[Chem. Pharm. Bull. 16(9)1779—1783(1968)]

UDC 581-19 : 547.597.02 : 542.975

Structure and Absolute Configuration of Faurinone[1]

Hiroshi Hikino, Yasuko Hikino, Kunio Agatsuma, and Tsunematsu Takemoto

Pharmaceutical Institute, School of Medicine Tohoku University[2]

(Received January 12, 1968)

Chemical and physico-chemical studies of the new sesquiterpenic ketone, faurinone, isolated from the valerian indigenous to Mt. Ibuki, Japan, have indicated it to be represented by the stereostructure I having a novel ring-contracted skeleton.

During our survey of the constituents of plants belonging to *Valeriana* genus, we have performed analysis of the essential oil from the valerian indigenous to Mt. Ibuki, central Honshu, and shown the presence of a number of sesquiterpenoids,[3] two of which are the new substances, fauronyl acetate and cryptofauronol, whose structures have been elucidated.[4] From this valerian, another hitherto unknown sesquiterpenic ketone of a molecular formula $C_{15}H_{26}O$, which gives a 2,4-dinitrophenylhydrazone, mp 126.5—127.5°, has also been isolated.[3] This ketone has later been found in several kinds of Japanese valerian. In an extention of our work, the structure of this substance has been investigated, and the evidence leading to the stereostructure I for this ketone, which has now been named faurinone, is described in the present paper.

The spectral properties of faurinone indicate the presence of an acetyl group (1709 cm^{-1} and 2.09 ppm). The nuclear magnetic resonance (NMR) spectrum of faurinone shows two more elements of the structure; a three-proton singlet at 1.04 ppm arising from a tertiary methyl goup and two three-proton doublets at 0.72 and 0.81 ppm assigned to two secondary methyl groups being visible. Faurinone shows the chemical and physical behavior of a saturated compound and, therefore, must be bicarbocyclic.

The situation of the acetyl group was indicated by base-catalyzed replacement of activated hydrogens for deuterium. Thus, the mass spectrum (MS) of the original ketone, faurinone, exhibits the expected parent peak at *m/e* 222, which shifted to *m/e* 225 in that of the deuterated ketone having no NMR signal attributed to acetyl methyl protons. Incorporation of only three atoms of deuterium is consistent with the fact that the acetyl group is located at a quaternary position.

We then tried to constract a sesquiterpenic molecule which could be formed according to the biogenetic mechanisms accepted for sesquiterpenoids, and at the same time satisfy the following structural requirements: two rings, one acetyl group attached to a quaternary carbon, one tertiary methyl group, and two secondary methyl groups being present. This was found impossible, unless some rearrangement was involved. Consequently, faurinone is considered to be a migrated isoprenoid. The co-occurrence of the rearranged sesquiterpenoids, faurinone and valeranone (III),[5] in the same plant suggests that both the ketones

1) This paper constitutes Part XXVIII in the series on Sesquiterpenoids. Preceding paper, Part XXVII: H. Hikino, K. Ito, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1608 (1968).
2) Location: *Kita-4-bancho, Sendai.*
3) H. Hikino, Y. Hikino, Y. Takeshita, H. Kato, and T. Takemoto, *Yakugaku Zasshi*, **85**, 179 (1965).
4) H. Hikino, Y. Takeshita, Y. Hikino, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 631 (1965); **14**, 735 (1966).
5) *cf.* H. Hikino, Y. Hikino, Y. Takeshita, K. Meguro, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **11**, 1207 (1963); **13**, 1408 (1965).

are derived from a common precursor (IV) or equivalent. From this biogenetic considerations faurinone is likely to be I.

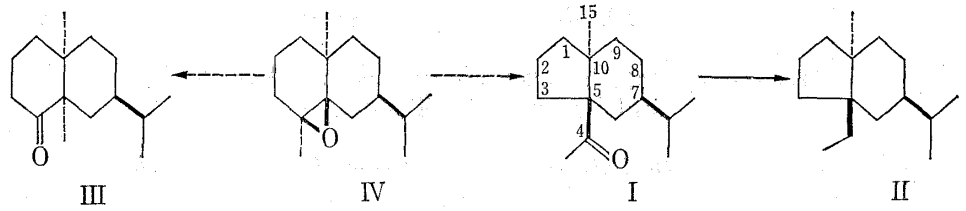

Chart 1

To confirm this assignment, the reference compound (IX), which may be a stereoisomer of faurinone, was prepared from cyperolone (V).[6] Thus, dihydrocyperolone (VI)[6] was converted to the corresponding *p*-toluenesulfonate (VII) by treatment with tosyl chloride in pyridine. Reduction of the *p*-toluenesulfonate (VII) with lithium aluminum hydride in ether gave a mixture of epimeric alcohols (VIII) which was oxidized with chromic acid to afford deoxydihydrocyperolone, cyperan-4-one (IX). On base-catalyzed deuteration cyperan-4-one (IX) yielded the expected trideuterio-derivative.

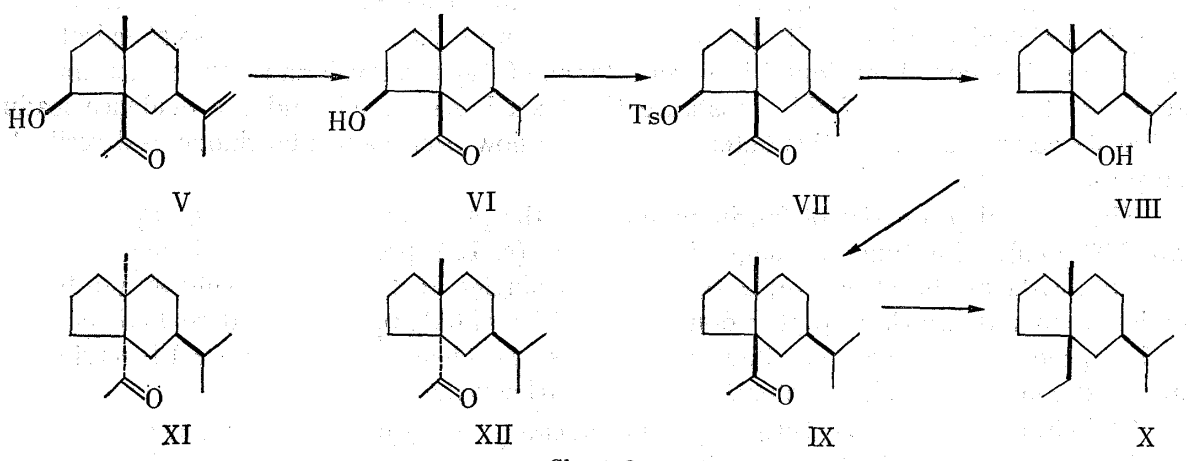

Chart 2

A direct comparison of faurinone and cyperan-4-one (IX) revealed them to be different. The mass spectra of faurinone and cyperan-4-one (IX), and those of their trideuterio-derivatives were then compared. Each pair of cracking patterns are similar but there are minor differences in the relative intensities in certain peaks, a fact which indicates that the plane structures of both ketones, faurinone and cyperan-4-one (IX), are identical. In order to make sure of this conclusion, further comparison of the mass spectra of deoxofaurinone (II) and cyperane (X) was planed. Thus Huang-Minlon reduction of cyperan-4-one (IX) gave cyperane (X). However, faurinone on reduction by Huang-Minlon procedure failed, recovering the starting ketone, faurinone. Therefore, reduction of faurinone by modified Wolff-Kishner method[7] was carried out to furnish deoxofaurinone, faurinane (II). Now it was found that the mass spectrum of faurinane (II) is indistinguishable from that of cyperane (X).

All these observations mentioned above permit the allocation of the structure I (without stereochemistry) to faurinone.

Therefore, the problem remaining is the absolute configuration of this sesquiterpenoid,

6) H. Hikino, K. Aota, Y. Maebayashi, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 1439 (1966); **15**, 1349 (1967).
7) W. Nagata and H. Itazaki, *Chem. Ind.* (London), **1964**, 1194.

for which there are eight possibilities. Biogenetical evidence indicates that the C–7 isopropyl group is β–oriented. Among the remaining four stereoformulas (I, IX, XI, and XII), the one (IX) for cyperan–4–one is of course not the representation of faurinone. Further, another stereoisomer (XI), which has been synthesized,[8] is found not to be identical with faurinone. It follows that faurinone may have either the stereostructure I or XII. The decision in favor of I, deduced from biogenetic consideration discussed above, is indicated by the physicochemical examinations of faurinone and its congeners, which will now be discussed.

First of all, validity of a consideration of conformational analysis, and circular dichroism (CD) and NMR studies in these types of ketones was examined on the known cyperane skeleton. In the molecule of cyperan–4–one (IX), there are three most preferred conformations for the acetyl group attached to the C–5 quaternary carbon, and they are such that the C=O is eclipsed to a C–C single bond at the C–5 carbon atom. According to the interaction of the C–10 angular methyl group, one conformation of the C–acetyl grouping related to the projection B seems to be most preferred. This is verified by the CD evidence. Thus the CD curve of cyperan–4–one (IX) exhibited a positive Cotton effect ($[\theta]_{max}$ $+4.1\times10^3$) at $+20°$ and this molecular elipticity showed an increment of $+25\%$ by going from high ($+20°$) to low temperature ($-189°$), at which the molecule is considered to have the thermodynamically most stable conformation. Since there are a number of possible conformational changes of the side chain and of the rings, a definite conclusion cannot be made about the actual changes upon lowering the temperature. However, the observed change of the molecular elipticity demonstrates that no drastic alteration takes place in the conformation, indicating that the molecule must be close to the thermodynamically most stable conformation as in perspective B even at room temperature. The preferred conformation of the C–5 acetyl group is further supported by NMR data. Thus, the solvent–induced shift for the C–15 methyl protons ($\Delta^{CHCl_3}_{C_6H_6}$) on passing from chloroform to benzene solution is -0.08 ppm, and that ($\Delta^{CCl_4}_{C_5H_5N}$) on passing from carbon tetrachloride to pyridine is -0.09 ppm. If it is assumed that the preferred conformation of the C–5 side chain is approximately the same in these solvents, these results indicate that the C–10 methyl group is located in front of the C–4 carbonyl group,[9–11] confirming the preferred conformation B for cyperan–4–one (IX).

This conclusion was further confirmed by its congener, cyperolone (V), havnig a hydroxyl group at the 3β–position. Thus cyperolone (V) gives a positive Cotton curve and shows no intramolecular hydrogen bond between the C–3β hydroxyl and the C–5 acetyl group, these observations indicate the molecule to have a similar conformation to that depicted in perspective B.[6] The reason of the absence of the chelation between the C–3β hydroxyl and the C–4 carbonyl may be explained by the assumption that an energy loss by an repulsion of the C–4 methyl and the C–10 methyl group in the parallel relation seems to be greater than an energy gain by an intramolecular hydrogen bonding in this case.[6]

The combined evidence points to the validity of a consideration of conformational analysis, and variable temperature CD and NMR studies in the cyperane skeleton. These arguments are now applied to faurinone for confirmation of its stereochemistry (I).

Since the ketone (I), a *trans*–hydrindane derivative, is of rigid conformation with regard to the ring junction, the isopropyl group should be axial provided that the B (isopropyl–bearing) ring is in the chair form. This is a very unfavorable situation, and the B ring is, therefore, most probably in a twist form so as to make the isopropyl group equatorial–like as shown in perspective A. If we try to figure out the preferred conformation of the C–5 acetyl group, we must again start with the assumption of having the C=O eclipsed with one of the C–C single bonds at the C–5 angular position. The most favored one is considered

8) H. Hikino, T. Kohama, and T. Takemoto, *Tetrahedron*, in press.
9) D.H. Williams and N.S. Bhacca, *Tetrahedron*, **21**, 2021 (1965).
10) D.H. Williams, *Tetrahedron Letters*, **1965**, 2305.
11) D.H. Williams and D.A. Wilson, *J. Chem. Soc.* (B), **1966**, 144.

to be as shown in the perspective A due to the repulsion between the C–4 methyl group and the C–1, 2, 8, and 9 methylenes, where the C–acetyl group is rotated slightly near the position indicated (projection A) owing to the non–bonded interaction of the carbonyl group with the C–5:C–10 bond and the C–8β hydrogen. Now, if we consider the ketone (I) in the conformation A in the light of the octant rule (octant diagram A), it will be seen that the ketone (I) will give a positive Cotton curve. Likewise, similar arguments together with inspection of the octant diagrams lead to the conclusion that the ketones (XI and XII) would afford negative Cotton curves. In fact, the ketone (XI) gave the negative Cotton curve.[8] Experimentally, faurinone exhibited the positive Cotton effect ($[\theta]_{max}$ $+6.3\times10^3$ at 20° and $[\theta]_{max}$ $+7.6\times10^3$ at −192°). Although the change of the molecular elipticity on passing from high to low temperature is again in accordance with the assumption of several conformational alterations, the relative change (+22%) shows that there is no drastic change in conformation on lowering the temperature, and the molecule has a conformation close to the thermodynamically most stable one at the room temperature. The observed positive Cotton effect is in accordance with the preferred conformation A. This observation was again supported by an NMR study. The very small solvent shifts ($\Delta^{CHCl_3}_{C_6H_6}$ +0.04 ppm and $\Delta^{CCl_4}_{C_5H_5N}$ +0.04 ppm) indicate that the C–10 methyl group lies behind but near both reference planes,[9–11] being also consistent with the assumption that faurinone has the stereochemistry I where the population of conformation close to A is much greater than that of any other conformation.

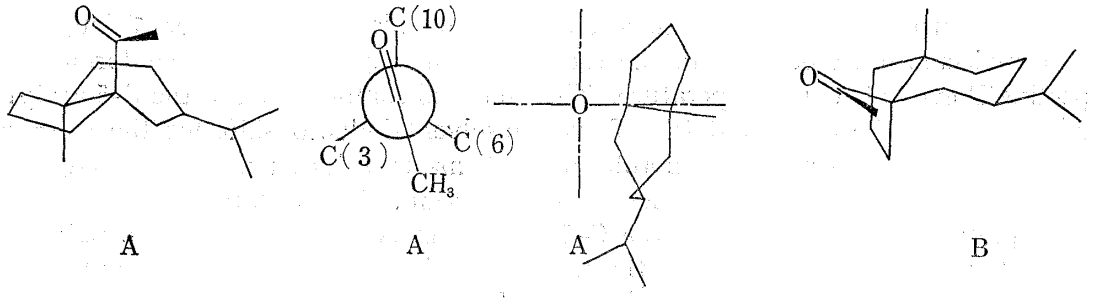

Chart 3

Experimental[12]

Faurinone——$C_{15}H_{26}O$, n_D^{25} 1.480, $[\alpha]_D$ +22.1° (c=10.0),[3] CD (c=0.0879): $[\theta]^{+20}_{288}$ $+6.3\times10^3$, $[\theta]^{-192}_{285}$ $+7.6\times10^3$, MS (m/e): 222, 207, 204, 189, 179, 161, 138, 123, 121, 109, 95, 83, 81, 69, 67, 55, 43, 41, IR (liquid) cm^{-1}: 1709 (acetyl), NMR: two doublets (3H each) at 0.72, 0.81 (J=5, $(CH_3)_2CH$–), singlet (3H) at 1.04 (CH_3–C$\leqslant$), singlet (3H) at 2.09 (CH_3–CO–), NMR ($CHCl_3$): two doublets (3H each) at 0.74, 0.81 (J=5, $(CH_3)_2CH$–), singlet (3H) at 1.03 (CH_3–C$\leqslant$), singlet (3H) at 2.18 (CH_3–CO–), NMR (C_6H_6): two doublets (3H each) at 0.84, 0.92 (J=5, $(CH_3)_2CH$–), singlet (3H) at 0.99 (CH_3–C$\leqslant$), singlet (3H) at 1.89 $(CH_3)_2CH$–), NMR (C_5H_5N): two doublets (3H each) at 0.83, 0.90 (J=5, $(CH_3)_2CH$–), singlet (3H) at 1.00 (CH_3–C$\leqslant$), singlet (3H) at 2.22 (CH_3–CO–).

Deuteration of Faurinone——Faurinone (33 mg) in 2N NaOD–D_2O (0.5 ml) and dioxane (1 ml) was heated under reflux under N_2 for 10 min. The solvent was distilled off under reduced pressure. The same sequence of experiments was repeated further twice. Extraction with ether followed by distillation *in vacuo* gave trideuteriofaurinone as a colorless oil, MS (m/e): 225 (parent peak), NMR: two doublets (3H each) at 0.73, 0.80 (J=5, $(CH_3)_2CH$–), singlet (3H) at 1.05 (CH_3–C$\leqslant$).

Wolff-Kishner Reduction of Faurinone——Faurinone (70 mg), NH_2NH_2 (3.9 ml), and $NH_2NH_2\cdot HCl$ (0.7 g) in triethylene glycol (7 ml) were heated at 130—150° under N_2 for 8 hr. KOH (14 g) was added. The mixture was kept at 220—230° for 4 hr. After isolation in the usual manner, the product was chromatographed on silica gel (4 g). Elution with light petroleum gave fuarinane (II) as a colorless oil, MS (m/e): 208, 180, 165, 138, 123, 109, 95, 81, 69, 67, 55, 43, 41.

12) Melting points are uncorrected. Optical rotations were measured in $CHCl_3$ solution. CD curves were recorded in methylcyclohexane–isopentane (1: 3) solution. NMR spectra were determined at 60 Mcps in CCl_4 solution unless otherwise indicated. Chemical shifts are given in ppm from Me_4Si as internal standard and coupling constants (J) in cps.

Tosylation of Dihydrocyperolone——Dihydrocyperolone (VI) (700 mg) in pyridine (2.5 ml) was treated with TsCl (800 mg) at room temperature overnight. Upon isolation in the usual manner, the product (1.05 g) was chromatographed over alumina (10 g). Elution with light petroleum gave the *p*-toluenesulfonate (VII) as a colorless oil (910 mg), IR (CCl_4) cm^{-1}: 1703 (acetyl), 1600, 1370, 1173 (tosylate).

Reduction of Dihydrocyperolone *p*-Toluenesulfonate with Lithium Aluminum Hydride——To *p*-toluenesulfonate (VII) (910 mg) in ether (10 ml) was added $LiAlH_4$ (90 mg) in ether (10 ml) dropwise at room temperature and the mixture was stirred for a further 3 hr. Isolation of the product (550 mg) in the customary way and distillation under reduced pressure yielded an epimeric mixture of the cyperan-4-ols (VIII) as a colorless oil. *Anal.* Calcd. for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.16; H, 12.25. IR (CCl_4) cm^{-1}: 3660, 3410 (hydroxyl). NMR: doublet (6H) at 0.91 ($J=7$, $(CH_3)_2CH$–), two singlets (3H) at 1.18, 1.27 (CH_3–C⩽), two doublets (3H) at 1.27, 1.31 ($J=6$, CH_3–CH(OH)–), two quadruplets (1H) at 4.13, 4.30 (CH_3–CH(OH)–C–).

This mixture on standing deposited crystals which on crystallization from light petroleum afforded one of the epimers (VIII) as colorless needles, mp 61—63°.

Oxidation of the Alcohols with Chromic Acid——The epimeric mixture of the cyperan-4-ols (VIII) (370 mg) in ether (10 ml) was stirred with $Na_2Cr_2O_7$-$2H_2O$ (200 mg) in dil. H_2SO_4 (conc. H_2SO_4–H_2O=1:2; 2 ml) at room temperature for 3 hr. After worked up as usual, the product (358 mg) was chromatographed over silica gel (40 g). Elution with light petroleum and distillation under diminished pressure furnished cyperan-4-one (IX) as a colorless oil, CD ($c=0.0998$): $[\theta]_{297}^{+20}$ $+4.1\times10^3$, $[\theta]_{293}^{-189}$ $+5.1\times10^3$, MS (*m/e*): 222, 207, 204, 189, 179, 161, 123, 121, 109, 95, 83, 81, 69, 67, 55, 43, 41, IR (CCl_4) cm^{-1}: 1697 (acetyl), NMR: doublet (6H) at 0.80 ($J=6$, $(CH_3)_3CH$–), singlet (3H) at 1.16 (CH_3–C⩽), singlet (3H) at 2.10 (CH_3–CO–O–), NMR ($CHCl_3$): doublet (6H) at 0.77 ($J=6$, $(CH_3)_2CH$–), singlet (3H) at 1.18 (CH_3–C⩽), singlet (3H) at 2.15 (CH_3–CO–), NMR (C_6H_6): doublet (6H) at 0.78 ($J=6$, $(CH_3)_2CH$–), singlet (3H) at 1.26 (CH_3–C⩽), singlet (3H) at 1.85 (CH_3–CO–), NMR (C_5H_5N): doublet (6H) at 0.75 ($J=6$, $(CH_3)_2CH$–), singlet (3H) at 1.25 (CH_3–C⩽), singlet (3H) at 2.14 (CH_3–CO–).

Deuteration of Cyperan-4-one——Deuterium exchange of cyperan-4-one (IX) was effected in a similar manner to that of faurinone described above. Trideuteriocyperan-4-one distilled as a colorless oil, MS (*m/e*): 225 (parent peak), NMR: doublet (6H) at 0.81 ($J=6$, $(CH_3)_2CH$–), singlet (3H) at 1.16 (CH_3–C⩽).

Huang-Minlon Reduction of Cyperan-4-one——Cyperan-4-one (IX) (170 mg), $NH_2NH_2\cdot H_2O$ (80%; 0.5 ml), KOH (0.3 g), and triethylene glycol (3 ml) were heated at 180—220° under N_2 for 4 hr. The mixture was worked up in the customary manner and the product was purified by chromatography over alumina (2 g). The fractions eluted with light petroleum were combined and distilled under reduced pressure to furnish cyperane (X) as a colorless oil, MS (*m/e*): 208, 180, 165, 137, 123, 109, 95, 81, 67, 55, 43, 41, NMR: doublet (6H) at 0.82 ($J=6$, $(CH_3)_2CH$–), singlet (3H) at 0.95 (CH_3–C⩽), triplet (3H) at 0.95 ($J=7$, CH_3–CH_2–).

Acknowledgement We wish to thank Dr. G. Snatzke, Universität Bonn, for carrying out the variable temperature CD determinations. The mass spectra were recorded by Research Laboratories, Takeda Chemical Industries, Ltd., and the NMR spectra run by Analytical Laboratory, this Institute, to whom thanks are also due.