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79. Michiko Kagawa: Action of Alkaline Substances on 10-Bromocamphor. I.

(*Scientific Research Institute, Ltd.**)

Forster and Howard[1] prepared 10-aminocamphor by heating 10-bromocamphor, ethanol, and ammonia in a sealed tube at 170°, and identified it as a benzylidene derivative, m.p. 95°. Iki,[2] by heating 10-bromocamphor with a potassium salt of phthalimide, obtained 10-phthalimidocamphor, which was then decomposed into 10-aminocamphor hydrochloride, m.p. 24°. The substances as prepared by Iki seem to bear sufficient evidence of identity, whereas Forster and Howard's 10-aminocamphor leaves much to be confirmed; in fact, the identity of their product remains a question. Later, however, Asahina and Tsukamoto[3] have shown that Forster's substance is not a true amine but is probably dihydro-β-campholenoiminolactone.

In the present investigation, with the same purpose as Asahina and Tsukamoto, the writer treated 10-bromocamphor with ammonia in a methanol solution under pressure, and obtained, instead of 10-aminocamphor, *d*-α-campholenic amide, m.p. 109°, $[\alpha]_D$ +8.6°. When this substance was dissolved in a 10% hydrochloric acid solution, treated with caustic soda, brought to a weak alkaline state, and extracted with ether, the resulting extract was isomerized to the levorotatory amide, $[\alpha]_D$ −5.7°, with a different melting point of 127°. The substance so obtained was in complete accord with Tiemann's α-campholenic amide,[4] m.p. 130°; $[\alpha]_D$ −4.4°, which was prepared by a caustic potash treatment of α-campholenonitrile, formed from camphor oxime with hydrochloric acid. When 10-bromocamphor was treated with ammonia, the camphor ring opened simultaneously with the debromination, giving α-campholenic amide. There was therefore no substitution as described by Forster and Howard of an amino for the bromine group to form 10-aminocamphor.

When these two amides, namely *d*- and *l*-α-campholenic amides are saponified, corresponding free acids are obtained which show the same physical properties ($b.p_3$ 120°; $[\alpha]_D$+9°). These two acids, when reacted with ammonia under pressure in a methanol medium, return again to *d*- and *l*-amides, the α-campholenic acid from *d*-amide giving a *d*-amide and the other from *l*-amide giving an *l*-amide. The stereoisomeric character of the amide, therefore, does not depend on the amido group but on the constitution of the α-campholenic acid, although the two acids are identical in physical properties.

Kachler and Spitzer,[5] and Burgess,[6] on the other hand, obtained ethyl α-cam-

* Kamifujimae-cho , Komagome, Bunkyo-ku, Tokyo (香川みち子).

1) M. O. Forster, H. A. H. Howard: J. Chem. Soc., **103**, 67(1913).
2) T. Iki: Sci. Papers. Inst. Phys. Chem. Res., Tokyo, **13**, 34(1934).
3) Y. Asahina, T. Tsukamoto: Ber., **71**, 305(1938).
4) F. W. Tiemann: Ber., **29**, 529, 3014, 5023(1896).
5) J. Kachler, F. V. Spitzer: Monatsh., **3**, 205(1882); **4**, 643(1883).
6) H. Burgess: J. Chem. Soc., **125**, 2376(1924).

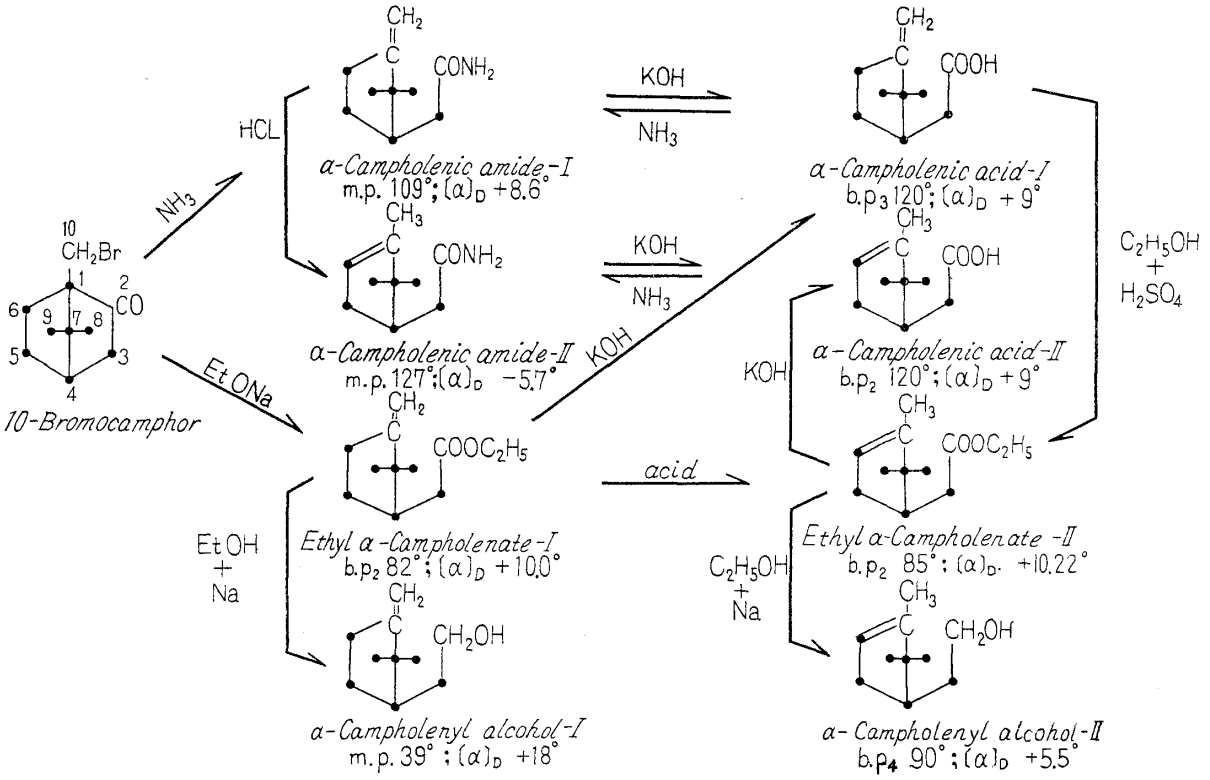

Chart 1.

pholenate by treating 10-bromocamphor or 10,3-dibromocamphor with sodium ethoxide. Since the substance was identical in physical properties with Tiemann's acid, they suggested Tiemann's formula for it, which has a cyclopentene ring.

In the present investigation, ethyl α-campholenate, b.p$_2$ 82°, $[\alpha]_D$ +10.0°, was prepared from 10-bromocamphor by Kachler's method, and from this ester, α-campholenic acid, b.p$_3$ 120°, $[\alpha]_D$ +9°, was obtained by saponification. The acid was then re-esterified with ethanol and sulfuric acid into ethyl α-campholenate, b.p$_2$ 85~86°, $[\alpha]_D$ +10.22°, which was saponified into α-campholenic acid, b.p$_3$ 120°, $[\alpha]_D$ +9°. In all these esters and acids, whether these were formed by alkaline or acidic treatment, no difference was observed in physical properties. From the ester of alkaline formation, by reducing with sodium in ethanol, α-campholenyl alcohol, m.p. 39°, $[\alpha]_D$ +18°, was obtained. Similarly, the ester of acidic formation was reduced to an alcohol, b.p$_4$ 90°, $[\alpha]_D$ +5.5°. These two alcohols differed greatly in physical properties, the one being crystalline and the other liquid. It may be inferred therefore that these original esters and acids, which show the same properties, are different in structure.

The constitution of these compounds were all determined by infrared absorption spectral method. Fig. 1 shows the infrared absorption spectra of pairs of α-campholenic acids, amides, esters, and alcohols, prepared by alkaline or acidic treatment.

It will be seen that all of the alkali-treated products show the absorption of $\overset{C}{C}>C=C<\overset{H}{H}$ in the vicinity of 11.5 μ, indicating the presence of a methylene group outside the cyclopentane ring of the α-campholenic structure, whereas the acid-treated products show the absorption of $\overset{C}{C}>C=C<\overset{H}{C}$ near 12.5 μ, indicating the presence of a double bond within the cyclopentene ring.

It is clear that Tiemann's α-campholenic amide has its double bond inside the cyclopentene ring. From the structure of the amide it may be inferred that α-campholenonitrile, which was formed by hydrochloric acid from camphor oxime, already

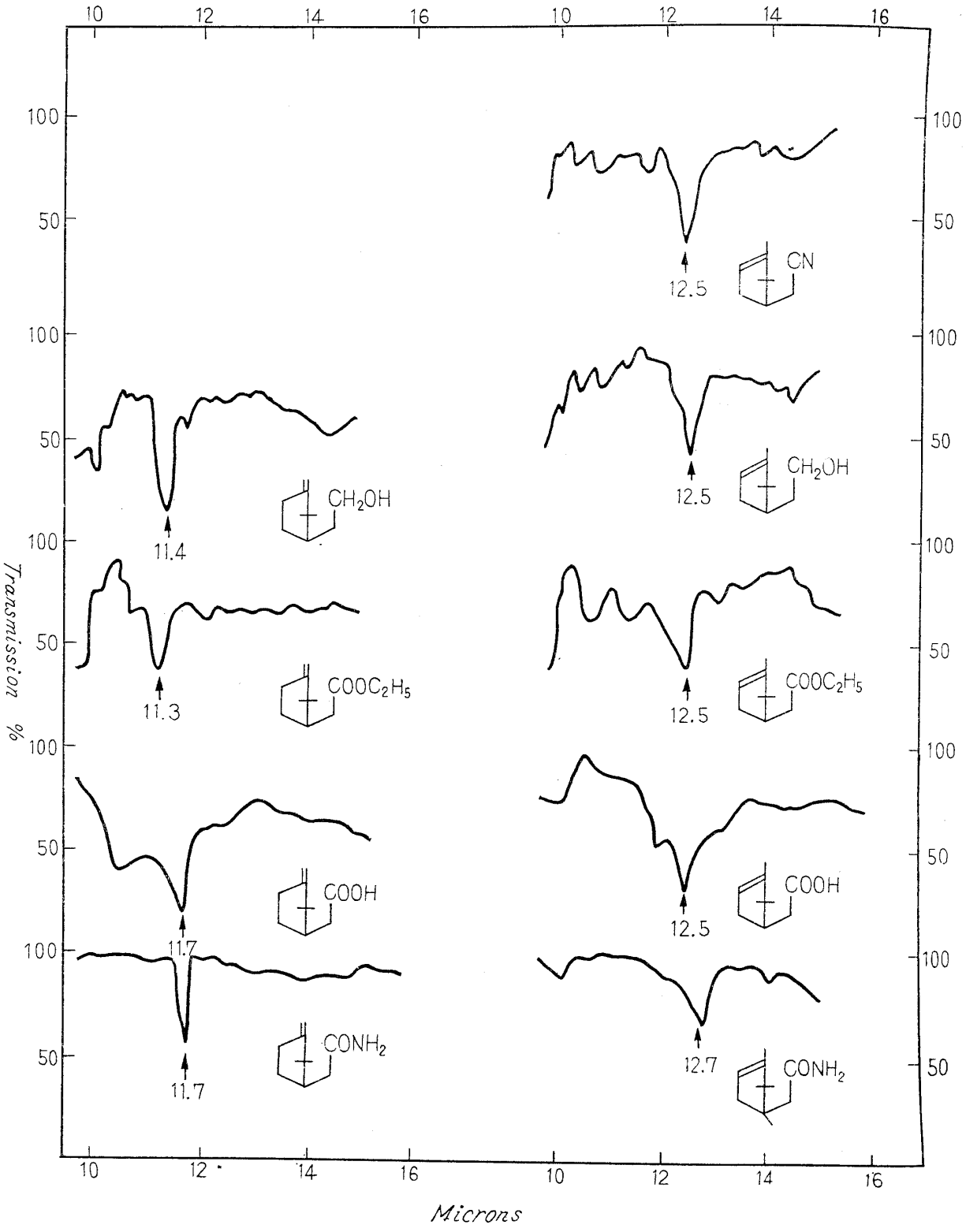

Fig. 1.

had its double bond inside the cyclopentene ring when the camphor ring was opened by the action of the mineral acid. Consequently, it is obvious that Kachler's α-campholenic acid does not fit the Tiemann's formula but has its double bond outside the cyclopentane ring. In the present paper the alkali-processed α-campholenic acid with its methylene linkage attached to the cyclopentane will be called α-campholenic acid-I and Tiemann's acid, which was prepared by acid treatment and which has one double bond in the cyclopentene ring, α-campholenic acid-II.

Experimental

1) ***d*-α-Campholenic Amide from 10-Bromocamphor**—90 g. of 10-bromocamphor in 300 cc. of MeOH was saturated with 38 g. of NH_3 gas. The solution was maintained at 160~170° with shaking in the autoclave for 5 hrs. MeOH was then removed, the residue was diluted with water, extracted with ether, washed, dried, and the solvent evaporated. The oily residue was recrystallized from a mixture of benzene and ligroine. m.p. 109°; $[\alpha]_D^{14}$ +8.6°(in abs. EtOH, *l*=1 dm., c=10). *Anal.* Calcd. for $C_{10}H_{17}ON$: C, 71.85; H, 10.25; N, 8.4. Found: C, 72.05; H, 10.42; N, 8.47.

2) **Isomerization of *d*-α-Campholenic Amide to *l*-Amide**—5 g. of *d*-amide, dissolved in 250 cc. of 10% HCl, was kept standing over ca. 2~3 hrs. When this was made alkaline with aq. Na_2CO_3 solution, crude crystals deposited, which were collected and then purified by recrystallization from a mixture of benzene and ligroine. m.p. 127°; $[\alpha]_D^{14}$ −5.7°(in abs. EtOH, *l*=1 dm., c=10). *Anal.* Calcd. for $C_{10}H_{17}ON$: C, 71.85; H, 10.25; N, 8.4. Found: C, 71.02; H, 10.28; N, 8.3.

3) **α-Campholenic acid-I from *d*-Amide; α-Campholenic acid-II from *l*-Amide**: (a) **α-Campholenic Acid-I**—A solution of 10 g. of *d*-amide and 100 cc. of 20% EtOH-KOH was refluxed for over 3 hrs. When the solvent was removed, the residue, slightly acidified with an addition of dil. HCl, was extracted with ether, the extract was washed and dried, and the solvent distilled off. The oily residue was then distilled *in vacuo*. $b.p_3$ 120°; $[\alpha]_D^{15}$ +9°.

(b) **α-Campholenic Acid-II**—By the same process as for *d*-amide, *l*-amide was saponified and treated. Finally the crude oil was fractionated by distillation *in vacuo*. $b.p_3$ 120°; $[\alpha]_D^{15}$ +9°.

4) ***d*- and *l*-Campholenic Amides from Acid-I and -II**: (a) ***d*-α-Campholenic Amide**—A solution of 10 g. of α-campholenic acid-I and 100 g. of MeOH was saturated with 12 g. of NH_3 gas and maintained at 160~170° in the autoclave for over 5 hrs. After cooling, MeOH was evaporated, the residue dissolved in water was extracted with benzene, and the dried solvent evaporated. The oily crystalline residue, on recrystallization from a mixture of benzene and ligroine, gave colorless plates, m.p. 109°; $[\alpha]_D^{15}$ +8.6°(in abs. EtOH, *l*=1 dm., c=10). The product was in agreement with *d*-α-campholenic amide.

(b) ***l*-α-Campholenic Amide**—*d*-Campholenic acid-II was treated similarly as with *d*-amide. m.p. 127°(from benzene and ligroine); $[\alpha]_D^{15}$ −5.7°(in abs. EtOH, *l*=1 dm., c=10).

5) **Ethyl α-Campholenate-I from 10-Bromocamphor**—To 200 g. of 10-bromocamphor was added 1 L. of abs. EtOH, into which 15 g. of fresh wired Na was dissolved. The solution was refluxed on a water bath for over 14 hrs., and when about half of EtOH distilled out, the residue was added into water, extracted with ether, and the solvent evaporated. The extract was distilled *in vacuo*, giving a colorless, somewhat viscous liquid, $b.p_2$ 82°; $[\alpha]_D^{20}$ +10.0°, n_D^{21} 1.4541.

6) **Ethyl α-Campholenate-II**—A solution of 100 g. α-campholenic acid-I, formed by saponification from ethyl α-campholenate-I, 300 cc. EtOH, and 25 g. conc. H_2SO_4, was refluxed for 3 hrs. After the esterification was complete, the mixture was neutralized with solid Na_2CO_3, extracted with ether, washed, and dried solvent evaporated. On distillation under a reduced pressure, a liquid was obtained, $b.p_2$ 85~86°; $[\alpha]_D$ +10.22°, n_D^{21} 1.4522.

7) **α-Campholenyl Alcohol-I from Ester-I**—To a solution of 25 g. of the ester-I and 125 cc. of abs. EtOH, 12.5 g. of Na was added with warming and the reaction mixture was refluxed on a sand bath. After cooling, the solution was diluted with water, extracted with ether, washed with water, and the solvent removed. On distillation of the oily residue *in vacuo*, colorless crystals separated, $b.p_5$ 93~94°, m.p. 39°; $[\alpha]_D^{20}$ +18°(in abs. EtOH, *l*=1 dm., c=10). *Anal.* Calcd. for $C_{10}H_{18}O$: C, 77.9; H, 11.7. Found: C, 78.12; H, 11.84.

8) **α-Campholenyl Alcohol-II from Ester-II**—The same reduction of 25 g. of the ester-II gave a liquid, $b.p_4$ 90°; $[\alpha]_D^{20}$ +5.5°. *Anal.* Calcd. for $C_{10}H_{18}O$: C, 77.9; H, 11.7. Found: C, 77.6, H, 11.7. The product, α-campholenyl alcohol-II differed in phase, rotation, and other properties from alcohol-I.

Summary

On treatment with ammonia, 10-bromocamphor gave *d*-α-campholenic amide which, on treatment with hydrochloric acid, stereochemically isomerized to the levorotatory amide. As a means of studying the principle that underlies this transformation, isomerization was attempted on original α-campholenic acid with mineral acid. It was clarified from infrared absorption spectra that the double bond in the case of alkali-formed products, is situated in a methylene group outside the cyclopentane ring and, in the case of acid-treated products, inside the ring. The former was termed α-campholenic acid-I and the latter α-campholenic acid-II. The properties of α-campholenyl alcohol-I and -II, formed by the respective reduction of the esters of acid-I and -II, were determined.

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80. **Michiko Kagawa**: Action of Alkaline Substances on 10-Bromocamphor. II.

(*Scientific Research Institute, Ltd.**)

In the preceding report[1] of this series it was made clear by spectral analysis that the double bond in the α-campholenic structure (acid, amide, or alcohol) shifts its position from 1—10** to 1—6 when treated with an acid. That acid with its double bond at 1—10 was termed α-campholenic acid-I and the other with the double bond at 1—6, α-campholenic acid-II. Now, the constitution of α-campholenic acid-II, as ascertained by Tiemann[2] by means of oxidation process, was identical with the result of spectral analysis. The spectral analysis of campholenic acid, prepared by Kachler and Spitzer[3] and by Burgess,[4] suggested it to be α-campholenic acid-I.

In the present series of work, a study was made on the structures of the two acids by examining their various oxidation products. First, α-campholenic acid-I, on oxidation with potassium permanganate in a weak alkaline state, yielded 1,1-dimethyl-2-hydroxymethylcyclopentan-2-ol-5-acetic acid, m.p. 151°, $[\alpha]_D$ +45.7°(Chart 1, a), the double bond being oxidized to glycol. The product was then treated with potassium permanganate in alkaline solution to produce 1,1-dimethyl-2-carboxycyclopentan-2-ol-5-acetic acid, m.p. 177°, $[\alpha]_D$ +46°. On oxidation with potassium hypobromide, this dibasic acid was converted first into 1,1-dimethylcyclopentan-2-one-5-acetic acid, m.p. 80°, $[\alpha]_D$ −46.7°, and then into isocamphoronic acid, m.p. 167°. It may be deduced therefore that α-campholenic acid-I and its ester have their methylene group outside the cyclopentane ring. Second, when α-campholenic acid-II was oxidized (Chart 1,b), its products were proved to agree with those obtained by Tiemann,[2] showing the presence of a cyclopentene ring in the α-campholenic structure.

When ethyl α-campholenate-I and -II were oxidized with ozone, ester-I produced

* Kamifujimae-cho, Komagome, Bunkyo-ku, Tokyo (香川みち子).

** The nomenclature for camphor skeleton was used for campholenic acid and others as a matter of convenience.

1) Part I. This Bulletin, **4**, 423(1956).
2) Tiemann: Ber., **29**, 529, 3014, 5023(1896); **30**, 243, 328(1897).
3) J. Kachler, F. V. Spitzer: Monatsh, **3**, 205(1882); **4**, 643(1883).
4) H. Burgess: J. Chem. Soc., **125**, 2376(1924).