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Triterpenoid Chemistry. XII.[1] Homo-Favorskii Rearrangement in Triterpenoid Series[2]

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Solvolysis of 3-keto-23-tosyloxy (**A**) and 3-keto-24-tosyloxy (**B**) derivatives of triterpenoid with *t*-butoxide proceeded in stereospecific manner to yield rearranged bicyclo [3,2,0]heptanones (**C**) and (**D**), being antipodal to one another with respect to the ketonic chromophor, whose structures were respectively established by spectral and chemical means. Reinvestigation of solvolysis for the simplest keto-tosylate (**13**) confirmed the formation of two bicyclo[3,1,1]- (**14**) and bicyclo[3,2,0]- (**15**) heptanones. The former rearranged by acid to a new bicyclo[3,2,0]heptanone (**20**), while the latter was stable to acid. Based on these evidences a plausible mechanism (Chart 4) of the homo-Favorskii rearrangement (**13**→**15**) was proposed. A new method of selectively converting a cyclobutanone to a γ-lactone in high yield was described.

In the previous paper[4] we showed that 3-hydroxy-23 or 24-tosyloxy triterpenoids on treatment with base such as *t*-butoxide yielded stereospecific products; *i.e.*, an A-seco-aldehyde when –OH and $-CH_2OTs$ groups are *trans*, or an oxetane when they are in *cis* configurations. Treatment of keto-tosylates (**A**) and (**B**) with LAH gave analogaus results which were implicated by considering that the first step of the reaction was the reduction of 3-keto group to 3β-alcohol.[4] Here we show that treatment of the keto-tosylate (**A**) and (**B**) with base gave entirely different results, no A-seco-acid (**E**) being isolated. The products were rearranged cyclobutanones (**C**) and (**D**) depending on the stereochemistry of the starting compounds indicating that the rearrangement preceeded in stereospecific manner.

We chose the compound (**1**) and (**2**) as models of (**A**) and (**B**) respectively. Cyclobutanones (**3**) and (**4**) were so rapidly formed as completed within 5 min on warming that the formation of them were faster than hydrolysis of acetoxy-group as evidenced by thin-layer chromatography (TLC) studies. Prolongation of the above base treatment of **1** and **2** gave the hydroxy-ketones (**3a**) and (**4a**) respectively, which afforded acetates **3b** and **4b** on acetylation, the latters being also isolated from the short reaction mixtures. The optical rotatory dispersion (ORD) (and also circular dichroism (CD)) spectra of **3a** and **4a** (Fig. 1) exhibited opposite Cotton effects, indicating that they have antipodal structures to one another in the environmental structure concerning the ketonic chromophors. The structural studies described below revealed that they are the bicyclo[3,2,0]heptanones (**C**) and (**D**) respectively rather than the bicyclo[3,1,1,]heptanones (**F**) and (**G**).

The compound **3a** had carbonyl absorption at 1771 cm^{-1}. In the nuclear magnetic resonance (NMR) spectrum it exhibited, in addition with AB quartet of $-CH_2OH$ at δ 3.38 ppm, a broad singlet corresponding of 2H at δ 2.74[5] and a doublet-doublet of 1H at δ 3.33 indicative of $-\overset{|}{C}-C\underline{H}_2-CO-$ and $-CO-C\underline{H}<$ respectively, both of which disappeared on heating the compound in D_2O-dioxane with a catalytic amount of NaOH hence showing that there are three hydrogens exchangable with deuterium around the carbonyl, while the alternative structure

1) Part XI: Y. Tsuda, T. Fujimoto, A. Morimoto, and T. Sano, *Chem. Pharm. Bull.* (Tokyo), **23**, 1336(1975).
2) Preliminary communication: Y. Tsuda, T. Tanno, A. Ukai, and K. Isobe, *Tetrahedron. Letters*, **1971**, 2009.
3) Location: *Tsurumaki 5-1-8, Setagaya-ku, Tokyo, 154, Japan.*
4) Y. Tsuda, K. Isobe, T. Sano, and A. Morimoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 98 (1975).
5) The value δ 2.47 in the communication[2] is misprint and must be revised to this value.

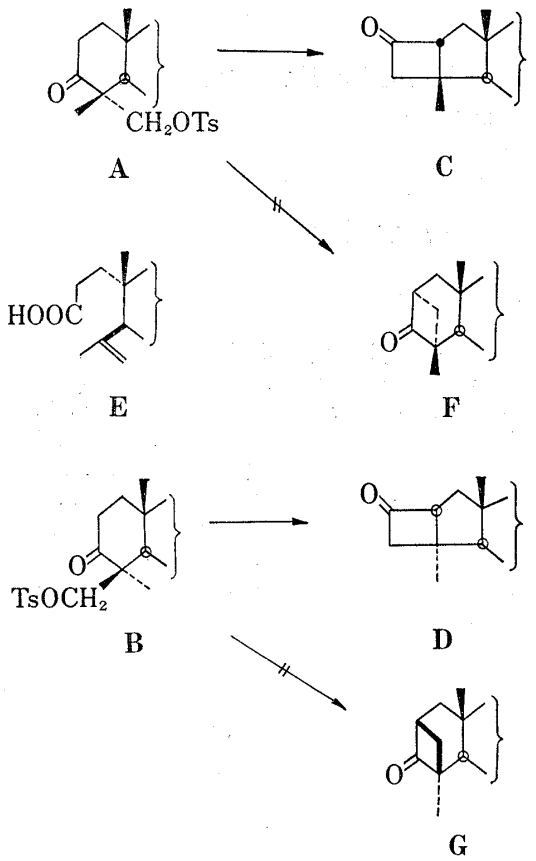


Chart 1

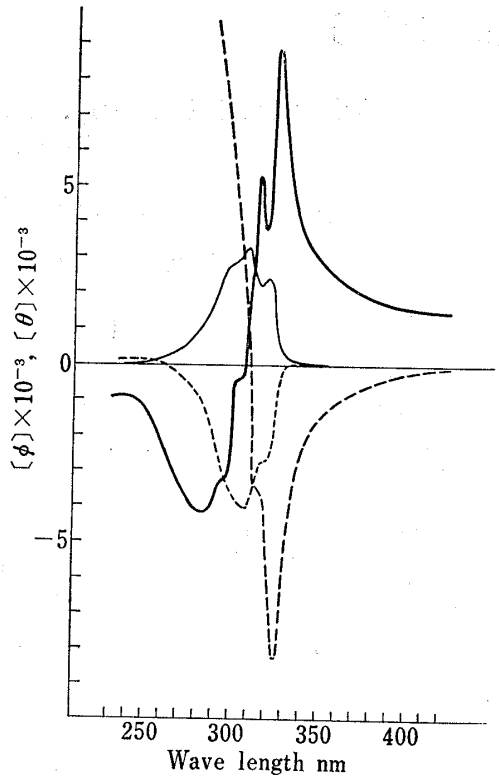


Fig. 1. ORD and CD Spectra of Cyclobutanones

cyclobutanone (**3a**) :ORD ------, CD --------
cyclobutanone (**4b**): ORD ——, CD ——

(**F**) has no such hydrogen. Hydride reduction of **3a** yielded a diol **5a**. In the NMR spectrum of its acetate (**5b**) the geminal proton to the newly formed acetoxy-group[6] appeared as a multiplet at δ 4.9—5.2 ppm., for the corresponding acetate derivable from (**F**) the signal would be a doublet (or a quartet if a large W-type coupling in cyclobutane system are considered).

The following transformations confirmed the above assignment. We found that dilute alkaline hydrogen-peroxide in methanol selectively oxidized cyclobutanone very rapidly even under cold conditions in a Baeyer-Villiger fashion to give γ-lactone. Accordingly, oxidation of **3a** yielded exclusively a γ-lactone (**6a**) of infrared (IR) absorption at 1760 cm^{-1} in a quantitative yield. The NMR signal attributable to >C<u>H</u>–O–CO of the lactone ring appeared at δ 4.68 as a triplet (J=7 Hz) and –OOC–C<u>H_2</u>– as an AB quartet at δ 2.46 (J=18, δ_{AB}=23 Hz). LAH reduction of **6a** gave a triol (**7a**), the acetate on which indicated in its NMR spectrum the presence of $-CH_2-C\underline{H}_2-OAc$ (2H, triplet at δ 4.16, J=8 Hz) and >C<u>H</u>–OAc (1H, multiplet at δ 4.9—5.3) in addition with $-\overset{|}{C}-C_{(28)}H_2-OAc$ at δ 3.90 (2H, ABq. J=12, δ_{AB}=23 Hz). These agreed with the structure **7b**.

Similarly the other cyclobutanone (carbonyl absorption at 1770 cm^{-1}) was established as **4a**. In its acetate (**4b**) three protons attributable to –C<u>H_2</u>CO– and >C<u>H</u>–CO– appeared at δ 2.2—3.3 as overlapped multiplets which were exchangable with deuterium as shown by disappearence of the signals on treatment with NaOH–D_2O in dioxane; in contrast to **3a** the couplings between H_A and H_B and between H_A and 5α-H (W-type) are causing complexity of the pattern (see **H** in Chart 2). The diacetate (**8b**) obtained from **4a** by hydride reduction followed by acetylation exhibited the signal due to the newly formed>C<u>H</u>–OAc on the cyclo-

6) The stereochemistry of this group is uncertain. We tentatively assume that it is in α-orientation, since hydride attack to the ketone **4** from the convex-face would be favoured.

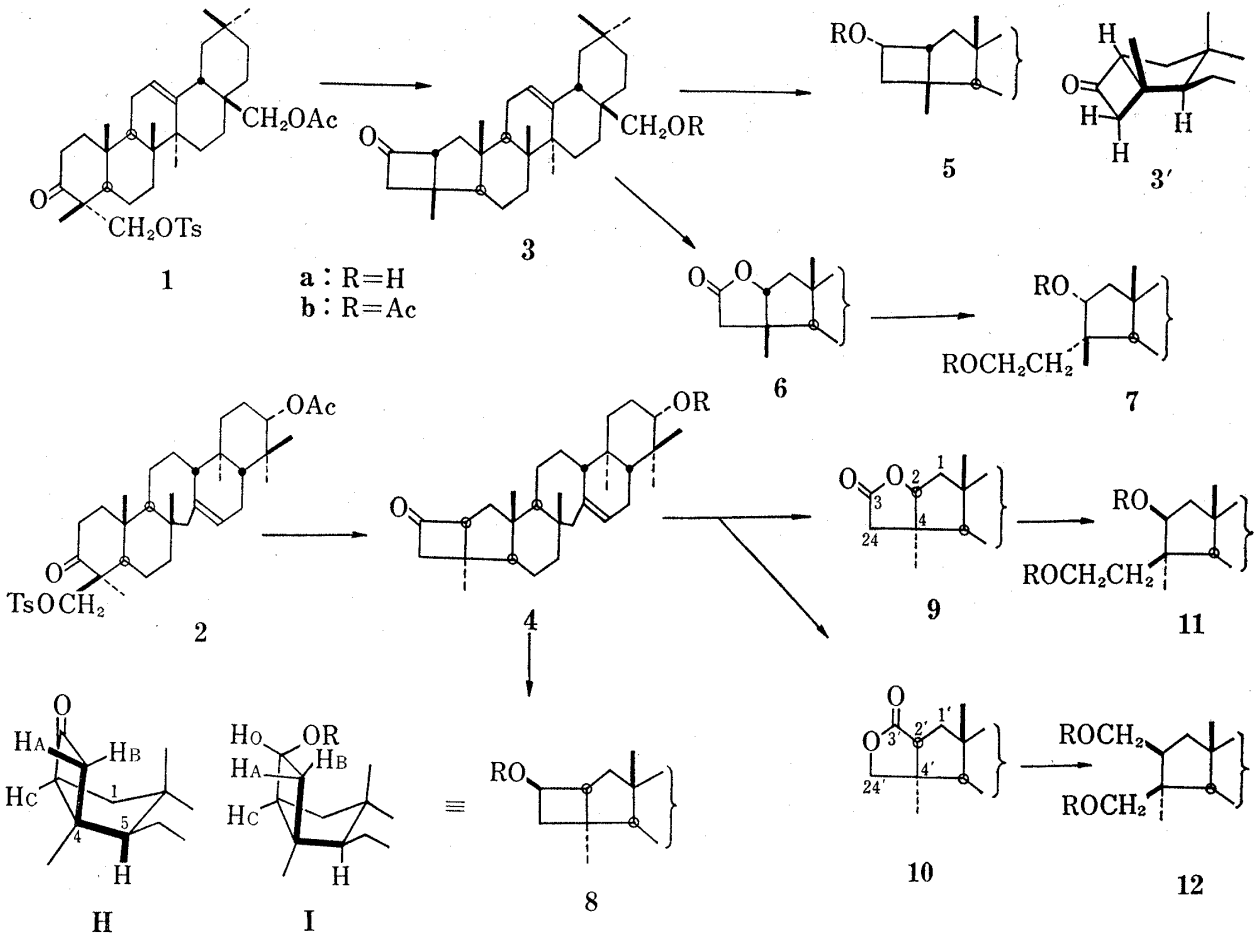


Chart 2

butane ring at δ 5.20 as a quartet (in ratio of 1: 3: 3: 1 with J=9 Hz). This is conceivable if the acetate has the configuration (**I**) in which all coupling constants, J (H_O–H_A), J (H_O–H_C), and J (H_O–H_B) will be almost equal since dihedral angles θ (H_O–H_C) and θ (H_O–H_C) should be about 30° and θ (H_O–H_B) about 150° due to the steric repulsion between the 3β-acetoxyl and 10-Me. Oxidation of **4a** with 1% H_2O_2–0.5% NaOH in dioxane–methanol gave a product having a γ-lactone absorption at 1770 cm^{-1}. Though this product showed a single spot on TLC, its NMR spectrum indicated that it is a mixture of γ-lactones (**9a**) and (**10a**) (see Fig. 2).

LAH reduction of the lactonic product yielded two triols in ratio of *ca.* 3: 1, which were easily separated by chromatography. In the NMR spectrum of their triacetates, the major compound exhibited signals at δ 4.95 (1H, q. J_1=3, J_2=5 Hz) and at δ 4.10 (2H, t. J=8 Hz) indicative of >C<u>H</u>–OAc and –CH_2–$C\underline{H}_2$OAc in addition with >$C_{(21)}$H–OAc at δ 4.47 (1H, m), while the minor compound had two –$C\underline{H}_2$–OAc groups as evidenced from the overlapped signals at δ 4.18 (2H, m) and at δ 4.15 (2H, broad s.). Consequently the structure of the former was elucidated as (**11b**) and that of the latter as (**12b**).

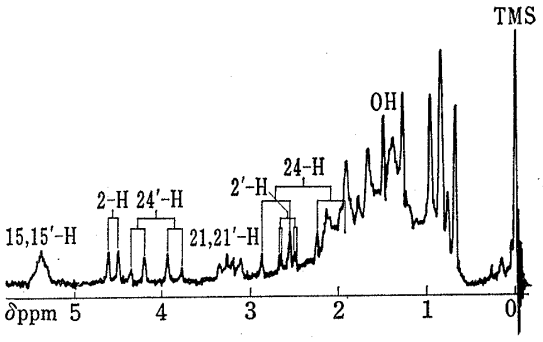


Fig. 2. NMR Spectrum of **9a** and **10a** (60MHz, solvent : $CDCl_3$)

The evidence described above substantiated the structure of the original cyclobutanone as **4a**.

Prolonged reaction with *t*-BuOK caused further changes on the cyclobutanones **3** and **4**, additional to the hydrolysis of the acetate grouping the products being the same as those of alkaline peroxide oxidation; *i.e.*, γ-lactones or their corresponding hydroxy-acids. Thus **3** yielded **6a**, and **4** gave a mixture of **9a** and **10a**. Apparently aerial oxygen must be working as an oxidizing agent in these cases though the yield of the products were not improved by bubbling air.

The similar homo-Favorskii rearrangement was firstly observed by Wiberg and Klein[7] who isolated a bicyclo[3,2,0]heptanone (**15**) together with the expected intramolecular alkylation product, bicyclo[3,1,1]heptanone (**14**) on solvolysis of a keto-tosylate (**13**) with methanolic potassium hydroxide, and they postulated that the former would be produced via **16** by the alkenyl migration followed by zwitter-ion collapse. The formation of such two kinds of bicycloheptanones was again confirmed by several workers.[8–10] According to Wiberg's mechanism a keto-tosylate (**13**) if it is optically active should lose its activity in a resulting bicyclo[3,2,0]heptanone since the intermediate carbonium ion (**16**) has no optically active center, hence either keto-tosylate (**A**) and (**B**) would give the products of the same sterically favoured configuration. However, this mechanism could not be responsible for the observed results with (**1**) and (**2**), which gave the antipodal bicyclo[3,2,0]heptanones in excellent yields as shown above, indicating that the reaction proceeded with complete retention of the comfiguration at C_4.

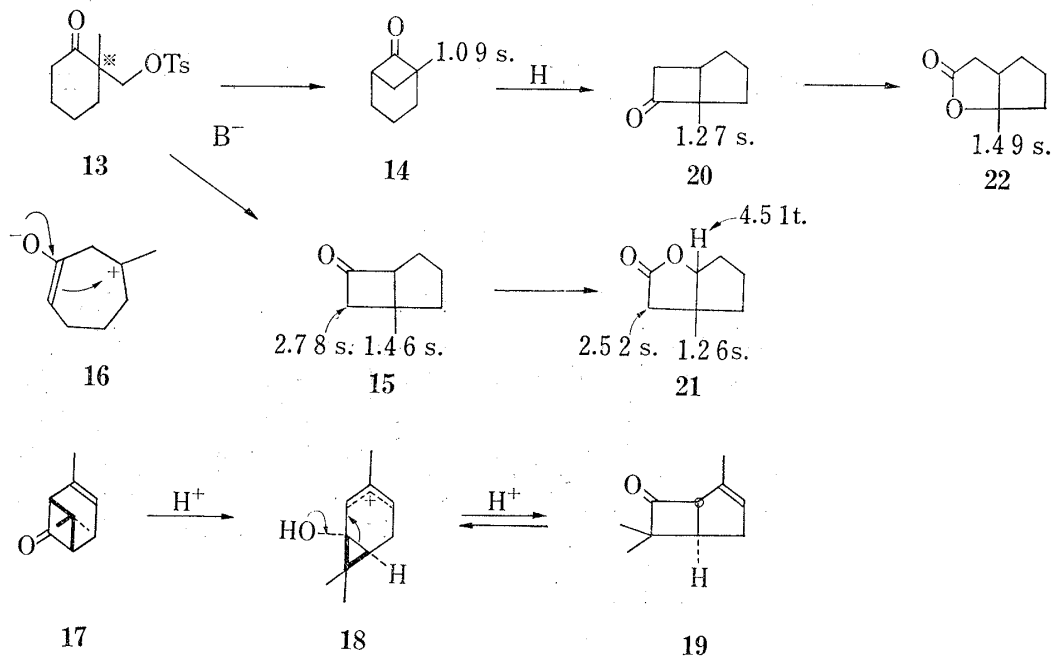


Chart 3

An alternate explanation for stereospecificity of the reaction is that they are produced, during the reaction or on working up, form an intermediate bicyclo[3,1,1]heptanones, (**F**) and (**G**), as in the case of the acid catalysed rearrangement of crythanthenone[11] (**17**) to (+)-2,4,4-trimethylbicyclo[3,2,0]hept-5-en-7-one (**19**), for bow-stern interactions in (**F**) and (**G**)

7) K.B. Wiberg and G.W. Klein, *Tetrahedron Letters*, **1963**, 1043.
8) F. Nerdel, D. Frank, and H. Marshall, *Chem. Ber.*, **100**, 720 (1967).
9) A. Barco, G.P. Dollini, M. Anastasia, G. Traverso, E. Taddie, and G. Begiuli, *Gazz. Chim. Italy*, **99**, 735 (1969).
10) E. Wenkert, P. Gakuzis, R.J. Baumgarten, C.L. Leicht, and H.P. Schenk, *J. Am. Chem. Soc.*, **93**, 3208 (1971).
11) W.F. Erman, *J. Am. Chem. Soc.*, **91**, 779 (1969).

would be large enough to cause such rearrangement, though in (**F**) and (**G**) there is no unsaturation, the presence of which is possibly a driving force in rearrangement of **17**.

To test a possibility of rearrangement of (**F**) and (**G**) we reinvestigated the solvolysis of **13**. The ratio (2: 3) of **14** and **15** obtained from **13** by action of *t*-BuOK in BuOH was estimated by gas chromatography (GC) and by intensity ratio of methyl peaks (δ 1.09 for **14** and δ 1.46 for **15**) in the NMR spectrum of the product, which was the same with that of the mixture obtained from the reaction of NaOH in MeOH[8,10] showing that solvents do not affect the formation of the two products. This ratio was not varied at any stage of the reaction, though the both peaks appeared in the earliest stage and increased their intensities as the reaction proceeded. Prolongation of heating the mixture in basic conditions did not produce any affection on the ratio of **14** and **15**. These facts indicate that bases affect neither to **14** nor to **15**. On the contrary, when the mixture of **14** and **15** was treated with acid (*e.g.* oxalic acid, hydrochloric acid), **14** was smoothly changed into a new compound (**20**) while **15** was remained unaffected. This was shown by disappearence of the NMR peak at δ 1.09 and appearence of a new peak at δ 1.27, the peak at δ 1.46 for **15** being remained unchanged. Although **15** and **20** was not separated by GC which gave overlapped single peak, the structure of **20** was elucidated as follows. The mixture showed a single cyclobutanone absorption at 1778 cm^{-1} and was transformed quantitatively by treatment with cold 1% H_2O_2 in 0.5% NaOH–MeOH to a mixture of γ-lactones, (**21**) and (**22**), which had the carbonyl band at 1760 cm^{-1} in the IR absorption and methyl peaks at δ 1.49 and at δ 1.26 respectively in a ratio of 2: 3 in the NMR spectrum. A singlet at δ 2.52 and a triplet at δ 4.51 were attributable to –C(=O)–C<u>H</u>$_2$–COO– and COO–C<u>H</u>< of **21** respectively, but no other proton to geminal to lactonic oxygen was observed suggesting that the other lactone had the structure (**22**). Appreciable down field shift (δ 1.27→δ 1.49) of the methyl peaks in **22** also supported this assignment.

These evidence indicate that the saturated bicyclo[3,1,1]heptanone (**14**) can actually rearrange to a bicyclo[3,2,0]heptanone by action of acid, though the product is not the expected **15** but the compound of the different structure **20**. This is conceivable by comparing the stability of two possible intermediates, the tertiary carbonium ion (**26**) being apparently more stable than the secondary ion (**25**; OH instead of O^-) (see Chart 4).

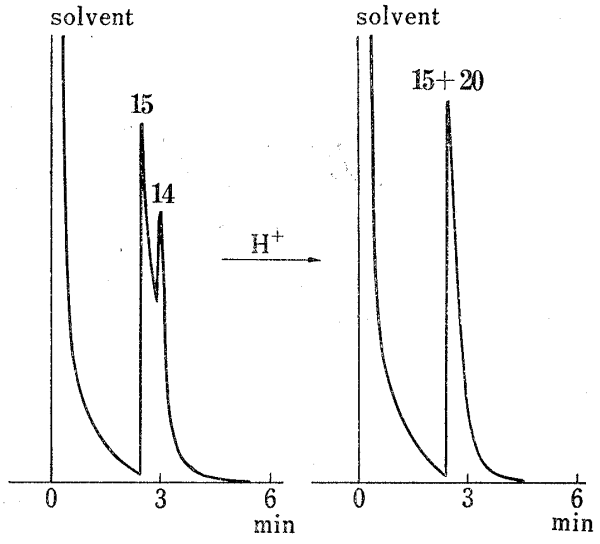
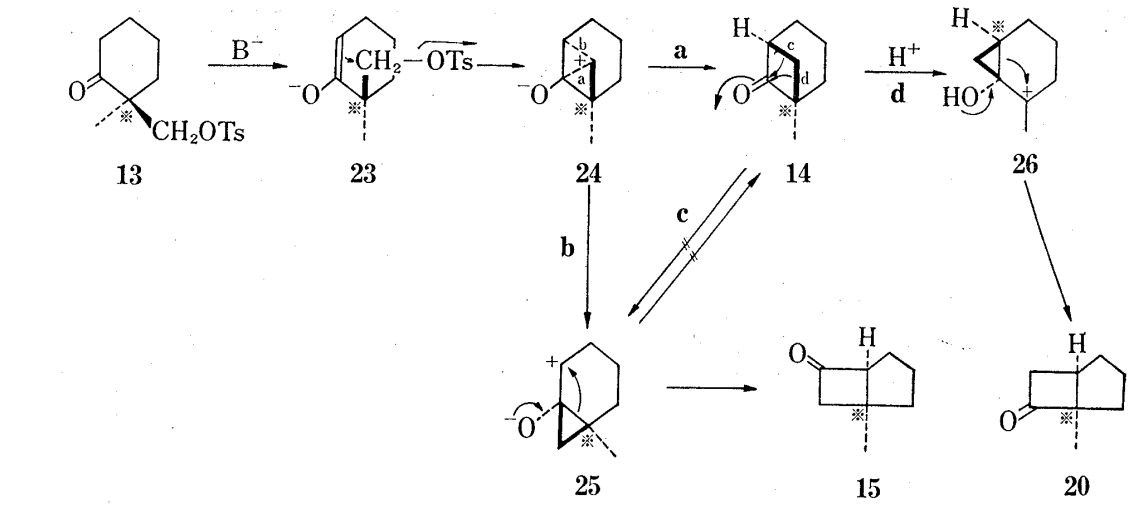


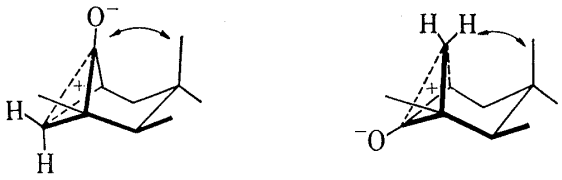
Fig. 3. Gas Chromatogram of **14**, **15** and **20**
condition: column, 3% SE-30; column temp., 50°; carrier gas, N_2, (30 ml/min)

Consequently the most probable mechanism of the formation of **14** and **15** from **13** is that as depicted in Chart 4. **14** and **15** are produced by an independent path from the common intermediate (**24**) which is formed by homoallylic conjugation of enolate (**23**) with the cation derived from the tosylate. Cleavage of bond **a** and ketonization of the resulting enolate will lead to the bicyclo[3,1,1]heptanone (**14**) (path **a**), while cleavage of bond **b** furnishes cyclopropanolate (**25**) which will rearrange to the bicyclo[3,2,0]heptanone (**15**) hence with retention of configuration at C* (path **b**).

The intermediacy of a cyclopropanolate (**25**) was firstly suggested by Mukharji, *et al.*[12] who assumed that the both cyclobutanones **14** and **15** were the rearranged products from **25**. According to their mechanism there must be increase of steric repulsion in transformation

12) P.C. Mukharji, P.K. SenGupta, and G.S. Sambamurti, *Tetrahedron*, **25**, 5287 (1969).





J from A K from B

Chart 4

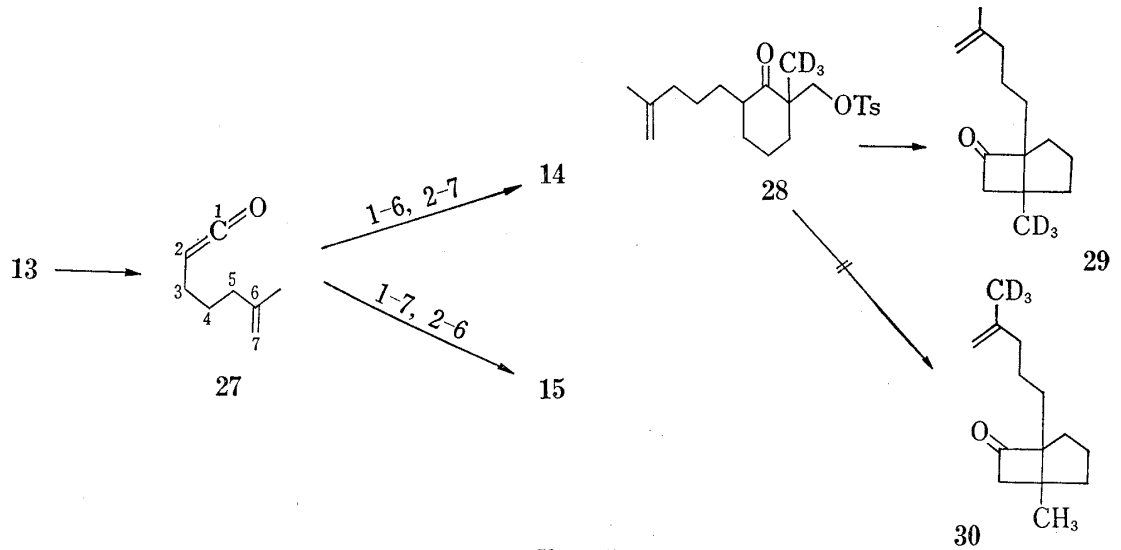


Chart 5

of **25** to **14**, this being quite unlikely. We saw above that cyclopropanolate (**26**) formed from **14** gave bicyclo[3,2,0]heptanone (**20**) only, and there is no reason to deny that **14** is the direct intramolecular alkylation product. Wenkert, *et al.*[10] showed that the enolate (**23**) is the reacting species in the solvolysis of the ketotosylate (**13**). Hence we propose that the common intermediate of formation of **14** and **15** is the bridged ion (**24**), in which there is an appreciable flag-pole interaction: this must be a driving force to follow the reaction by path **b**. In the triterpenoids, the presence of 10-Me will serve serious non-bonded interactions in the intermediates (**J**) and (**K**), and this non-bonded interaction will increase in converting the intermediate to the bicyclo[3,1,1]heptanones (**F**) and (**G**), hence prevent the cleavage of bond **a** completely and direct the reactions toward relieves of the interactions, thus giving bicyclo[3,2,0]heptanones (**C**) and (**D**) as sole products respectively.

After our communication appeared Baldwin and Page jun.[13] suggested the ketene intermediacy (**27**) which by 1, 6 and 2, 7 addition would lead to **14**, and by 1, 7 and 2, 6 addition would give **15**. However, the ketene mechanism again does not explain the stereospecificity observed in the triterpenoid keto-tosylates, and recently there were accumulated several evidence[14,15] to reject the ketene mechanism. Particularly the clear evidence presented by Wolff and Cheer[15] that solvolysis of **28** gave a sole bicyclo[3,2,0]heptanone (**29**) is a strong support of our proposal.

Experimental

Unless otherweise stated, the IR spectra were taken as a KBr disc, the ORD and CD spectra for dioxane solution, and the NMR spectra were measured in $CDCl_3$ solution by using a 60 MHz machine and the chemical shifts are given in δ ppm referred to the internal tetramethylsilane. Melting points were determined on Yanagimoto mp apparatus and uncorrected. Acid-washed alumina was used for column chromatography, and for TLC silica gel G as an absorbent and $CHCl_3$–MeOH as a developing solvent. Acetylations were carried by heating the compound with excess acetic anhydride and pyridine for a few min and keeping the mixture overnight at room temp, then worked up as usual. Identities were confirmed by IR and TLC comparisons, and by mixed fusion with the authentic specimens.

The Cyclobutanone (3)——The hederagenin derivative **1** (500 mg) was dissolved in 50 ml of *t*-BuOH containing 50 mg of *t*-BuOK and heated on a water-bath for 3 min. The mixture was poured into ice-water, acidified with 5% HCl, and extracted with ether. The ethereal extract was washed with water, dried over $MgSO_4$, and evaporated to give a residue which showed mainly two spots corresponding to **3a** and **3b**. The residue was hydrolysed with 5% K_2CO_3–MeOH under reflux for 2 hr, and the product obtained by acidification and ether extraction was chromatographed over alumina. *n*-Hexane–benzene (1 : 1) elute was collected and crystallized from ether or methanol to afford **3a** as needles, mp 223—225°. IR cm^{-1}: 1771. NMR: 0.90 (9H), 0.96 (3H), 1.20 (3H), 1.37 (3H), 2.74 (2H, broad s.), 3.33 (1H, d.d., $J_1=4$, $J_2=9$ Hz), 3.38 (2H, ABq., $J=11$, $\delta_{AB}=22$ Hz), 5.20 (1H, m.). ORD ($c=0.5\times10^{-3}$) [ϕ] (nm): −8200° (325) (trough). CD (0.5×10^{-3}) [θ] (nm): −4100 (309) (negative maximum). *Anal.* Calcd. for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57. Found: C, 81.85; H, 10.39. On acetylation **3a** gave an acetate **3b** as a gum. IR ($CHCl_3$) cm^{-1}: 1765, 1730. NMR: 0.90 (9H), 0.96(3H), 1.18(3H), 1.36(3H), 2.05(3H), 2.77 (2H, broad s.), 3.35 (1H, d.d., $J_1=4$, $J_2=10$ Hz), 3.88 (2H, ABq., $J=11$, $\delta_{AB}=22$ Hz), 5.23 (1H, m.).

The Cyclobutanone (3a)-d_3——The cyclobutanone **3a** (50 mg) in dioxane (20 ml) was heated with NaOH (70 mg) and D_2O (0.3 ml) for 2.5 hr. Working up as usual, **3a-d_3**, mp 223—225°, was obtained. The signals at δ 2.74 (2H, s.) almost disappeared, and that at δ 3.33 (1H, d.d.) weakened.

The Cyclobutanol (5)——The cyclobutanone **3a** (50 mg) and lithium aluminum hydride (LAH) (15 mg) in tetrahydrofuran (THF) (15 ml) were heated under reflux for 2.5 hr. Excess of LAH was decomposed by adding a saturated solution of Na_2SO_4, filtered, and the precipitate was washed with CH_2Cl_2. The combined filtrate was dried over $MgSO_4$ and evaporated to dryness to give a residue which was crystallized in needles from MeOH to give **5a**, mp 217—219°. IR cm^{-1}: 3250. On acetylation **5a** gave an acetate **5b**, mp 110—113°. IR (Nujol) cm^{-1}: 1740. NMR: 0.76 (3H), 0.90 (6H), 0.96 (3H), 1.08 (3H), 1.25 (3H), 2.03 (3H), 2.05 (3H), 3.88 (2H, ABq., $J=11$, $\delta_{AB}=22$ Hz), 4.9—5.2 (2H).

H_2O_2–NaOH Oxidation of 3a——To a solution of a cyclobutanone **3a** (50 mg) and 4N NaOH (1 ml) in MeOH (30 ml), 30% H_2O_2 (1 ml) was added and the mixture was stirred for 5 min at 0°. The mixture was poured into ice-water, acidified with 5% HCl, and extracted with ether which was dried over $MgSO_4$ and evaporated to dryness to give **6a** as a gum. IR ($CHCl_3$) cm^{-1}: 1760. NMR: 0.90 (6H), 0.95 (6H), 1.20 (3H), 1.23 (3H), 2.46 (2H, ABq., $J=18$, $\delta_{AB}=23$ Hz), 3.40 (2H, ABq., $J=11$, $\delta_{AB}=22$ Hz), 4.68 (1H, t., $J=7$ Hz), 5.21 (1H, m.). On acetylation **6a** gave an acetate **6b**, gum. IR ($CHCl_3$) cm^{-1}: 1760, 1725. NMR: 0.90 (6H), 0.93 (3H), 0.96 (3H), 1.20 (3H), 1.23 (3H), 2.06 (3H), 2.46 (2H, ABq., $J=18$, $\delta_{AB}=23$ Hz), 3.90 (2H, ABq., $J=11$, $\delta_{AB}=22$ Hz), 4.73 (1H, t., $J=7$ Hz), 5.26 (1H, m.).

LAH Reduction of γ-Lactone (6a)——The γ-lactone **6a** (50 mg) and LAH (15 mg) in THF (15 ml) were heated under reflux for 2.5 hr and worked up as usual. The product was acetylated and the acetate in CH_2Cl_2 was purified by passing through a short column of alumina. The acetate (**7b**), gum, showed one spot on TLC and had following spectral data. IR ($CHCl_3$) cm^{-1}: 1725. NMR: 0.90 (6H), 0.98 (6H), 1.07 (3H), 1.20 (3H), 2.06 (9H), 3.90 (2H, ABq., $J=12$, $\delta_{AB}=23$ Hz), 4.16 (2H, t., $J=8$ Hz), 4.9—5.3 (1H), 5.26 (1H, m.).

Action of *t*-BuOK on the Cyclobutanone (3a)——The cyclobutanone **3a** (70 mg) in *t*-BuOH (10 ml) containing 200 mg of K was heated under reflux for 5 hr. The product obtained as above showed mainly two

13) S.W. Baldwin and E.H. Page, jun, *Chem. Comm.*, **1972**, 1337.
14) R.H. Bisceglia and C.J. Cheer, *Chem. Comm.*, **1973**, 165.
15) S. Wolff and W.C. Agosta, *Chem. Comm.*, **1973**, 771.

spots, which was chromatographed in benzene over alumina (1×1.5 cm). The benzene eluate (80 ml) gave γ-lactone (**6a**). The residue obtained from methanol eluate was heated with Ac_2O (20 ml) at 160° for 1 hr. The product after evaporation of the solvent showed a spot identical with **6b** which was accompained with small amount of more mobile spot.

The Cyclobutanone (4)——The Serratriol derivative **2** (200 mg) in 0.5% *t*-BuOK–*t*-BuOH (20 ml) was warmed on a water-bath for 20 min. The mixture was poured into water, acidified with 5% HCl, and extracted with CH_2Cl_2. The organic extract was washed with water, dried over $MgSO_4$, and evaporated to dryness. The residue was acetylated and the product was crystallized from CH_2Cl_2–MeOH to give **4b** (140 mg) as colorless needles, mp>300°. IR cm^{-1}: 1778, 1735. NMR: 0.70 (3H), 0.80 (3H), 0.85 (6H), 0.91 (3H), 1.37 (3H), 2.06 (3H), 2.2—3.3 (3H), 4.53 (1H, m.), 5.41 (1H, m.). ORD ($c=0.5\times10^{-3}$) [ϕ] (nm): +9000° (325) (peak). CD ($c=0.5\times10^{-3}$) [θ] (nm): +3280 (309) (positive maximum). *Anal.* Calcd. for $C_{32}H_{48}O_3$: C, 79.95; H, 10.07. Found: C, 79.65; H, 9.87.

The alcohol (**4a**) was obtained by hydrolysis of **4b** with 5% KOH–MeOH. It formed needles from CH_2Cl_2–MeOH, mp 264—268°. IR cm^{-1}: 1770. NMR: 0.68 (3H), 0.82 (3H), 0.83 (6H), 0.97 (3H), 1.37 (3H), 2.2—3.3 (4H), 5.39 (1H, m.).

The Cyclobutanone (4)-d_3——The cyclobutanone **4a** (50 mg) and NaOH (70 mg) in D_2O (0.3 ml) and dioxane (2 ml) were heated on a steam-bath for 4 hr. The mixture was poured into ice-water, and extracted with CH_2Cl_2. The dried extract on evaporation of the solvent left **4a-d_3**, mp 264—267°. The signals at δ 2.2—3.3 (4H) markedly weakered (1—1.5 H). On acetylation a signal corressponding to 1H (>CH–OAc) shifted to down-field and there was left signals corresponding to 0.5 H in this region.

The Cyclobutanol (8)——The cyclobutanone **4b** (70 mg) and LAH (20 mg) in THF (20 ml) were stirred overnight at room temperature. After addition of a few drops of water, the mixture was filtered and the residue extracted repeatedly with CH_2Cl_2. The combined filtrate was dried over Na_2SO_4, evaporated to dryness, and the residue was acetylated. Crystallization of the product from CH_2Cl_2–MeOH yielded **8b** (63 mg) as needles, mp 238—239°. IR cm^{-1}: 1730. NMR: 0.70 (3H), 0.86 (6H), 0.91 (3H), 1.10 (3H), 1.19 (3H), 2.05 (6H), 4.53 (1H, m.), 5.20 (1H, q., $J=9$ Hz), 5.37 (1H, m.).

Oxidation of Cyclobutanone (4) with H_2O_2–NaOH——i) To a solution of **4a** (100 mg) in dioxane (30 ml) and MeOH (60 ml) was added 4N-NaOH (4 ml) and 30% H_2O_2 (4 ml), and the mixture was kept for 1 hr at 0°. After acidification with 5% HCl the mixture was extracted with CH_2Cl_2 which was dried over $MgSO_4$. Evaporation of the solvent from the extract left a crystalline residue, a mixture of **9a** and **10a**, which showed one spot on TLC. IR cm^{-1}: 1770. CD: no Cotton effect.

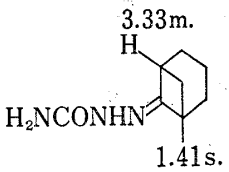
ii) The acetate **4b** (50 mg) was likewise oxidized to yield a mixture of **9b** and **10b** (45 mg), mp>300°, which showed one spot on TLC. IR (Nujol) cm^{-1}: 1765, 1730.

LAH Reduction of γ-Lactones, (9a) and (10a)——The above obtained mixture of **9a** and **10a** (80 mg) and LAH (30 mg) in THF (20 ml) were heated under reflux for 2 hr. After decomposition of excess LAH by addition of water saturated with Na_2SO_4. The mixture was diluted with CH_2Cl_2 and filtered. Evaporation of the solvent from the dried filtrate left a crystalline residue which was acetylated and the product was separated by chromatography in benzene over alumina to **11b** (50 mg) and **12b** (18 mg). The major triacetate (**11b**) crystallized in needles from MeOH–CH_2Cl_2, mp 174—176°. IR cm^{-1}: 1730. NMR: 0.70 (3H), 0.84 (6H), 0.91 (3H), 0.95 (3H), 1.10 (3H), 2.03 (3H), 2.06 (6H), 4.10 (2H, t., $J=8$ Hz), 4.47 (1H, m.), 4.95 (1H, q., $J_1=3$, $J_2=5$ Hz), 5.36 (1H, m.). *Anal.* Calcd. for $C_{36}H_{56}O_6$: C, 73.93; H, 9.65. Found: C, 73.69; H, 9.62. The minor triacetate (**12b**) crystallized in needles from MeOH–CH_2Cl_2, mp 201—203°. IR cm^{-1}: 1740. NMR: 0.70 (3H), 0.80 (3H), 0.85 (3H), 0.92 (6H), 1.15 (3H), 2.03 (9H), 4.15 (2H, broad s.), 4.18 (2H, m.), 4.50 (1H, m.), 5.35 (1H, m.). *Anal.* Calcd. for $C_{36}H_{56}O_6$: C, 73.93; H, 9.65. Found: C, 73.72; H, 9.58.

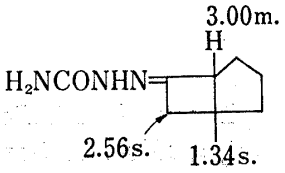
Action of *t*-Butoxide on the Cyclobutanone (4a)——Cyclobutanone **4a** (100 mg) in 5% *t*-BuOK–*t*-BuOH (10 ml) was heated under reflux for 5 hr. The mixture was poured into water, acidified with d. HCl, and extracted with $CHCl_3$. The residue obtained from the dried extract was chromatographed in benzene over alumina and the benzene elute was acetylated to give a mixture of γ-lactones, **9b** and **10b** (60 mg), mp>300°, shown by TLC and IR. CH_2Cl_2–MeOH eluate which was immobile on TLC was collected and heated with Ac_2O (15 ml) on a water-bath for 1 hr. The solvent was evaporated *in vacuo* and the residue chromatographed in benzene over alumina. Benzene eluate gave crystals, whose IR spectrum was identical with that of the mixture of **9b** and **10b**.

Action of *t*-BuOK on the Ketotosylate (13)——To a solution of the ketotosylate **13**, (1.0 g) in *t*-BuOH (20 ml) was added *t*-BuOK solution (8 ml) (containing 6.0 g of K in 300 ml of *t*-BuOH), and the mixture heated under reflux for 20 min, whereupon a GC of the mixture showed two peaks corressponding to **14** and **15** (see Fig. 3). The mixture was extracted with ether and the extract was washed with water, dried, and evaporated to give an oily residue. IR (film) cm^{-1}: 1776. NMR: 1.09 (s), 1.46 (s) (2: 3). This was converted to a semicarbazone by heating with semicarbazide hydrochloride (1.0 g) and AcONa (1.5 g) in ethanol (10 ml). On crystallization several times from EtOH–H_2O the product formed prisms, mp 164—167°, whose NMR spectrum showed that it is still a mixture oı two semicarbazones (**14′**+**15′**).

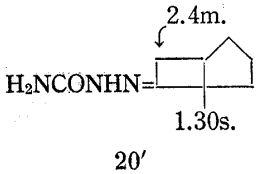
Action of Acid on the Cyclobutanones (14) and (15)——The mixture of **14** and **15** prepared from 1 g of **13** and oxalic acid dihydrate (5.0 g) in EtOH (20 ml) and water (20 ml) were heated under reflux for 10 hr. The mixture diluted with water, basified with NaOH, and extracted with CH_2Cl_2. The extract was washed with



14′



15′



20′

water, dried over Na_2SO_4, and evaporated to give a mixture of **15** and **20** as an oil. GC: single peak (see Fig. 3). IR (film) cm^{-1}: 1778. NMR: 1.27 (s), 1.46 (s), (2: 3). This was converted to a semicarbazone mixture as described above. NMR: (**15′**+**20′**). Several wasteful crystallization of the product from EtOH–H_2O afforded prisms, mp 173—177°, which was almost pure **15′** as shown from its NMR spectrum. Isolation of the semicarbazone (**20′**) was failed.

H_2O_2–NaOH Oxidation of 20 and 15——The 2: 3 mixture of **20** and **15** (1 g) was oxidized with 1% H_2O_2 in 0.5% NaOH–MeOH at 0° as described above. Extraction of the product from the mixture with ether quantitatively gave an oil (**21**+**22**) which showed single carbonyl absorption in IR at 1760 cm^{-1}. NMR: 1.49 (s), 1.26 (s) (2: 3), and see Chart 3.

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