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PREPARATION OF TERPENE ALCOHOLS

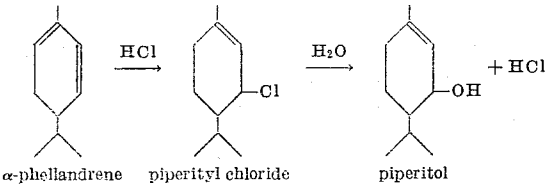
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The present invention relates to the preparation of terpene alcohols and particularly relates to the preparation of alcohols from the phellandrenes and derivatives possessing the conjugated systems thereof.

In British Patent No. 532,614, accepted January 28, 1941, there is described a process for producing piperitol from phellandrenes. This process involves first forming phellandrene hydrochloride and then replacing the chlorine atom with an —OH radical by hydrolysis under displacement conditions to form piperitol. Since the hydrolysis is an exchange or displacement reaction, the phellandrene hydrochloride is piperityl chloride, and the reactions can be illustrated in the following equation:



α-phellandrene piperityl chloride piperitol

As indicated in the British patent, the piperitol is useful for the preparation of piperitone, thymol and menthol. These are all valuable odor and taste chemicals, and the production of any or all of them in increased yields would be highly desirable.

It is therefore an object of the present invention to provide an improved process for producing terpene alcohols from the phellandrenes and their derivatives.

A further object is to provide a process for increasing the yields of alcohols from the hydrochlorides of the phellandrenes and their derivatives.

Another object is to provide a process for increasing the yields of alcohols oxidizable to piperitone from phellandrene hydrochloride.

Other objects will be apparent from the following description.

We have found that if the phellandrene hydrochloride, piperityl chloride, is treated under such conditions that favor not a displacement reaction but a solvolytic reaction, there is formed principally the alcohol 2-menthene-1-ol in both the cis- and trans-forms, with only small amounts of the piperitols. Under these conditions the chlorine atom is not replaced by a hydroxyl group, but the chloride is removed from one position and the hydroxyl group enters a different position in the molecule.

Besides being a product difficult of attainment by conventional synthesis, 2-menthene-1-ol also gives piperitone upon chromic acid oxidation, as does piperitol to which it is allylically related. We have also found that the 2-menthene-1-ol compounds may be converted in good yields to the corresponding 1-menthene-3-one derivatives by oxidations conducted in other acidic systems and employing oxidizing reagents known to be suitable for conversion of secondary alcohols to ketones, i. e., precipitated manganese dioxide. Menthone and menthol can be produced from piperitone by known methods.

The solvolytic reaction produces its alcohols from phellandrene hydrochloride in much better yield than does the displacement reaction known to the art, and if the object is to produce piperitone from phellandrene by subsequent oxidation of the alcohols, a very much better yield of piperitone can be obtained from a given amount of phellandrene hydrochloride by practice of this invention. Thus, in British Patent No. 532,614, there was produced 50 parts of piperitol from 172 parts of phellandrene hydrochloride, whereas by our invention we obtained 80 parts of alcohols oxidizable to piperitone from the same amount of the hydrochloride.

As with British Patent No. 532,614, our preparation was made with commercial α-phellandrene from E. Dives. Optical activity is retained unless destroyed by improper handling of the piperitone.

Suitably substituted phellandrenes can be similarly treated to give the corresponding substituted alcohols.

The displacement reaction is widely used in organic chemistry, and a very common example is the displacement of halogen from an organic molecule by another group such as hydroxyl, cyanide, alkoxyl, etc. In such reactions the new group becomes attached to the carbon atom to which the halogen had been attached. In solvolytic reactions, however, it is considered that the halogen is removed from the organic molecule as an anion by the solvent molecules, and the organic compound is left as a carbonium cation which is very reactive. This type of ionization occurs most readily when the halogen is bound to a tertiary carbon or to an allylic carbon, since it is loosely held in these types of compounds. In the case of the allylic halide there is considered to be formed, by removal of the halogen, a resonant ion which is capable of forming an alcohol in either of the 2 allylic positions. In some systems the alcohol group becomes attached almost entirely to the carbon atom other than that which originally bore the halogen, but this is not predictable in the present state of the art. It is nevertheless evident that the solvolytic reaction is different from the displacement reaction.

Theoretical considerations as to mechanisms of nucleophilic and second order displacement reactions as contrasted to the widely differing mechanism of solvolytic and first order substitutions are provided in many reference works, among which are:

(1) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., 1940. See chapter VI and elsewhere in this book.

(2) Remick, "Electronic Interpretations of Organic Chemistry," Wiley, 1949, pages 72–75, 328–341.

(3) Bartlett's, "The Study of Organic Reaction Mechanisms," chapter 1, vol. III of Gilman's "Organic Chemistry," Wiley, 1953.

(4) Wheland's, "Advanced Organic Chemistry," second ed., Wiley, 1949, pages 535–542, etc.

These and like references refer to the original research publications wherein experimental conditions leading to solvolytic reactions of halides are outlined. In general, it is recognized that the solvolysis reaction is favored when conducted in a medium of high dielectric constant, water is ideal, and in a medium which is capable of solvating the halide ion, again water is ideal. It may be considered that the water attacks the halide ion, causing it to part from the organic portion of the molecule which is itself now a reactive carbonium ion. This ion, in the case of our invention, may be considered the piperityl ion (or substituted or unsaturated piperityl ion), which, however, is capable of very rapid transformation to a mixture of piperityl and 2-menthene-1-yl ions, the former capable of reacting with a hydroxyl ion to yield a piperitol, the latter with hydroxyl ion to yield a

2-menthene-1-ol. It is not necessary to visualize separate identities for the two ions involved, as a transitional resonance complex might also be envisioned. However, it is clear that conditions which we employ do tend to permit an allylomerization of the organic skeleton. It is also clear that these conditions are substantially different from those described in British Patent No. 532,614 and do lead to a different product very rich in 2-menthene-1-ol. It will be appreciated that such reactions as we are concerned with can be conducted under conditions which are part displacement, part solvolysis conditions, there being no sharp demarcation between solvolytic and displacement conditions, though favorable conditions for each type of reaction are widely recognized. We prefer to employ those conditions leading to higher proportions of 2-menthene-1-ols and lower proportions of the piperitols, rather than conditions resulting in direct attack of the hydroxyl or acetate ions on the carbon skeleton at position 3.

It is to be understood that we regard our process as involving the reaction of the solvent, water is best, with the halide to cause removal of halide in solvated form and simultaneously to produce a carbonium ion complex capable of accepting a hydroxyl ion from the solvent to form the mixture of allylomeric alcohols. It is clear that this reaction as it proceeds will produce acidity in the aqueous phase, thus reducing the availability of the hydroxyl ion for reaction with the carbonium complex and that such acidity should be neutralized in some convenient manner as by employing an alkali, preferably a relatively mild one such as lime, soda ash, dilute sodium hydroxide, an amine, calcium carbonate or the like. It is to be understood that we do not employ hot, strong, concentrated alkalies, etc., as in such a system dehydrochlorination of the terpenic hydrochloride would become excessive. The base can be added to the terpenic hydrochloride-water mixture, preferably with good agitation, at such a rate that it neutralizes the acidity as formed, or it may be added all at once.

The reaction can be carried out at room temperature or slightly above, but it occurs more rapidly at higher temperatures, suitably at 85 to 100° C., though some sacrifice in yield is involved at the highest temperatures due to the tendency toward dehydrochlorination. Generally it will be found most economic to at least complete the reaction at the higher temperatures and recycle the hydrocarbons formed to a new hydrochlorination step. It will be appreciated that our mixture of reactants will consist of more than one liquid phase, unlike the reaction mixtures of British Patent No. 532,614, and that, therefore, we prefer to employ good agitation. Also, we can add some solvent, either polar or non-polar, but such addition is not necessary and is detrimental to the extent that the added solvent depresses the solvation of the halide ion.

Further, as is shown in copending application Serial No. 382,839, filed September 28, 1953, compounds of the 2-methene-1-ol type are readily converted by contacting with acids to an equilibrium mixture consisting of 2-methene-1-ol and piperitol-type compounds. Thus, if we conduct the solvolysis under conditions of mild acidity, we may obtain a mixture of the tertiary and secondary forms approaching the composition of the acid equilibrated allylomers, but if we conduct the solvolysis under definitely but mildly alkaline conditions, we obtain that ratio of the allylomeric alcohols corresponding to the solvolysis only and not changed by any subsequent acidic allylomerization due to acidity of the solvolysis medium.

The following examples are illustrations.

Example 1

200 grams of commercial α-phellandrene from E. Dives was treated with dry HCl at 20–25° C. until 36.5 grams of HCl was taken up. The object was to produce 172 grams of phellandrene hydrochloride dissolved in excess hydrocarbon.

This hydrochloride was added to 500 cc. of 20% K_2CO_3 solution in water with vigorous stirring, warming slowly to 90° C. until CO_2 evolution was complete. There was recovered 210 grams oil assaying about 40% of alcohol. The balance was mostly hydrocarbon as the material contained only a trace of chlorine. The hydrocarbon was then removed by column distillation under vacuum and there was recovered 80 grams of alcohols.

Infrared examination of the alcohols showed that the mixture consisted mostly of cis- and trans-forms of 2-menthene-1-ol, identical with those we have obtained by treating cryptone with methyl Grignard reagent, a treatment reported in the literature, although the separation of the product into the two forms was not reported. Cis- and trans-piperitols were present in smaller amounts.

Beckmann oxidation of the mixture of alcohols gave a crude mixture which assayed 75% 1-piperitone by ultraviolet or infrared spectrophotometry.

Infrared examination of the hydrocarbons recovered from the treatment of the phellandrene hydrochloride with aqueous K_2CO_3 solution showed that in addition to α-phellandrene and cymene originally present in the commercial product, there was also present some β-phellandrene. Thus, the addition of HCl to α-phellandrene and its subsequent removal leads in part to the formation of β-phellandrene and constitutes a process for producing the latter from the former.

Example 2

104 grams of 1,5,8-p-menthatriene, which is a triene having an α-phellandrene nucleus and an additional isolated double bond, was cooled and dry HCl passed in, keeping the temperature below 30° C. until 17.7 grams had been added.

This hydrochloride was hydrolyzed with 400 cc. of 20% K_2CO_3 solution, as in Example 1, yielding a mixture of alcohols and hydrocarbons. After removal of the hydrocarbons by column distillation under vacuum, the alcohols were examined by infrared spectrophotometry and shown to be a mixture of cis- and transisopiperitenols (1,8-p-menthadiene-3-ols) and cis- and trans-2,8-p-menthadiene-1-ols. By Beckmann chromic acid oxidation, this mixture of alcohols was converted to the ketone isopiperitenone, all four members of this alcohol group yielding the same ketones, which can, of course, be hydrogenated to menthone or menthol by known means.

1,5,8-p-menthatriene and its preparation are described in copending application Serial No. 368,210, filed July 15, 1953. Isopiperitenol and its preparation are described in copending application Serial No. 348,825, filed April 14, 1953, and 2,8-p-menthadiene-1-ol and its preparation are described in copending application Serial No. 377,000, filed August 27, 1953.

The identifications of the products prepared in the above example were made by comparison of their infrared spectra with those of authentic specimens of the alcohols. Isopiperitenone is a compound known to the art.

Example 3

220 grams of 8-hydroxy-α-phellandrene, prepared in accordance with the teachings of copending application Serial No. 368,210, filed July 15, 1953, was dilluted with an equal amount of light petroleum and cooled to 0° C. Dry hydrogen chloride was then passed in slowly at 0° to —5° C. with good agitation until 40 grams was absorbed. Toward the end of the absorption a white crystalline solid separated. This redissolved when the mixture was allowed to come to room temperature. No water separated. As soon as the HCl addition was completed, the mixture was poured into a flask containing 165 grams of $K_2CO_3 \cdot 1\frac{1}{2}H_2O$ diluted to a 20% solution with water and with vigorous stirring warmed slowly to reflux for about 2 hours.

After cooling, the petroleum was distilled off under vacuum and a sample examined by infrared spectrophotometry. There was observed in addition to some unreacted 8 - hydroxy - α - phellandrene, 8-hydroxy-β-phellandrene, a small amount of a secondary alcohol having its secondary alcohol absorption at the same wavelengths as isopiperitenol, thereby characterizing it as 8-hydroxypiperitol, and as principal product 2-p-menthene-1,8-diol. It will be observed that these products are entirely analogous to those obtained from α-phellandrene.

2-p-menthene-1,8-diol was characterized by comparison of the infrared spectrogram of the crude containing it with the spectrogram of an authentic specimen prepared by autoxidation of α-terpineol and whose identity was established by reduction to p-menthane-1,8-diol, terpin, a well-known compound. 2-p-menthene-1,8-diol and its preparation from α-terpineol are described in copending application Serial No. 377,000, filed August 27, 1953.

The aqueous layer from the hydrolysis was salted with additional K_2CO_3 and a few grams of viscous oil separated which soon crystallized.

2-p-menthene-1,8-diol exists in cis- and trans-forms. The higher melting form, in which the hydroxyls are trans, is a derivative of cis-2-p-menthene, and the low melting form, in which the hydroxyls are cis, is a derivative of trans-2-menthene. This latter form hydrogenates to cis-terpin, and like cis-terpin appears to form a hydrate.

Example 4

97 grams of 8-hydroxy-β-phellandrene, see copending application Serial No. 368,210, filed July 15, 1953, was diluted with 97 grams of light petroleum and cooled to 0° C. Dry hydrogen chloride gas was passed in slowly, maintaining the temperature between 0° and —10° C. until 19 grams weight increase had occurred. The product was then worked up as in Example 3. Infrared spectrophotometry showed that the principal product of the reaction was again 2-p-menthene-1,8-diol with a small amount of the secondary allylomer.

On salting the aqueous layer from the hydrolysis wtih additional K_2CO_3, there was obtained a few more grams of viscous oil which crystallized when seeded with crystals from Example 3, i. e., it was 2-p-menthene-1,8-diol.

Having described the invention, we claim:

1. The process which comprises hydrolyzing phellandrene monohydrochloride with water in the presence of a mild base sufficient to neutralize hydrochloric acid formed during the treatment.

2. The process which comprises hydrolyzing the monohydrochloride of 1,5,8-p-menthatriene with water in the presence of a mild base sufficient to neutralize hydrochloric acid formed during the treatment.

3. The process which comprises hydrolyzing the monohydrochloride of 8-hydroxy-phellandrene with water in the presence of a mild base sufficient to neutralize hydrochloric acid formed during the reaction.

4. The monohydrochloride of 8-hydroxy-phellandrene.

5. The monohydrochloride of 1,5,8-p-menthatriene.

6. The process which comprises hydrolyzing a Δ^1-3-chloro compound of the p-menthane series with water in the presence of a mild base sufficient to neutralize hydrochloric acid formed during the treatment.

References Cited in the file of this patent

FOREIGN PATENTS

532,614 Great Britain ---------- Jan. 28, 1941

OTHER REFERENCES

Simonsen: The Terpenes, vol. I (2nd ed.), pp. 92 and 287 (1947).

Wheland: "Advanced Organic Chemistry," 2nd ed. (1949), pp. 437 and 536.