The Reaction of 1, 8-Cineole with Acid Solutions

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On the oxidation of 1, 8-cineole with chromic acid in acetic acid[1] or with Beckmann's chromic acid mixture[2], terpin hydrate or α-terpineol has been obtained in a poor yield together with the main reaction products such as homoterpenyl methyl ketone or terpenylic acid. As terpin hydrate and α-terpineol are not oxidation products, it is of interest to clarify the effect of acid solutions on 1, 8-cineole.

No work has been reported about the reaction of 1, 8-cineole with an aqueous acetic acid solution and only a little attention has been paid to the reaction of cineole with sulfuric acid[3-6]. In 1887, Wallach observed that when cineole and sulfuric acid (sp. gr. 1.64) in alcohol were heated for 5 hours on a water bath, α-terpinene and terpinolene were obtained[3]. Recently Lombard et al. treated this subject somewhat in detail[4]. They studied the problem at various concentrations of sulfuric acid (at 55 and 64% mainly) for various reaction times under stirring at 15°C, and obtained the following compounds: terpin hydrate, *trans*-terpin, α-terpineol and hydrocarbons. Limonene, α-terpineol and terpin hydrate were also studied. Before Lombard's observation, it was reported from this laboratory that when cineole and 21% aqueous sulfuric acid solution were heated at 70°C under stirring, terpin hydrate, α-terpineol, α-terpinene and *p*-cymene were obtained[5]. In this case, it was observed that as the time of contact increases, cineole gives progressively less terpene alcohols and more hydrocarbons.

In this investigation we intended to make clear the actions of acetic acid and sulfuric acid solutions on 1, 8-cineole under conditions similar to those described in the foregoing papers[1,2], and to propose a reaction mechanism for the formation of terpins and α-terpineol from 1, 8-cineole.

Results and Discussion

1, 8-Cineole was treated with an aqueous acetic acid solution (60 wt. %) and an aqueous sulfuric acid solution (21 wt. %) and terpin hydrate was also treated with the same reagents. Further, the reaction of *trans*-terpin with 60% acetic acid solution and that of 1, 8-cineole with 0.6% sulfuric acid solution were examined. The reaction conditions and the products

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[1] T. Matsuura and H. Matsuo, *J. Sci. Hiroshima Univ.*, **A16**, 153 (1952).

[2] T. Matsuura and S. Yasuda, ibid., **15**, 273 (1952).

[3] O. Wallach, *Ann.*, **239**, 22 (1887).

[4] R. Lombard and E. Geiger, *Bull. soc. chim. France*, **1956**, 1564.

[5] T. Matsuura and T. Furukawa, *J. Sci. Hiroshima Univ.*, **A18**, 447 (1956).

[6] I. Ogura et al., *J. Pharm. Soc. Japan*, (*Yakugaku Zasshi*), **77**, 1355 (1957).

TABLE I

RESULTS OF THE REACTIONS OF CINEOLE AND TERPINS WITH ACID SOLUTIONS AT 70°C

Expt. No.	Reaction condition		Reaction time hr.	Yield of reaction products (wt. percentage to the charged sample)			
	Reagent	Sample		Terpineol	Terpin hydrate	*trans*-Terpin	Hydrocarbons
1	60% Acetic acid	Cineole	10	0.12	0	0.03	0
2	64% Acetic acid	Terpin hydrate	10	2.7	—	trace	0
3	60% Acetic acid	*trans*-Terpin	10	1.8	0	—	0
4	21% Sulfuric acid	Cineole	3	4.6	0.20	0.12	small
5	21% Sulfuric acid	Terpin hydrate	0.25	17.8	—	0.20	11
6	0.6% Sulfuric acid	Cineole	10	0.02	0	0.004	0

are shown in Table I. Among the reaction products, α-terpineol was identified as its phenylurethane and nitrosochloride. Fractional crystallization was employed for the separation of terpin hydrate and *trans*-terpin. For the identification of a small amount of the reaction products, strip-chromatography and I. R. and U. V. absorption spectra were used.

The reaction of cineole (1400 g.) with the acetic acid solution gave *dl*-α-terpineol (0.12% to cineole used) and *trans*-terpin (0.03% to cineole used). Under the same conditions terpin hydrate (90 g.) was converted into *trans*-terpin (trace) and *dl*-α-terpineol (2.7%) which was confirmed to be free from its acetate by the measurement of ester value. In order to compare the action of the acetic acid solution on *trans*-terpin with that on terpin hydrate, the former (4.0 g.) was treated under the same conditions as in the case of the latter. The reaction product was *dl*-α-terpineol (1.8%). The unsuccessful detection of terpin hydrate in the reaction product may result from the small scale of the experiment.

Cineole was attacked more easily by the aqueous sulfuric acid solution (21%) than by the aqueous acetic acid solution (60%), and converted into terpin hydrate, *trans*-terpin, *dl*-α-terpineol and monocyclic hydrocarbons consisting of α-terpinene and *p*-cymene*. In addition, the presence of $\Delta^{2,4(8)}$-*p*-methadiene was confirmed by the U. V. absorption maximum at 244 mμ7). The reaction of terpin hydrate with the sulfuric acid solution gave the following products: *dl*-α-terpineol, monocyclic hydrocarbons, *trans*-terpin and 1,8-cineole. The fact that terpin hydrate is attacked more easily than cineole shows that the cleavage of the ether ring in cineole is more difficult than the dehydration of terpin. A remarkable difference between the reaction of cineole with 60% acetic acid solution and that with 21% sulfuric acid solution lies in the point that the latter gives both *cis*- and *trans*-terpins in comparable amounts while the former gives *trans*-terpin predominantly. Since the reaction of cineole with a very dilute aqueous sulfuric acid solution (0.6%), having the same pH value as 60% aqueous acetic acid (pH 1), gives *trans*-terpin predominantly, it seems that the ratio of *cis*-terpin to *trans*-terpin is largely changed by the hydrogen ion concentration of the reagent.

From the above results, the mechanism of the reaction for the formation of the products obtained by the action of aqueous acid solutions on cineole is probably as shown in Fig. 1.

In this mechanism we consider that the main course of the reaction is as follows:

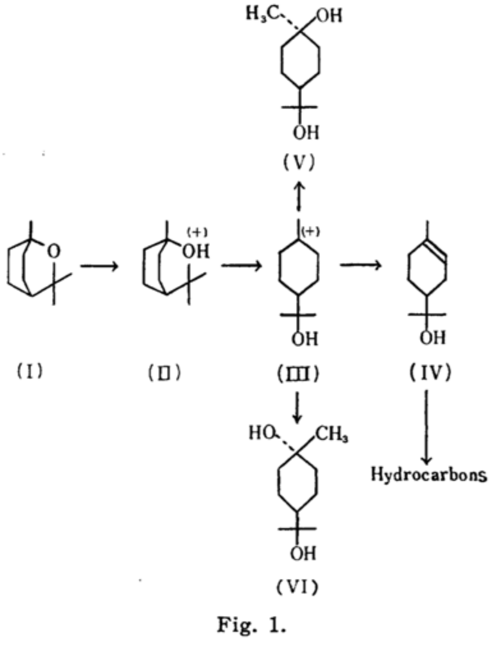

Fig. 1.

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* cf. 5).

7) R. T. O'Connor and L. A. Goldblatt, *Anal. Chem.*, **26**, 1726 (1954).

cineole (I) → oxonium ion (II) → carbonium ion (III) → α-terpineol (IV) → hydrocarbons.

The main reaction product of cineole with the acid solutions is *dl*-α-terpineol under the above conditions (Expt. 1, 4, 6). We see, also, that *cis*- and *trans*-terpins (V and VI) are considerably stable to the action of 60% acetic acid (Expt. 2, 3). If terpin were the intermediate in the main reaction course, a considerable amount of terpin should be accumulated as a reaction product. But the yield of terpin is very small in comparison with that of α-terpineol (Expt. 1, 4, 6). Furthermore, terpin hydrate is converted easily into hydrocarbons by the action of 21% sulfuric acid (Expt. 5), while in the case of cineole this is not true (Expt. 4). Therefore, one may probably assume that *cis*- and *trans*-terpins are not intermediates in the main reaction course but only by-products formed by the hydration of a carbonium ion (III) derived from an oxonium ion (II). The formation of the carbonium ion (III) may be considered on the basis of the presence of both *cis*- and *trans*-terpins in the reaction products.

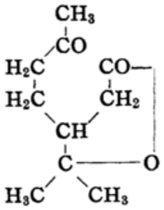
In the cases of Expt. 1 and 6, where aqueous acetic acid and very dilute sulfuric acid solutions are the reagents, the terpin found in the reaction products is the only *trans* modification. This may be explained by taking into consideration that the stability of the carbonium ion (III) is decreased greatly in Expt. 1 and 6 as compared with in Expt. 4, owing to the difference of the hydrogen ion concentration. Thus in Expt. 1 and 6, the unstable carbonium ion (III) may react very rapidly with water while the departing group $\underset{\cdot\cdot}{\ddot{\mathrm{O}}}\mathrm{H}{-}\mathrm{C(CH_3)_2}{-}\mathrm{R}$ in the formation of the carbonium ion (III) from the oxonium ion (II) is still partially screening one side of the planar carbonium ion (III).

(VII)

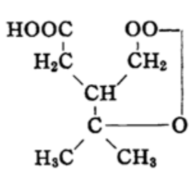
Although, Lombard et al. have proposed a carbonium ion (VII) as an intermediate in the hydrolysis of mono- and di-sulfates5), the above obtained results can be explained by assuming the carbonium ion (III) instead of that of Lombard. In the reaction of 1,8-cineole with acid solutions, the transitory carbonium ion (III) which is derived from the oxonium ion (II) formed by the addition of the hydrogen ion to 1,8-cineole may react with a water molecule to form terpins ($\mathrm{S_N}$ 1 type reaction), or may liberate a proton to form α-terpineol (E 1 type reaction). The above $\mathrm{S_N}$ 1 and E 1 processes will be competed with each other, but in the E 1 reaction there will not be a steric hindrance which is possibly included in the $\mathrm{S_N}$ 1 reaction. Thus it seems probable that the elimination process which results in the formation of α-terpineol is predominating.

If an $\mathrm{S_N}$ 2 type reaction proceeded by the attack of an anion such as acetate on the oxonium ion (II) in Expt. 1, there would be a change of the configuration at $\mathrm{C_1}$ atom resulting in a Walden inversion. In this case, however, an ester thus produced would give both *cis*- and *trans*-terpins by a successive hydrolysis*. Also, if the acetate were formed, it would be so stable that the hydrolysis could not occur under our conditions. Thus an $\mathrm{S_N}$ 2 type reaction may be left out of consideration in our experiments.

Considering the results of this investigation, in the cases of the oxidation of 1,8-cineole with chromic acid in acetic acid1) and with Beckmann's chromic acid mixture2), the reaction seems to proceed in the intermediary formation of α-terpineol by the above mechanism. α-Terpineol thus formed is then oxidized to homoterpenyl methyl ketone (VIII) which in turn goes to terpenylic acid (IX).



(VIII)



(IX)

Experimental

Reaction of Cineole with Acetic Acid Solution.—Cineole (700 g.) isolated from a camphor white oil according to the method described before8) (b. p. 173∼173.5°C, n_{D}^{25} 1.4540, d_4^{25} 0.9195) and 60% aqueous acetic acid solution (1309 g.) were mixed in a flask. After the mixture was heated at 70°C for 10 hours under stirring, it separated into two parts, an oil and an aqueous solution, and they were neutralized with sodium

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* It has been reported that hydrolysis of tertiary alkyl acetate by acid proceeds in alkyl-oxygen fission (C. K. Ingold et al., *Nature*, **166**, 680 (1950)).

8) S. Hayashi, T. Matsuura and B. Masumoto, *J. Sci. Hiroshima Univ.*, **A15**, 165 (1951).

carbonate. A large amount of sodium acetate was obtained from the aqueous solution. The oil was repeatedly washed with water and dried. The oil (1190 g.) obtained from two runs of the above treatment was distilled under a reduced pressure, b. p.$_{40}$ 80∼85°C, n_{D}^{25} 1.4532, d_4^{25} 0.9196, yield 1173 g. Treatment of this fraction with *o*-cresol gave needle crystals, m. p. 55∼56°C, which were identified as cresineol by the mixed melting point determination. Thus, it was confirmed that this fraction consisted of unchanged cineole.

The residue remaining in the flask was a pale yellow oil possessing a fragrant odor. After it was dissolved in ether and stood over night, white needle crystals (Crystal I), m. p. 155∼156°C, deposited and were taken up by filtration. From the filtrate (the ether solution) a viscous oil (2.3 g.) was obtained, which on distillation gave the following fractions: (1) b. p.$_{20}$ 69∼105°C, n_{D}^{25} 1.4580, yield 0.1 g.; (2) b. p.$_{20}$ 105∼135°C, n_{D}^{25} 1.4730, d_4^{25} 0.9444, yield 1.7 g.; (3) residue (0.4 g.). Fraction (2) was distilled and the main fraction, (b. p.$_{17.5}$ 103∼107°C, n_{D}^{25} 1.4742, d_4^{25} 0.9388, yield 0.8g.), phenylurethane m. p. 112.5°C, and nitrosochloride m. p. 113∼113.5°C, were obtained. This fraction was identified as *dl*-α-terpineol by mixing its derivatives with authentic specimens. The residue (0.4 g.) was washed with a little ether and recrystallized from water-ethanol mixture twice. Colorless needle crystals (Crystal II), m. p. 156∼156.5°C, were obtained. A large amount of sodium acetate which was produced by the neutralization of both the aqueous and the oily layers of the reaction mixture was extracted with ethanol. The ethanol extract was evaporated up to dryness and then repeatedly extracted with ether. From the ether extract colorless needle crystals (Crystal III), m. p. 152∼154°C, were obtained. The aqueous layer separated from the precipitated sodium acetate was extracted with ether several times and crystals (Crystal IV), m.p. 155.5∼156°C, were obtained from the ether extract. Crystals I, II, III and IV, which amounted to 0.427 g. in all, were identified as *trans*-terpin by the mixed melting point determination.

Reaction of Terpin Hydrate with Acetic Acid Solution. — Terpin hydrate, m. p. 119∼121°C (90 g.), was heated with 64% aqueous acetic acid solution (132 g.)* at 70°C for 10 hours under stirring. Unchanged terpin hydrate was filtered off and washed with water until the odor of acetic acid vanished. The aqueous layer of the reaction mixture and the water washings were neutralized with sodium carbonate. The precipitated sodium acetate was filtered and washed with a small amount of ether in order to catch the oily product adhering to it and then exracted with ethyl acetate. The aqueous layer separated from sodium acetate was extracted with ether and then evaporated up to dryness. The non-volatile material thus obtained was again extracted with ethyl acetate. The ether extracts gave an oily matter (4.4 g.) which on distillation gave a main fraction, b. p.$_{18}$ 98∼103°C, n_{D}^{25} 1.4759, d_4^{25} 0.9264, E. V. 16.26, yield 2.4 g. Phenylurethane and nitrosochloride of this fraction were identical with those of *dl*-α-terpineol.

Unchanged terpin hydrate (71.6 g.) was recovered. On the other hand crystals, m. p. 154.5∼155.5°C, which were identified as *trans*-terpin by the mixed melting point determination, were obtained in a very small amount from the ethyl acetate extracts mentioned above. Furthermore, strip-chromatography of these crystals was tried, and only one spot (Rf 0.45) corresponding to that of *trans*-terpin was found on the chromatogram developed with *n*-butanol-ethyl acetate (1 : 9) mixture[9].

Reaction of *trans*-Terpin with Acetic Acid Solution. — *trans*-Terpin[10], m. p. 156°C (4.0 g.), was heated with 60% aqueous acetic acid solution (6.9 g.) at 70°C for 10 hours under stirring. An oily product (0.07 g.) was separated according to the procedure described in the above section.

A strip-chromatogram of the oil gave one spot (Rf 0.24) corresponding to α-terpineol when the oil was developed with 15% ethyl acetate in *n*-hexane[11].

Unchanged *trans*-terpin, m. p. 155∼156°C (3.00 g.), was recovered.

Reaction of Cineole with Sulfuric Acid Solution.—Cineole (100 g.) was heated with 21% aqueous sulfuric acid solution (303 g.) at 70°C for 3 hours under stirring. After the neutralization with sodium carbonate, the reaction mixture was steam-distilled. The oily distillate (97.3 g.) was fractionated into the following fractions under reduced pressure. (1) b. p.$_{28}$ 74°C, n_{D}^{25} 1.4546, d_4^{25} 0.9175, yield 83.7 g.; (2) b. p.$_{28}$ 74∼112°C, n_{D}^{25} 1.4554, d_4^{25} 0.9163, yield 2.4 g.; (3) b. p.$_{28}$ 112∼113°C, n_{D}^{25} 1.4769, d_4^{25} 0.9276, yield 4.6 g.; (4) residue (1.1 g.). Fractions 1 and 2 were mainly unchanged cineole, because their odors and physical properties were close to those of cineole. But their U. V. absorption spectra (Fig. 2) showed absorption maxima at 244, 265 and 273 mμ corresponding to the characteristic absorption maxima for $\Delta^{2,4(8)}$-*p*-menthadiene, α-terpinene and *p*-cymene, respectively. I. R. spectrum of fraction (3) is shown in Fig. 3. The absorption curve coincides with that of α-terpineol and has no strong bands at 1643 and 885 cm^{-1} such as are characteristic of the end methylene group presented in β-terpineol[12].

When the aqueous solution remained in a flask after the steam-distillation was evaporated up, a solid material including sodium sulfate was obtained. It was extracted thoroughly with ethyl

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* In the case of terpin hydrate 64% acetic acid solution was employed under consideration of crystallization water in terpin hydrate.

[9] K. Yamamoto and T. Furukawa, *Educational studies* (*J.* Faculty of Education), *Hiroshima Univ.* (2), **4**, 45 (1956).

[10] *trans*-Terpin was prepared by the hydrolysis of *trans*-dipentene dihydrochloride with silver oxide and water (R. Lombard and E. Geiger, *Bull. soc. chim. France*, **1953**, 927).

[11] J. G. Kirchner, J. M. Miller and G. J. Keller, *Anal. Chem.*, **23**, 420 (1951).

[12] T. Aratani and T. Matsuura, *J. Sci. Hiroshima Univ.*, **A20**, 199 (1957).

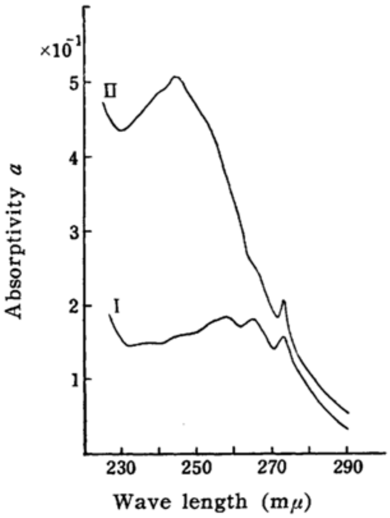

Fig. 2. Ultraviolet absorption spectra of hydrocarbon fractions: I fraction (1), II fraction (2) (in ethanol).

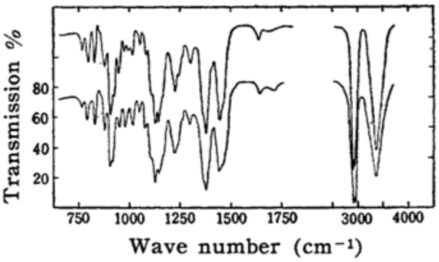

Fig. 3. Upper α-terpineol (liquid film). Lower fraction (3) (liquid film).

acetate. Colorless crystals (0.48 g.), which were obtained from the extract by evaporating the solvent, were recrystallized from water. The crystals, m.p. 117~119°C (0.20 g.), obtained by the repeated recrystallizations were identified as terpin hydrate by mixing with an authentic specimen. Evaporation of the mother liquor of the first recrystallization gave crystals possessing larger solubility in water than that of terpin hydrate. By recrystallization from ethyl acetate, the crystals were purified to colorless ones, m.p. 155~156°C (0.12 g.), which showed no depression of melting point on admixture with *trans*-terpin.

Reaction of Terpin Hydrate with Sulfuric Acid Solution. — Terpin hydrate (50 g.) was heated with 21% aqueous sulfuric acid solution (945 g.)* at 70°C for 15 minutes under stirring. Unlike the result in the case of acetic acid, terpin hydrate disappeared rapidly and was attacked easily. The reaction mixture which consisted of two layers, an oil and an aqueous solution, was neutralized with sodium carbonate under vigorous stirring, and then steam-distilled. The distillate was extracted with ether. After removal of the solvent, an oil (17.8 g.) was obtained, which was fractionated to the following fractions: (1) b.p.$_{50}$ 80~90°C, n_D^{25} 1.4600, d_4^{25} 0.8818, yield 4.4 g.; (2) b.p.$_{50}$ 90~103°C, n_D^{25} 1.4773, d_4^{25} 0.8661, yield 1.6 g.; (3) b.p.$_{50}$ 125~130°C, n_D^{25} 1.4789, d_4^{25} 0.9296, yield 8.9 g.; (4) residue (1.6 g.).

Condensation of fraction (1) with maleic anhydride at 80°C for half an hour was carried out, and the reaction mixture was separated to an unchanged oil and an addition product by distillation. The adduct was treated with a dilute sodium carbonate solution and a dilute aqueous sulfuric acid successively. Thus there were obtained crystals, m.p. 133.5~134°C, undepressed with the free acid of α-terpinene maleic anhydride adduct by the mixed melting point determination. The U.V. absorption curve of fraction (1) shows a λ_{max}^{alc} 265 mμ (*a*: 4.25), characteristic of α-terpinene (Fig. 4). The oil which remained unchanged by the maleic-anhydride treatment was extracted with a saturated resorcine solution. Steam-distillation of the extract gave an oil (0.3 g.) which was identified as 1,8-cineole by the formation of cresineol, m.p. 55~56°C, and by strip-chromatography (Rf 0.48)[11]. After the above treatment of fraction (1) there remained an oil consisting of dipentene and *p*-cymene. The former was characterized by its tetrabromide, m.p. 124~125°C, and the latter was confirmed by the absorption maxima at 258 and 273 mμ characteristic of *p*-cymene in a U.V. absorption spectrum (Fig. 4).

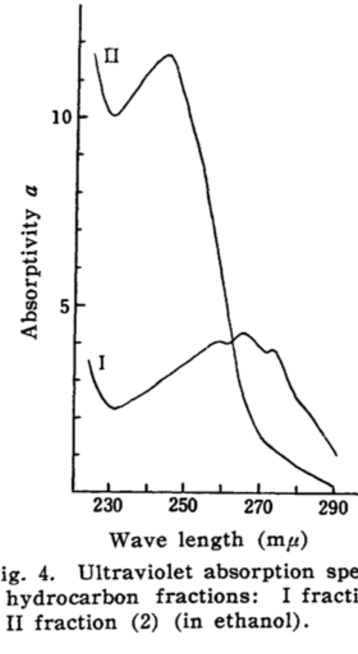

Fig. 4. Ultraviolet absorption spectra of hydrocarbon fractions: I fraction (1), II fraction (2) (in ethanol).

Fraction 2 consisted of dipentene (tetrabromide, m.p. 124~125°C) mainly and of a small amount of $\Delta^{2,4(8)}$-*p*-menthadiene (λ_{max}^{alc} 244 mμ, *a*: 11.67, in U.V. absorption curve in Fig. 4).

Redistillation of fraction (3) gave a main fraction: b.p.$_{20}$ 105~108°C, n_D^{25} 1.4793, d_4^{25} 0.9260,

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* In this case the amount of crystallizaton water in terpin hydrate was so small that the concentraton of the acid was practically not changed.

phenylurethane m. p. 112∼113°C characteristic of *dl*-α-terpineol.

The aqueous layer containing sodium sulfate was evaporated up on a water bath and the solid matter thus obtained was extracted with the same procedure described in the case of cineole. Unchanged terpin hydrate, m. p. 119.5∼120°C (6.8 g. after repeated recrystallizations), was recovered, and *trans*-terpin, m. p. 156°C (0.1 g.), which was identified by mixing with an authentic specimen, was obtained.

Reaction of Cineole with Dilute Sulfuric Acid Solution. — Cineole (1000 g.) was heated with 0.6% aqueous sulfuric acid solution (706 g.) at 70°C for 10 hours under stirring. The acid solution used here showed the pH value (pH 1) equal to 60% aqueous acetic acid solution. After neutralization of the reaction mixture, and steam-distillation, a large amount of oil (952 g.) was obtained. Fractional distillation under reduced pressure gave a main fraction (935 g.) consisting of unchanged cineole and a higher boiling fraction (b. p.$_{20}$ 71∼96.5°C, n_D^{25} 1.4783, yield 0.2 g.) whose I. R. spectrum agreed with that of α-terpineol.

Terpin was obtained from the aqueous layer according to the method mentioned above. Separation of *cis*- and *trans*-terpins by fractional crystallization was tried, and only *trans*-terpin, m.p. 154.5∼155°C (0.04 g.), was obtained.

Summary

The reaction of 1,8-cineole with 60% acetic acid at 70°C for 10 hours under stirring gave *dl*-α-terpineol (0.12%) and *trans*-terpin (0.03%). By the action of 21% sulfuric acid at 70°C for 3 hours, cineole yielded *dl*-α-terpineol (4.6%), terpin hydrate (0.20%), *trans*-terpin (0.12%) and monocyclic hydrocarbons (a small amount). On the other hand, the reaction of cineole with 0.6% sulfuric acid solution at 70°C for 10 hours gave *dl*-α-terpineol and *trans*-terpin in poor yields. In this case the reaction products are the same as in the case of 60% acetic acid.

Next, terpin hydrate was treated with 64% acetic acid at 70°C for 10 hours. The reaction products were *dl*-α-terpineol (2.7%) and *trans*-terpin (trace). By the action of 21% sulfuric acid at 70°C, terpin hydrate was attacked easily, and after 15 minutes it was converted to *dl*-α-terpineol (17.8%), *trans*-terpin (0.20%), 1,8-cineole and monocyclic hydrocarbons (11%). The monocyclic hydrocarbons consisted of α-terpinene, dipentene, $\Delta^{2,4(8)}$-*p*-menthadiene and *p*-cymene. *trans*-Terpin was, also, treated with 60% acetic acid at 70°C for 10 hours, the reaction product being *dl*-α-terpineol (1.8%).

On the basis of the above experiments a reaction mechanism for the action of acid solutions on 1,8-cineole was proposed.

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