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.

(Received May 22, 1956)

U. D. C. 547.599.6

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).

a monoester, b.p$_2$ 100~102°, $[\alpha]_D$ −44°, which on saponification yielded 1,1-dimethylcyclopentan-2-one-5-acetic acid. On the other hand, when ester-II was similarly treated with ozone, isoketocamphoric acid, m.p. 130~133°, $[\alpha]_D$ ±0°, was obtained. These two products were respectively identified as one of the stepwise oxidation products of α-campholenic acid-I and -II with potassium permanganate.

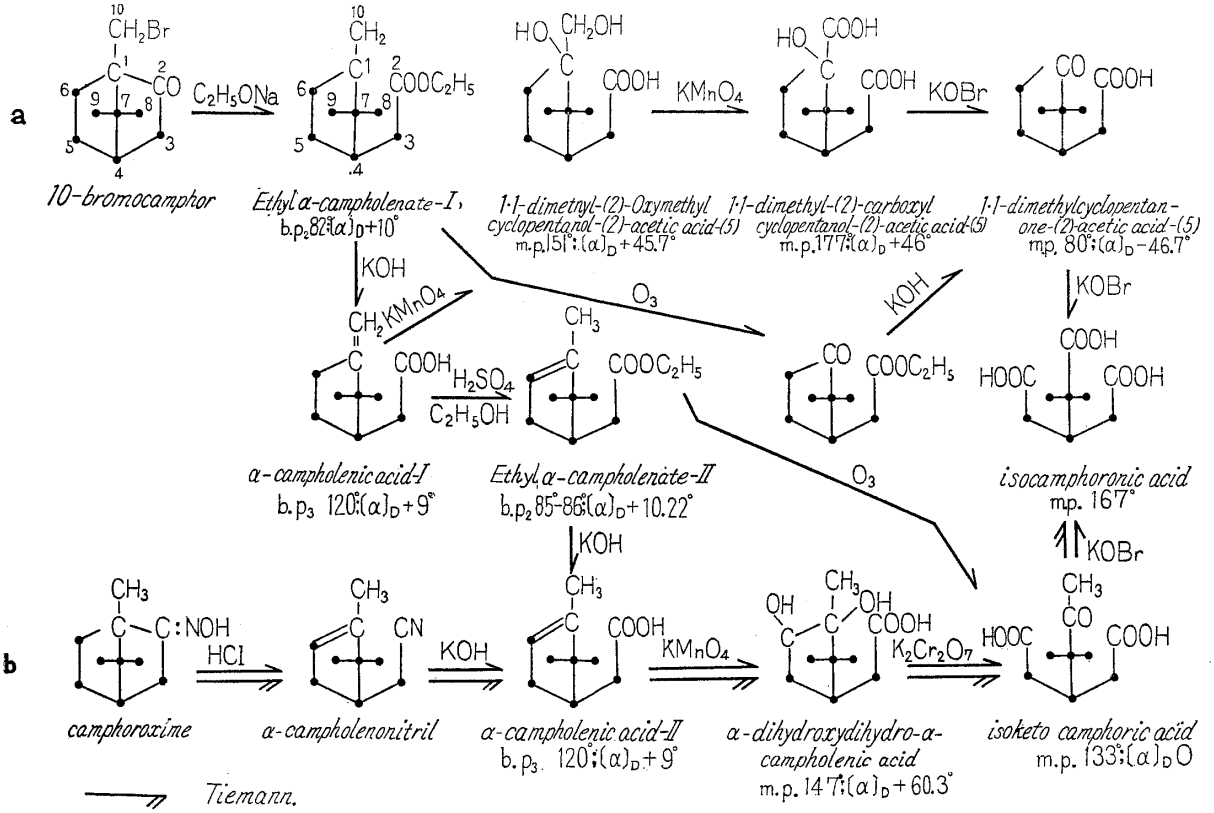

Chart 1.

Again, when α-campholenyl alcohols were oxidized mildly, alcohol-I was converted into 1,1-dimethyl-2-hydroxymethylcyclopentan-2-ol-5-acetic acid, m.p. 151°, $[\alpha]_D$ +45.7°, 1,1-dimethyl-2-carboxycyclopentan-2-ol-5-acetic acid, m.p. 177°, $[\alpha]_D$ +46°, 1,1-dimethylcyclopentan-2-one-5-acetic acid, m.p. 80°, $[\alpha]_D$ −46.7°, isocamphoronic acid, m.p. 167°, etc., at respective stages.

Similarly, alcohol-II gave *d*-dihydroxydihydro-α-campholenic acid, m.p. 147°, $[\alpha]_D$ +60.3°, isoketocamphoric acid, m.p. 133°, $[\alpha]_D$ ±0°, isocamphoronic acid, m.p. 167°, etc., at their respective stages. All these products were found analogous to the corresponding degradation products of α-campholenic acid-I and -II.

It may be evident therefore that in the structures of α-campholenyl alcohol-I and -II, the double bond is situated, in the former, at 1—10** and, in the latter, at 1—6,** just as in the case of acid-I and -II. As mentioned above, while the physical properties of these two classes of amides and alcohols show differences, those of their acids and esters are identical, which is probably the reason why Kachler, Spitzer, and Burgess adopted the Tiemann's structure.

In observing the transformation mechanism of 10-bromocamphor into α-campholenic acid, it might be assumed that the reaction undergoes two stages—the formation of α-camphenone as intermediate on elimination of hydrogen bromide from 10-bromocamphor, followed by the transformation of this intermediate to α-campholenic acid-I. However, actual testing of α-camphenone with various reagents in ethanolic solution in acidic, neutral, and alkaline states reveals that ethyl α-campholenate-II can be

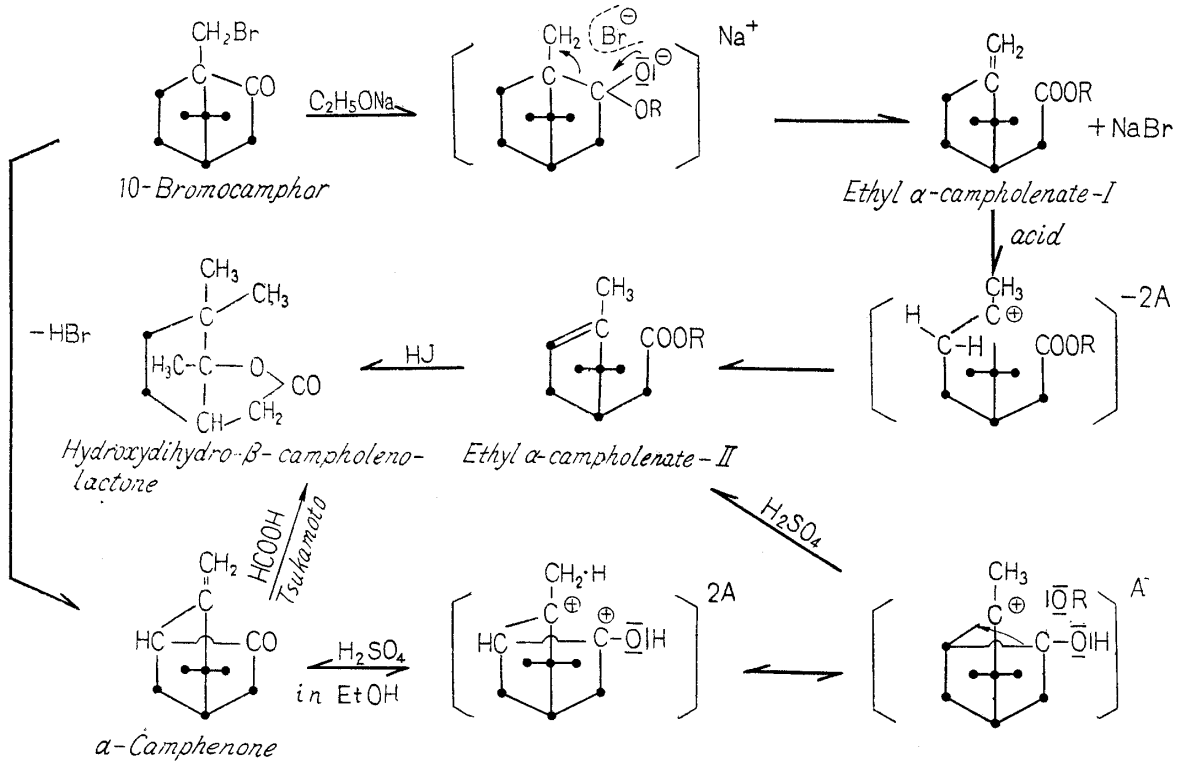

Chart 2.

formed only in acid states. Tsukamoto,[5] treating α-camphenone with formic acid, prepared hydroxydihydro-β-campholenic acid by decomposing the reaction mixture with alkali. He states that camphenone was converted into the lactone through α-campholenic acid-II by isomerization in accordance with Tiemann's theory.[2]

When α-camphenone is treated with dilute sulfuric acid in ethanolic solution, ethyl α-campholenate-II is obtained as was anticipated by Tsukamoto. The formation mechanism diagram (Chart 2) will show that the double bond at 1—10** position of α-camphenone is activated by a proton, which facilitates the transposition of 2—6 bond to 1—6 position,** thereupon an ethoxyl group immediately enters the ketone and forms ethyl α-campholenate-II. With a dilute acid, the transformation ceases at ethyl α-campholenate-II without reaching hydroxydihydro-β-campholenolactone.

On testing similarly, in neutral and alkaline conditions, however, no reaction could be observed. This inactivity of α-camphenone against neutral and alkaline substances may be attributed to a greater difficulty in the polarization of the double bond at 1—10 position, which leaves no chance for an opening of the ring.

The fact that α-camphenone is always inactive to alkalis makes it difficult to assume that α-campholenic ester-I is formed from 10-bromocamphor via two stages mentioned above.

It may be inferred therefore that the mechanism of ring opening of 10-bromocamphor is an ionic reaction taking place in an alkaline state. Sodium ethoxide stimulates the ketone group to polarization and to the entrance of an ethoxyl group, whereupon, by debromination with alkali, the 1—10 double bond is formed simultaneously with the fission of the ring at 1—2 position, thus completing the α-campholenic structure. When weak alkaline reagents are applied to 10-bromocamphor, the following substitution reactions may be observed. 10-Hydroxycamphor[6] with potassium acetate in

5) T. Tsukamoto: J. Pharm. Soc. Japan, **59**, 149(1939).
6) T. Shimamoto, M. Kagawa: Repts. Sci. Research Inst., Tokyo, **28**, 245(1952).

ethanol; 10-acetoxycamphor[7] with potassium acetate in acetic acid solution; and 10-phenoxycamphor[6] with potassium phenoxide. In all these reactions, the substitution occurs with bromine at the 10-position, there being no opening of the cyclohexanone ring of the camphor.

Experimental

I] Stepwise Oxidation of α-Campholenic Acid-I: (1) 1,1-Dimethyl-2-hydroxymethylcyclopentan-2-ol-5-acetic Acid (Glycol-1) from Ester-I—After saponifying 60 g. of the ester-I with 15 g. of NaOH and 250 cc. of MeOH, the solvent was completely removed. To the residue diluted with 500 cc. of H_2O, 56.4 g. of $KMnO_4$ in 1 L. of H_2O was added dropwise with cooling at 0°. After standing over night, the reaction mixture was filtered, the filtrate was brought to pH 7, and concentrated at 45~50° under reduced pressure. The concentrate was strongly acidified, extracted thoroughly with ether, which was washed with a little water and the solvent removed. On addition of some ether the oily residue solidified. Recrystallization of the crude crystals from water gave colorless prisms, m.p. 151°, $[\alpha]_D^{20}$ +45.7°(in abs. EtOH, l=1 dm., c=10). Neut. equiv. Calcd. for $C_{10}H_{18}O_4$: 278. Found: 314. *Anal.* Calcd. for $C_{10}H_{18}O_4$: C, 59.47; H, 8.92. Found: C, 59.47; H, 8.92.

(2) 1,1-Dimethyl-2-carboxycyclopentan-2-ol-5-Acetic Acid (D.B. Acid-I) from Ester-I—The acid-I, formed by saponifying 15 g. of the ester-I, was dissolved in 500 cc. of 2.5% NaOH solution, oxidized by addition of 42 g. of $KMnO_4$ in 1 L. of water at room temp., and treated as in (1). Finally, 8 g. of oil was obtained, which solidified on addition of some ether and recrystallized from water. m.p. 177°, $[\alpha]_D^{20}$ +46°(in abs. EtOH, l=1 dm., c=10). Neut. equiv. Calcd. for $C_{10}H_{16}O_5$: 519. Found: 515. *Anal.* Calcd. for $C_{10}H_{16}O_5$: C, 55.5; H, 7.47. Found: C, 55.9; H, 7.4.

(3) D.B. Acid-I from Glycol-I—To a solution of 3.6 g. of glycol-I in 100 cc. of 3% NaOH, 180 cc. of 5% $KMnO_4$ solution was added. After warming up to the point of disappearance of the red violet color, the reaction mixture was filtered and then treated as usual. Finally the crude acidic substance was purified by recrystallization from water. m.p. 177°, $[\alpha]_D^{20}$ +45.8°(in abs. EtOH, l=1 dm., c=10). Neut. equiv. Calcd. for $C_{10}H_{16}O_5$: 519. Found: 518. *Anal.* Calcd. for $C_{10}H_{16}O_5$: C, 55.5; H, 7.47. Found: C, 55.9; H, 7.5.

(4) 1,1-Dimethylcyclopentan-2-one-5-acetic Acid (M.K. Acid) from D.B. Acid-I—To 5 g. of D.B. acid-I dissolved in 150 cc. of 5% NaOH solution, 9.4 g. of Br_2 was added dropwise. After standing over night, the mixture was acidified weakly, then the excess of Br_2 was removed with benzene, and the residue extracted thoroughly in a strong acidic state with ether. The acidic product, 3 g. of crude crystals, was purified by recrystallization from benzene. m.p. 80°; $[\alpha]_D^{20}$ −46.7° (in abs. EtOH, l=1 dm., c=10). Neut. equiv. Calcd. for $C_9H_{14}O_3$: 330. Found: 329. *Anal.* Calcd. for $C_9H_{14}O_3$: C, 63.53; H, 8.23. Found: C, 63.22; H, 8.14.

The oxime was obtained by the addition of 0.3 g. of $NH_2OH \cdot HCl$ and 0.3 g. of AcONa to a solution of 0.5 g. of this acid and 60 cc. of MeOH. Recrystallization of the crude crystals from MeOH gave prisms, m.p. 167°. *Anal.* Calcd. for $C_9H_{15}O_3N$: C, 58.32; H, 8.10; N, 7.56. Found: C, 58.30; H, 8.29; N, 7.49.

(5) Isocamphoronic Acid from M.K. Acid—To a dilute alkaline solution of 2 g. of M.K. acid was added dropwise NaOBr prepared by adding 6 g. of Br_2 to 12 cc. of 33% NaOH ice-water solution. After standing over night, the reaction mixture was treated as usual. Finally, 0.9 g. of crystals were obtained, which were recrystallized from a mixture of $CHCl_3$ and AcOEt to m.p. 167~168°C. Neut. equiv. Calcd. for $C_9H_{14}O_6$: 772. Found: 751. *Anal.* Calcd. for $C_9H_{14}O_6$: C, 49.8; H, 6.42. Found: C, 50.22; H, 6.36.

II] Oxidation with Ozone: (1) M.K. Acid Ethyl Ester from Ester-I—Through a solution of 50 g. of ester-I in ca. 150~200 cc. of petroleum ether, ozone was passed at 0°. On completion of the reaction (50 hrs.), the ozonide layer was separated and decomposed with saturated $NaHSO_3$ solution at 0°. The mixture was then gradually warmed. After cooling, it was made alkaline with Na_2CO_3 and extracted with ether, the extract being washed with Na_2CO_3 solution, and the solvent evaporated. Fractional distillation of the residue (17 g. of neutral oil) gave a colorless liquid, $b.p_2$ 100~102°, $[\alpha]_D^{25}$ −44°.

Saponification of the Esters: A solution of 2.2 g. of the ester and 20 cc. of 20% EtOH-NaOH was refluxed for 4 hrs. EtOH was then removed, the residue was acidified, extracted with ether, and the solvent removed. The crude prisms obtained were purified by recrystallization from benzene, m.p. 89°, $[\alpha]_D^{25}$ −47°(in abs. EtOH, l=1 dm., c=10). *Anal.* Calcd. for $C_9H_{14}O_3$: C, 63.53; H, 8.23. Found: C, 63.53; H, 8.12.

Oxime: m.p. 162°. *Anal.* Calcd. for $C_9H_{15}O_3N$: C, 58.32; H, 8.10; N, 7.56. Found: C, 58.74; H, 8.01; N, 7.63.

7) T. Shimamoto, M. Kagawa: *Ibid.*, **25**, 117(1949).

(2) **Isocamphoronic acid**—Prepared by the oxidation of M. K. acid with NaOBr. m.p. 168°. Neut. equiv. Calcd. for $C_9H_{14}O_6$: 772. Found: 755. *Anal.* Calcd. for $C_9H_{14}O_6$: C, 49.8; H, 6.42. Found: C, 49.3; H, 6.48.

III] Stepwise Oxidation Product of α-Campholenic Acid-II—Prepared according to the method of Tiemann.[2]

(1) ***d*-Dihydroxydihydro-α-campholenic Acid (Glycol-II)**—Prepared by the oxidation of the ester-II with $KMnO_4$. Glycol-II, m.p. 147°. $[\alpha]_D^{20}$ +60.3°(in EtOH, l=1 dm., c=10) (Tiemann[2]: m.p. 144°, $[\alpha]_D$ +58.2°).

(2) **Isoketocamphoric Acid (D. B. acid-II)**—Prepared by the oxidation of glycol-II with $K_2Cr_2O_7$ and H_2SO_4. D. B. acid-II, m.p. 133°, $[\alpha]_D$ ±0°. (Tiemann[2]: m.p. 129~130°; Miyake: m.p. 133~134°).

(3) **Isocamphoronic acid**—Prepared by the oxidation of D. B. acid-II with NaOBr. Isocamphoronic acid, m.p. 168~169°. Neut. equiv. Calcd. for $C_9H_{14}O_6$: 772. Found: 745.

IV] Oxidation with Ozone: (1) D. B. Acid-II from Ester-II—Ozone was passed through 15 g. of ester-II in petroleum ether. On completion of ozonization (10 hrs.), the ozonide layer was separated and decomposed with 30% NaOH solution. The neutral matter was removed from the mixture with ether and the aqueous layer extracted in acidic state. Recrystallization of the crude crystals gave prisms, m.p. 133°, $[\alpha]_D$ ±0°. Neut. equiv. Calcd. for $C_{10}H_{16}O_5$: 519. Found: 521. *Anal.* Calcd. for $C_{10}H_{16}O_5$: C, 55.50; H, 7.40. Found: C, 55.6; H, 7.38.

V] Stepwise Oxidation of α-Campholenyl Alcohol-I: (1) Glycol-I from Alcohol-I—To a mixture of 30 g. of alcohol-I and 200 cc. of 10% NaOH, 38 g. of $KMnO_4$ in 800 cc. of water was added dropwise with chilling at 0°. The reaction mixture, after standing over night, was treated as usual. Recrystallization from water gave prisms, m.p. 151°, $[\alpha]_D^{20}$ +45.7°(in abs. EtOH, l=1 dm., c=10). Neut. equiv. Calcd. for $C_{10}H_{18}O_4$: 278. Found: 305. *Anal.* Calcd. for $C_{10}H_{18}O_4$: C, 59.47; H, 8.92. Found: 59.3; H, 8.86.

(2) **D. B. Acid-I from Alcohol-I**—To a mixture of 20 g. of alcohol-I and 300 cc. of 10% NaOH, 60 g. of $KMnO_4$ in 300 cc. of water was added at room temp. The reaction mixture was treated similarly and the crude crystals were purified by recrystallization from water. m.p. 177°, $[\alpha]_D^{20}$ +46° (in abs. EtOH, l=1 dm., c=10). Neut. equiv. Calcd. for $C_{10}H_{16}O_5$: 519. Found: 518. *Anal.* Calcd. for $C_{10}H_{16}O_5$: C, 55.5; H, 7.47. Found: C, 55.49; H, 7.49.

In the following oxidation the same procedure as for acid-I was employed. The resulting products are given individually.

(3) **D. B. Acid-I from Glycol-I**—m.p. 177°, $[\alpha]_D^{20}$ +45.6°(in EtOH, l=1 dm., c=10). Neut. equiv. Calcd. for $C_{10}H_{16}O_5$: 519. Found: 515. *Anal.* Calcd. for $C_{10}H_{16}O_5$: C, 55.5; H, 7.47. Found: C, 55.7; H, 7.4.

(4) **M. K. Acid from D. B. Acid-I**—Colorless crystals, m.p. 80°, $[\alpha]_D^{20}$ −46.7°(in abs. EtOH, l=1 dm., c=10). Neut. equiv. Calcd. for $C_9H_{14}O_3$: 330. Found: 332. *Anal.* Calcd. for $C_9H_{14}O_3$: C, 63.53; H, 8.23. Found: C, 62.98; H, 8.16.

(5) **Isocamphoronic Acid from M. K. Acid**—Prisms, m.p. 168°. Neut. equiv. Calcd. for $C_9H_{14}O_6$; 772. Found: 768. *Anal.* Calcd. for $C_9H_{14}O_6$: C, 49.8; H, 6.42. Found: C, 50.6; H, 6.50.

VI] Stepwise Oxidation of α-Campholenyl Alcohol-II: (1) Glycol-II from Alcohol-II—To a mixture of 15 g. of alcohol-II and 100 cc. of 2.5% NaOH, 400 cc. of 5% $KMnO_4$ was added at 0°. The reaction mixture was treated as usual, after standing over night. Recrystallization of the crude acidic solid from water gave prisms, m.p. 147°, $[\alpha]_D^{20}$ +60.2°(in abs. EtOH, l=1 dm., c=10). *Anal.* Calcd. for $C_{10}H_{18}O_4$: C, 59.4; H, 8.92. Found: C, 59.28; H, 9.0.

For the following reactions, the same treatment was applied as for acid-II.

(2) **D. B. Acid-II from Glycol-II**—m.p. 133°, $[\alpha]_D$ ±0°. *Anal.* Calcd. for $C_{10}H_{16}O_5$: C, 55.50; H, 7.40. fond: C, 55.7; H, 7.5.

(3) **Isocamphronic Acid from D. B. Acid-II**—Prisms, m.p. 169°. Neut. equiv. Calcd. for $C_9H_{14}O_6$: 772. Found: 767. *Anal.* Calcd. for $C_9H_{14}O_6$: C, 49.8; H, 6.42. Found: C, 50.0; H, 6.5.

VII] Ethyl α-Campholenate-II from α-Camphenone with abs. EtOH and H_2SO_4—A solution of 5 g. of α-camphenone, prepared from tricyclene by Nametzkin's procedure,[8] 60 cc. of abs. EtOH, and 1 g. of 98% H_2SO_4 was refluxed over 7 hrs. One-half of EtOH was removed from the reaction mixture and the residue was extracted with ether. The ether layer was washed with Na_2CO_3 solution and then with water, and dried over Na_2SO_4. After removal of the solvent, steam distillation was applied to remove residual α-camphenone and further distillation *in vacuo* gave an odoriferous liquid. This liquid was confirmed as ester-II by the following oxidation with O_3.

In a solution of 2 g. of the sample and ca. 20 cc. of petroleum ether, ozone was passed at 0° for 4 hrs. The ozonide layer was treated as usual and the acidic product in prisms was purified by recrystallization from benzene. m.p. 132~133°, $[\alpha]_D$ ±0°. Neut. equiv. Calcd. for $C_{10}H_{16}O_5$: 519.

8) S. Nametzkin, A. S. Zabrodina: Ann., **491**, 181(1925); Ber., **59**, 368(1926).

Found : 510. *Anal.* Calcd. for $C_{10}H_{16}O_5$: C, 55.50; H, 7.40. Found : C, 55.76; H, 7.39. The product was identical with isoketocamphoric acid.

VIII] Reaction of Neutral or Alkaline Reagent on α-Camphenone—The following mixtures (1) to (5) were maintained each at 130° for 5 hrs. in sealed tubes. No effect, however, was found, only unreacted raw material being recovered.

(1) A mixture of 1 g. of α-camphenone, 0.5 g. of KBr, and 3 cc. of abs. EtOH.
(2) A mixture of 1 g. of α-camphenone, 0.2 g. of $CaCl_2$, and 5 cc. of abs. EtOH.
(3) A mixture of 1 g. of α-camphenone, 0.5 g. of AcOK, and 5 cc. of abs. EtOH.
(4) A mixture of 1 g. of α-camphenone, 1 g. of KOH, and 5 cc. of abs. EtOH.
(5) A mixture of 1 g. of α-camphenone enolated in hexane by the addition of Na line and warming, and 10 cc. of abs. EtOH.

Summary

The positions of the double bonds in α-campholenic acid-I and -II were determined by investigating their respective oxidation products, confirming thereby the results obtained by the spectrum method. An attempt was also made to clarify the process of conversion from 10-bromocamphor into α-campholenic acid, proving it to be a straight reaction without passing through any intermediates such as α-camphenone.

(Received May 22, 1956)

U.D.C. 547.92 : 542.944

81. Ken'ichi Takeda and Taichiro Komeno : Bile Acids and Steroids. IX. Dibromination of Some 7-Oxosteroids.

(*Research Laboratory, Shionogi & Co., Ltd.**)

In 1938, Barr and Heilbron[1] obtained a dibromide, m.p. 177°, by dibromination of 7-oxocholestanyl acetate (Ia), which was presumed to be 6,6-dibromo compound by comparison of the bromination velocity of each epimer of 6-monobromides. In 1954, Cookson[2] discussed the ultraviolet absorptions of α-substituted bromo-oxosteroids and deduced that the above dibromide would be 6α,8β-dibromide from the fact that the contribution of axial bromine is considerably higher than that of the *gem*-dibromide. We reëxamined Heilbron's experiments and obtained a dibromide (IIa), m.p. 183~185°(decomp.), which agrees nearly well with the Heilbron's dibromide in respect to the melting point, crystal form, and ultraviolet spectrum, but differs a little in optical rotation (see Table I). It seems that from the optical data, the Heilbron's dibromide

Table I. Comparison between Heilbron's and the Authors' Dibromide

Dibromide	m.p. °C	$[\alpha]_D$ in $CHCl_3$	λ_{max}^{EtOH} mμ	log ε
Heilbron's	176~177°	+38.1°(at 19°)	304	2.2
Authors'	183~185°(decomp.)	+13.5°(at 23°)	302	2.08

was contaminated with 6β-monobromide, and these dibromides are assumed to be identical. Dibromination of 7-oxocholestanyl benzoate (Ib) also gave a dibromide (IIb), m.p. 163~165°.

The dibromination reactions proceed very easily in the 7-oxocholestane series, but it is somewhat difficult in the 7-oxocholanic acid series and the reactions tend to stop at a monobromide. Further bromination of methyl 3α,12α-diacetoxy-6α-bromo-7-

* Imafuku, Amagasaki, Hyogo-ken (武田健一, 米野太一郎).

1) T. Barr, I.M. Heilbron, E.R.H. Jones, F.S. Spring : J. Chem. Soc., **1938**, 334.
2) R.C. Cookson : J. Chem. Soc., **1954**, 282.