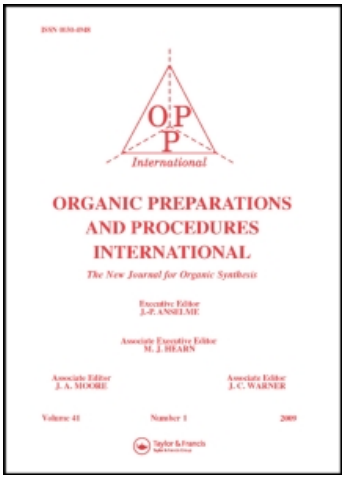

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A NEW METHOD FOR THE SYNTHESIS OF 3β-HYDROXY-4α-BROMOCARANE AND OF *cis*-3-CARENE EPOXIDE

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fine needles, mp. 150-152°; lit.[3] mp. 153°, identified additionally by ^{1}H NMR comparison.

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A NEW METHOD FOR THE SYNTHESIS OF 3β-HYDROXY-4α-BROMOCARANE AND OF *cis*-3-CARENE EPOXIDE

Submitted by (03/04/91)

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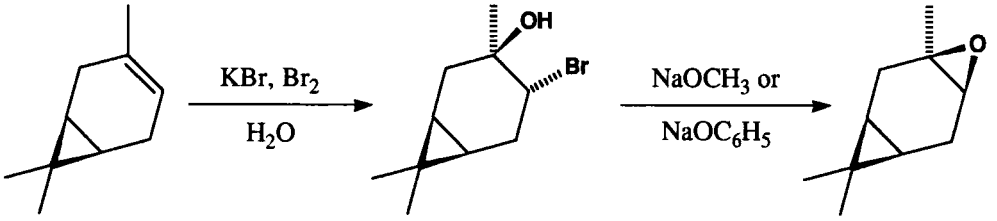
The objective of our research was to synthesize 3β-hydroxy-4α-bromocarane. Both *cis*-3-carene epoxide and 3β-hydroxy-4α-bromocarane are important starting materials in the synthesis of some pyrethroids[1,2] and in terpene chemistry.[6] A synthesis of 3β-hydroxy-4α-bromocarane using N-bromosuccinimide and 3-carene has been reported.[3] The reactions of 3α,4α-epoxycarane with HBr resulted in formation of 3β-bromo-4α-hydroxycarane while 3β,4β-epoxycarane gave a mixture of 3α-bromo-4β-hydroxycarane and 3α-hydroxy-4α-bromocarane.[4]

Using a method for the synthesis of trimethylethylene bromohydrin reported in 1944,[5] we found that the synthesis of *trans*-3β-hydroxy-4α-bromocarane can be easily achieved by titration of a mixture of 3-carene and water with an aqueous solution of bromine and potassium bromide at room temperature until the reaction mixture is light orange in color. If the addition is stopped before obtaining this color, 3-carene does not react completely. The reaction product was recrystallized from hexane to yield pure *trans*-3β-hydroxy-4α-bromocarane in 52% yield. ^{1}H NMR analysis of the crude reaction product indicated that the rest of the material corresponds to 3β-hydroxy-4α-bromocarane and 3,4-dibromocarane which can easily be converted back to 3-carene; no attempts were made to

recover it. The major features of this approach are simplicity of the reaction, very brief reaction time, easy work-up, good yield and the possibility of reconverting the by-products to 3-carene.

When *trans*-3β-hydroxy-4α-bromocarane was treated with sodium methoxide and sodium phenoxide, 3β,4β-epoxycarane was formed. ^{1}H NMR analysis of the reaction mixture did not show the formation of any substituted product. The ^{1}H NMR spectrum of this epoxide was the same as that reported in the literature for *cis*-3-carene epoxide.[6] *trans*-3-Carene epoxide was prepared by oxidation of 3-carene with *m*-chloroperbenzoic acid as reported by Young.[7] The GC retention times for *cis* and *trans*-3-carene epoxide are 18.5 and 13.9 minutes, respectively. ^{1}H-NMR of *cis* and *trans*-3-carene epoxides are different. The C_4 epoxy proton in the *trans* epoxide is unresolved triplet at δ 1.8, while in the *cis* epoxide, it appears as a sharp doublet at δ 2.8.[6] GC analysis of this compound indicated that it was 95% pure. Hydrolysis of the epoxide with aqueous acid gave a mixture of two caranediols. It is known that 3α, 4α-epoxycarane affords only 3β,4α-caranediol on hydrolysis.[6] These facts confirm the product is 3β-hydroxy-4α-bromocarane. Thus, a very simple, improved method has been developed for the synthesis of 3β-hydroxy-4α-bromocarane in 52% yield. This method gives good yields and is much faster and cheaper than the NBS method.[3]



EXPERIMENTAL SECTION

Infrared spectra of samples were recorded on a Perkin Elmer model 237B Infrared Spectrophotometer as a liquid film unless otherwise stated. NMR spectra were measured on a Varian T-60 instrument at 60 MHz using TMS as an internal standard and deuteriochloroform as a solvent. Gas chromatography was carried out on a Varian Aerograph 920. Melting points were taken on a Mel-Temp apparatus. 3-Carene was obtained from SCM corporation. Identification of compounds was based primarily on comparison of spectral data with those of authentic compounds.

Reaction of 3-Carene with Bromine and Potassium Bromide.- A 1L flask fitted with a stirrer and an addition funnel was charged with 3-carene (22.4 g, 0.16 mole) and 350 mL of water. To this vigorously stirred mixture, 14 mL of bromine (0.27 mole) dissolved in 560 mL water containing potassium bromide (42 g, 0.35 mole) was slowly added until the reaction mixture was light orange in color. After addition was complete, the organic layer was separated from the aqueous layer. The aqueous layer was extracted twice with equal volumes of diethyl ether and then the combined organic layers were dried over anhydrous sodium sulfate. After removal of the solvent at reduced pressure, a pale brown oil was obtained. This oil (35 g) on mixing with an equal volume of hexane

gave *trans*-3β-hydroxy-4α-bromocarane (20 g, 52%) as a white solid, mp. 59-60°, lit.[1] mp. 60-62°. IR: 3350 (OH stretch) and 1110 cm^{-1} (tertiary OH bend). ^1H NMR: δ 4.05 (1H, t, C_4-H), 2.24 (1H, s, C_3-hydroxyl), 1.9-2.5 (4H, m, C_2, C_5-methylene), 1.3 (3H, s, C_{10}-methyl), 1.0 (6H, s, C_8, C_9-methyls), 0.7 (2H, m, C_1, C_6-H).

Reaction of 3-Hydroxy-4-bromocarane with Sodium Methoxide.- A 250 mL three neck round bottom flask fitted with a reflux condenser and an inlet for nitrogen gas was charged with sodium metal (1.84 g, 0.08 atom) and 60 mL of methanol. The solution was maintained under an atmosphere of nitrogen. After the sodium had dissolved, solid 3-hydroxy-4-bromocarane (17.6 g, 0.075 mole) was added to the reaction mixture, which was allowed to stand at room temperature for 7 hrs. The reaction mixture was then diluted with diethyl ether and filtered to remove precipitated sodium bromide. The ethereal extracts were combined, washed with water and dried over anhydrous sodium sulfate. On removal of solvent *cis*-3-carene epoxide (7.4 g, 64%) was obtained as a yellow oil. Identification of compounds was primarily based on comparison of their spectral data with those of authentic compounds.[6] IR: 1225 (epoxide C-O stretch), 1060 (asymmetrical C-O bend), 810 cm^{-1} (symmetrical C-O bend). ^1H NMR: δ 2.8 (1H, d, C_4-H), 1.25-2.7 (4H, m, C_2, C_5-methylene), 1.24 (3H, s, C_{10}-methyl), 0.9 (6H, s, C_8, C_9-methyls), 0.6 (2H, m, C_1, C_6-H). GC: 95% pure.

Reaction of 3-Hydroxy-4-bromocarane with Sodium Phenoxide.- To a 250 mL three-necked round bottom flask fitted with a reflux condenser, sodium (2.9 g, 0.13 atom) and 65 mL absolute ethanol were added. The solution was maintained under an atmosphere of nitrogen. After all the sodium had dissolved, phenol (11.8 g, 0.13 mole) dissolved in 15 mL of absolute ethanol was then added. The mixture was stirred for 10 min and pure *trans*-3-hydroxy-4-bromocarane (26.3 g, 0.11 mole) was then added. The mixture was maintained at room temperature for 7 hrs and then extracted three times with equal volumes of diethyl ether. The ethereal extracts were combined and filtered to remove the precipitated sodium bromide. They were then washed with water, dried with anhydrous sodium sulfate and evaporated, yielding *cis*-3-carene epoxide (12.2 g, 0.080 mole, 61%) as a yellow oil, identical to the *cis*-3-carene epoxide obtained by the reaction of the 3-hydroxy-4-bromocarane with sodium methoxide. IR: 1225 (epoxide C-O stretch), 1060 (asymmetrical C-O bend), 810 cm^{-1} (symmetrical C-O bend). ^1H NMR: δ (ppm) 2.8 (1H, d, C_4-H), 1.25-2.7 (4H, m, C_2, C_5-methylene), 1.24 (3H, s, C_{10}-methyl), 0.9 (6H, s, C_8, C_9-methyls), 0.6 (2H, m, C_1, C_6-H). GC: 95% Pure.

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A NOVEL CLASS OF OXAZOLE DERIVATIVES.

4-ACYL-2-ARYLTHIO-5-ETHOXYOXAZOLES

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Oxazole derivatives are an important class of heterocycles[1], and substituted oxazoles[2,3] are useful intermediates in organic synthesis. In a previous paper,[2] we described the synthesis of 2-arylthio-5-ethoxyoxazoles **1** starting from alkyl isocyanoacetates and aryl sulfenyl chlorides. In order to evaluate the reactivity of these compounds towards electrophilic species, we attempted their acylation with acyl chlorides in the presence of aluminum chloride. These attempts were successful, giving 4-acyl-2-arylthio-5-ethoxyoxazoles **2** in fair yields.