE-30).

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References

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6) Isolation yields of both **2** and **3** were poor, a large amount (55—80%) of **1** being recovered unchanged. This was due to a) reaction products (**2** and **3**) being unstable on silica gel, and b) R_f values on TLC of **1**, **2**, and **3** being very close to one another. When the first three reactions, namely, NBS bromination and dehydrobromination followed by hydroboration, were carried out without purification, 200 mg of 3β-hydroxyliguloxide (**6**) was obtained from 1.0 g of guaioxide (overall yield, 18.5%).

7) E. Funke, T. Tozyo, H. Ishii, and K. Takeda, *J. Chem. Soc., C*, **1970**, 2548.

8) By the same treatment, **8** yielded a *ca.* 1: 1 equilibrium mixture of **8** and **9**.[4]