U. D. C. 547.599.6

91. Morizo Ishidate and Akiharu Kawada*: The Cleavage of Camphor Ring. V.[1] 7-Hydroxy-π-apocamphane and 1-Hydroxy-10-apocamphor.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo***)

In the series of this work, Yoshida[2] has demonstrated that the 7-hydroxy-π-apocamphor (II) anticipated by diazotization of 7-amino-π-apocamphor (I) is not stable enough to exist and coverts under spontaneous ring cleavage between C_1 and C_7 to an optically inactive 1-methyl-4-acetylcyclohexan-2-one (III). This lability of the 7-hydroxy compound was considered to be attributable to the particular tension caused by the bicycloheptanone ring, especially by the presence of a carbonyl bond at C_2. The attempt to prepare 7-hydroxy-π-apoborneol from 7-amino-π-apoborneol in order to verify the assumption was hindered by the simultaneous oxidation of the alcohol at C_2 to a ketone by nitrous acid.

Now in order to supply positive evidence of the above assumption and at the same time to elucidate the steric configuration of hydroxyl group at C_7 introduced by diazotization of the corresponding amino compound, preparation of 7-hydroxy-π-apocamphane (7-hydroxysantenone) (XIII) was undertaken, which provides a most appropriate method for these purposes.

l-trans-π-Apocamphane-7-carboxylic acid[3](IV), taken as the starting material, was subjected to the Hofmann degradation as usual. *l*-7-Methoxycabonylamino-π-apocamphane (V) obtained was hydrolysed with concentrated hydrochloric acid without any sign of ring cleavage, giving *l*-7-amino-π-apocamphane (VII). The same active amino compound was also obtained by the Curtius reaction of the acid (IV).

Unlike 7-amino-π-apocamphor (I), 7-amino-π-apocamphane (VII) is stable to alkalis and not hydrolysed by it even on warming. On deamination with nitrous acid the amino compound gives an optically inactive product which in all raspects agrees with 7-hydroxyapocamphane.

It is out of question that no steric inversion was involved during the degradation of the carboxylic acid to the amine (VII). The deamination reaction, however, took place with complete racemization. The mechanism of the racemization would be easily explained as follows:

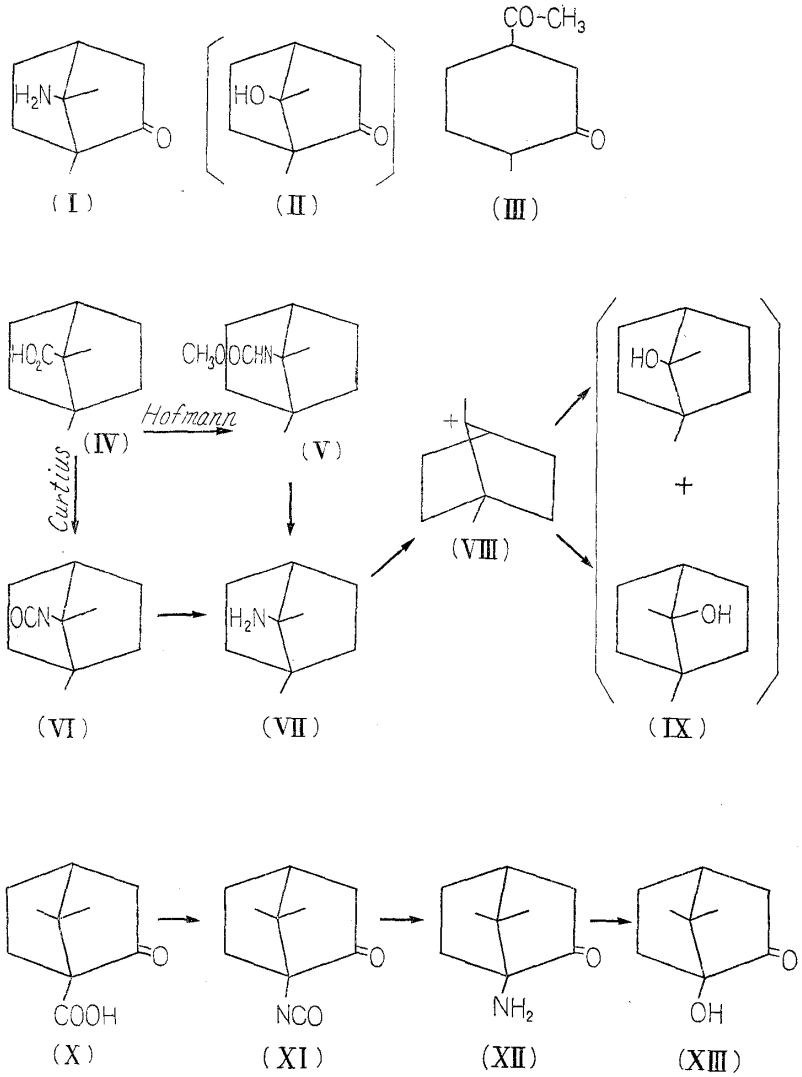
A bimolecular substitution reaction (S_N2) hardly takes place at C_7 of the bridged ring, because the opposite side of the carbon is shielded by the pyramidal ring. Consequently, on the decomposition of the diazonium ion, S_N1 reaction predominates, affording an intermediate carbonium cation (VIII). In this case C_1, C_7, C_5, and C_π may lie on one plane, then hydroxyl anion can combine with the cation center at C_7 on both sides by equal probability, thereby providing a pair of enantimorphous 7-hydroxy-π-apocamphane (IX).

This compound (IX) is quite stable even on warming with alkalis or acids. This indicates that the reduction of carbonyl at C_2 decreases the intramolecular tension of the bicycloheptanone ring that leads to stabilization of the bridged bond.

It seems worth while to study the stability of 1-hydroxy-10-apocamphor (XIII) in which the hydroxyl group is placed on a bridged edge vicinal to the carbonyl group.

* Present adress: Pharmaceutical Institute, University of Hokkaido, Sapporo (河田明治).
** Hongo, Tokyo (石館守三).

1) Part IV. This Bulletin, **4**, 108(1956).
2) Parts I and II. M. Yoshida: *Ibid.* **3**, 216, 219(1955).
3) Y. Asahina, M. Ishidate: Ber., **66**, 1673(1933).



For the preparation of this new compound, 1-amino-10-apocamphor (XII) was synthesized by the Curtius reaction of *d*-ketopinic acid (X), which was derived from *d*-camphor through *d*-10-hydroxycamphor[4]. 1-Amino-10-apocamphor (XII) thereby obtained is dextrorotatory and quite stable to both alkalis and acids.

On treatment with nitrous acid it gives without difficulty a camphor-like product which forms a monosemicarbazone, and this is none other than 1-hydroxy-10-apocamphor. Though the compound is strongly levoratory it does not indicate the occurrence of steric inversion during deamination, because in this case, unlike in the case of 7-hydroxy-π-apocamphane (IX) discussed above, the substitution (S_N1 reaction) would occur at the tetrahedral position of the fixed bridge end which enables the original configuration to be maintained.

It should be mentioned that 1-hydroxy-10-apocamphor is as stable as 4-hydroxycamphor.

We are indebted to Messrs. E. Kimura and M. Endo for carrying out the microanalyses, and also to Mr. H. Shindo, Sankyo Co. Ltd., for the determination of infrared spectra. The work was financed in part by the Grant of Pharmacological Research Foundation, to which our thanks are also due.

Experimental

Hofmann degradation of *l-trans*-π-Apocamphane-7-carboxylic Acid (IV): *l*-π-Apocamphane-7-carbonylamide—*l*-π-Apocamphane-7-carboxylic acid (*l*-dihydroteresantalic acid)[3] (IV), prepared from

d-isoketopinic acid by the Wolff-Kishner reduction, was derived to its carbonyl chloride (b.p_{48} 112～113°, $[\alpha]_D^{13.5}$ −26.1°(c=4.6 in $CHCl_3$) by treatment with $SOCl_2$ The chloride dissolved in ether was treated with NH_3 gas. π-Apocamphane-7-carbonylamide was obtained as colorless prisms, m.p. 206～205°, from ligroine; $[\alpha]_D^{13.5}$ −15.3°(c=6.70 in EtOH). *Anal.* Cald. for $C_{10}H_{17}ON$: C, 71.81; H, 10.25; N, 8.38. Found : C, 71.74; H, 9.72; N, 8.55.

***l*-7-Methoxycarbonylamino-π-apocamphane**(V)—To a mixture of MeONa(0.3 g. Na in 23 cc. MeOH) and 1 g. of the carbonylamide was added dropwise 1 g. of Br_2 under cooling, the mixture was heated for 4 hrs., and left standing over night. The reaction mixture was treated with ice water and extracted with ether. The residue (1 g.) from the dried ether solution was recrystallized from light petroleum to colorless prisms, m.p. 69～70°, $[\alpha]_D^{13.5}$ −37.3°(c=10.10 in EtOH). *Anal.* Cald. for $C_{11}H_{19}O_2N$: C, 66.97; H, 9.71; N, 7.10. Found : C, 66.76; H, 9.65; N, 7.09.

***l*-7-Amino-π-apocamphane** (VII)—The compound (V) (0.9 g.) was heated with 5 cc. of 36% HCl on a water bath until the mixture completely dissolved. On cooling, the crystals that separated were recrystallized from EtOH to colorless prisms, m.p. 285～290°(decomp.) (hydrochloride of (VII) *cf.* below). The hydrochloride was dissolved in water, the solution was made alkaline with NaOH, and extracted with ether. The residue of the dried ethereal solution was purified by sublimation to give colorless plates, m.p. 161～162°, $[\alpha]_D^{13.5}$ −10.4°(c=6.70 in EtOH).

Hydrochlorid of (VII) : (VII) was dissolved in 10% HCl and evaporated to dryness. The residue was recrystallized from EtOH to colorless prisms, m.p. 285～290°(decomp.). *Anal.* Calcd. for $C_9H_{17}N \cdot HCl$: C, 61.53; H, 10.26; N, 7.98. Found : C, 61.70; H, 10.02; N, 7.94.

***p*-Toluenesulfonyl Derivative of (VII)**—A solution of 0.5 g. of (VII) in 3 cc. pyridine was mixed with 0.75 g. *p*-toluenesulfonyl chloride and left standing over night. The reaction mixture was diluted with water and the precipitate was recrystallized from dil. EtOH to colorless plates, m.p. 175°. *Anal.* Cald. for $C_{16}H_{23}O_2NS$: N, 4.78. Found : N, 4.72.

Curtius Degradation of (IV); π-Apocamphane 7-Isocyanate (VI)—To a solution of 5 g. of *l*-π-apocamphane-7-carbonyl chloride in 20 cc. xylene was added 3 g. of NaN_3 and the mixture sealed in a tube was heated at 170～180° for 16 hrs. The reaction mixture, after filtration, was purified by fractional destillation, yielding 2.5 g. of oil, b.p_7 193～198°.

The isocyanate (2.5 g.) dissolved in 5 cc. HCl (38%) was heated under reflux for 4 hrs. After cooling the reaction mixture was washed with ether, made alkaline with NaOH, and extrated with ether. The residue from the evaporated ethereal solution was purified by sublimation. The separated 7-amino-π-apocamphane (m.p. 161～162°, $[\alpha]_D^{13.5}$ −10.3°(10% solution in EtOH)), and its *p*-toluenesulfonyl derivative (m.p. 175°) were identified with those obtained by the Hofmann degradution of (IV).

***rac*-7-Hydroxy-π-apocamphane (IX)**—7-Amino-π-apocamphane (VII) (3 g.) was dissolved in 21 cc. of 10% H_2SO_4 and 90 cc. of 5% $NaNO_2$ solution was added dropwise during 3 hrs. The separated oil was extracted with ether, the ether extract was washed successively with NaOH solution and water, dried, and evaporated at room temperature. The residue (yield, 2.1 g.) was recrystallized from light petroleum using dry ice, to fine needles, m.p. 128°, $[\alpha]_D^{18}$ ±0°(c=4.10 in EtOH). The infrared spectrum of (IX) exhibited no carbonyl band in 5.8 μ region but characteristic absorptions at 2.8 μ and 8.3～9.9 μ were observed, indicating the presence of an aliphatic tertiary hydroxyl group $\left(\rightarrow\!\!\!\!\diagup C\text{-}OH\right)$.

Preparation of *l*-1-Hydroxy-10-apocamphor : *l*-10-Apocamphor-1-isocyanate (XI)—The starting material, *d*-10-apocamphor-1-carboxylic acid (X) (*d*-ketopinic acid), m.p. 234°, $[\alpha]_D^{24}$ +31.2°, was prepared from 10-hydroxycamphor[4] derived from *d*-camphor by CrO_3 oxidation. Ketopinic chloride (37 g.) obtained from ketopinic acid and $SOCl_2$ was treated with 20 g. of NaN_3 in benzene (120 cc.). The benzene layer was evaporated and the residue was recrystallized from light petroleum to colorless plates, m.p. 105°; $[\alpha]_D^{16}$ −24.4°(5% solution in EtOH). *Anal.* Cald. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31. Found : C, 67.22; H, 7.56.

***d*-1-Amino-10-apocamphor (XII)**—The isocyanate (XI) was hydrolyzed at 70° with 20% HCl solution. The reaction mixture after washing with ether was made alkaline with NaOH and extracted with ether. The residue from evaporation of ether was recrystallized from light petroleum to colorless needles, m.p. 194°; $[\alpha]_D^{17.5}$ +107.5°(c=2.45 in EtOH). *Anal.* Cald. for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found : C, 70.19; H, 9.71.

***l*-1-Hydroxy-10-apocamphor (XIII)**—To a solution of 3 g. of (XII) 45 cc. of 20% $NaNO_2$ solution was gradually added at 60° while stirring. On cooling, the reaction mixture was extracted with ether. The ethereal solution was washed successively with Na_2CO_3 solution and water, dried, and evaporated. The product was recrystallized from petroleum ether to fine needles, m.p. 153°; $[\alpha]_D^{8}$ −81.0°(c=0.28 in EtOH). Yield, 0.7 g.

4) T. Shimamoto, M. Kagawa : Rept. Sci. Res. Inst. Tokyo, **25**, 45(1949).

Semicarbazone : Prepared from (XIII) and semicarbazide in dil. AcOH and recrystallized from acetone; m.p. 200°(decomp.). *Anal.* Calcd. for $C_{10}H_{17}O_2N_3$: C, 56.85; H, 8.11. Found : C, 56.85; H, 8.13.

Summary

7-Hydroxy-π-apocamphane (IX) and 7-hydroxy-10-apocamphor (XIII) were prepared from *l*-π-apocamphane-7-carboxylic acid (IV) and α-ketopinic acid (X) by the Hofmann or Curtius reaction and followed by deamination of the corresponding amines. Both compounds were found to be quite stable in constrast to 7-hydroxy-π-apocamphor (II). 7-Hydroxy-π-apocamphane (IX) was obtained in an optically inactive form, whereas 7-hydroxy-10-apocamphor (XIII) in an active form without steric inversion. The reaction mechanism was discussed.

(Received September 12, 1957)