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180. Hiroshi Hikino, Yasuko Hikino, Yasuyoshi Takeshita, Kanji Meguro, and Tsunematsu Takemoto : Structure and Absolute Configuration of Valeranone.*1

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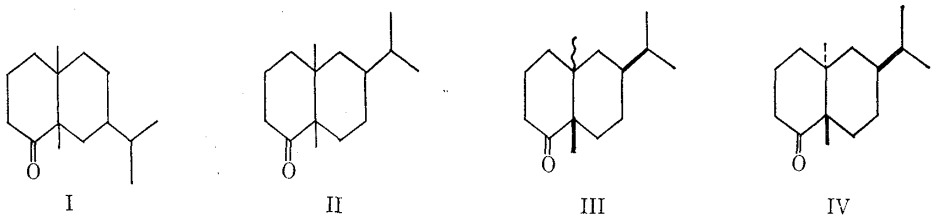
Valeranone is the sesquiterpenoid ketone which is widely distributed in members of the valerianaceous family : *viz.* a European valerian,[1] an Indian nard[2] (as jatamansone later identified as valeranone[3]), a Russian valerian,[4] several Japanese valerians,[5~7] a Chinese spikenard,[8] and an Indian valerian.[9]

The constitution of valeranone has been the subject of protracted controversy in recent years and has presented an outstanding problem in sesquiterpenoid chemistry. Structural investigations were first undertaken by Govindachari, *et al.*,[2,10] who prepared a number of derivatives, and followed by Křepinský, *et al.*,[11] who postulated two alternative formulae I and II from degradative evidence. Shortly thereafter, Govindachari, *et al.*[12] proposed structure III and, on the basis of this skeleton and rotatory dispersion measurements, Djerassi, *et al.*[13] suggested the absolute configuration shown in formula IV. Later, Křepinský, *et al.*,[14] on re-investigating the alleged



I II III IV

Chart 1.

conversion by Govindachari, *et al.*[12] of monobromojatamansic anhydride to (−)-carvomenthone, conclusively showed this to be incorrect and, on further evidence, again proposed formula I (without stereochemistry) for valeranone. Recently, we have isolated from a number of Japanese valerians, besides valeranone, the new sesquiterpenoid, kanokonol,[5~7] studied the chemistry of these substances, and shown kanokonol

*1 This paper is Part I in the series on Sesquiterpenoids.

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1) A. Stoll, E. Seebeck, D. Stauffacher : Helv. Chim. Acta, **40**, 1205 (1957).
2) T. R. Govindachari, S. Rajadurai, B. R. Pai : Chem. Ber., **91**, 908 (1958).
3) J. Křepinský, V. Herout, F. Šorm : Tetrahedron Letters, No. 3, 9 (1960).
4) *Idem* : Chem. listy, **52**, 1784 (1958); Collection Czechoslov. Chem. Communs., **24**, 1884 (1959).
5) H. Hikino, Y. Hikino, H. Kato, Y. Takeshita, T. Takemoto : Yakugaku Zasshi, **83**, 219 (1963).
6) H. Hikino, Y. Hikino, Y. Takeshita, Y. Isurugi, T. Takemoto : *Ibid.*, **83**, 555 (1963).
7) H. Hikino, Y. Hikino, Y. Takeshita, H. Kato, T. Takemoto : *Ibid.*, **85**, 179 (1965).
8) Y.R. Naves : Helv. Chim. Acta, **46**, 2139 (1963).
9) C. S. Narayanan, K. S. Kulkarni, A. S. Vaidya, S. Kanthamani, G. Lakshmi Kumari, B. V. Bapat, S. K. Paknikar, S. N. Kulkarni, G. R. Kelkar, S. C. Bhattacharyya : Tetrahedron, **20**, 963 (1964).
10) T. R. Govindachari, B. R. Pai, K. K. Purushothaman, S. Rajadurai : Tetrahedron Letters, No. 15, 5 (1959).
11) J. Křepinský, M. Romaňuk, V. Herout, F. Šorm : *Ibid.*, No. 7, 9 (1960).
12) T. R. Govindachari, B. R. Pai, K. K. Purushothaman, S. Rajadurai : Chem. & Ind. (London), **1960**, 1059; Tetrahedron, **12**, 105 (1961).
13) C. Djerassi, T. R. Govindachari, B. R. Pai, K. K. Purushothaman : Tetrahedron Letters, **1961**, 226.
14) J. Křepinský, M. Romaňuk, V. Herout, F. Šorm : *Ibid.*, **1962**, 169; Collection Czechoslov. Chem. Communs., **27**, 2638 (1962).

to be 15-hydroxyvaleranone.[15] Further, we have established the structure and absolute configuration of valeranone as shown in formula V and, in a preliminary communication,[16] outlined the evidence. The present paper describes full details of this work.

The first object was to ascertain the nature and absolute configuration of the substituents at C-7 and C-10 by comparison of the key compounds, Ⅷ (R=O, X=H) and Ⅸ, derived from valeranone, with suitable model compounds, *e.g.*, XV (X=H) and XVI. The sequence of reactions leading to Ⅷ (R=O, X=H) and Ⅸ have already been described by Křepinský, *et al.*,[14] however, since the compounds have not been fully characterized, the sequence was repeated.

Valeranone, by peracid oxidation followed by hydrolysis and methylation, gave the hydroxy-ester (Ⅶ; R=CH_3, R′=H), which was acetylated to afford the acetoxy-ester (Ⅶ; R=CH_3, R′=$COCH_3$). Pyrolysis of Ⅶ (R=CH_3, R′=$COCH_3$) formed the unsaturated ester (Ⅷ; R=CH_2, X=H), whose vinylidene grouping was confirmed by infrared bands at 3090, 1634, and 888 cm^{-1}. On ozonolysis Ⅷ (R=CH_2, X=H) yielded the first key compound, the keto-ester (Ⅷ; R=O, X=H), which showed infrared bands at 1743 (ester) and 1706 cm^{-1} (cyclohexanone) and nuclear magnetic resonance signals at 9.10 τ (6H, doublet, J= 5.2 c.p.s., $(CH_3)_2CH$-), 9.06 τ (3H, singlet, CH_3-C<CO-), and 6.40 τ (3H, singlet, CH_3-O-CO-). By bromination and subsequent dehydrobromination, Ⅷ(R=O, X=H)

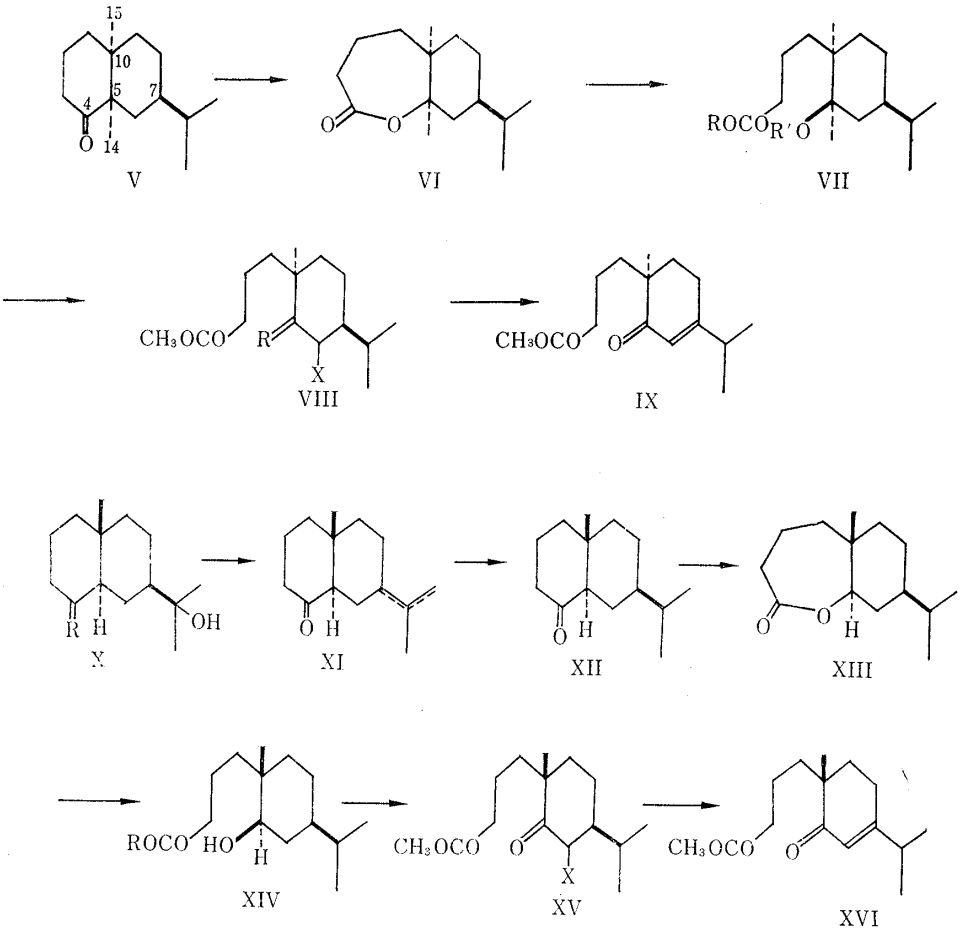


Chart 2.

15) H. Hikino, Y. Hikino, T. Takemoto : This Bulletin, **11**, 1210 (1963).
16) H. Hikino, Y. Hikino, Y. Takeshita, K. Meguro, T. Takemoto : *Ibid.*, **11**, 1207 (1963).

gave the second key compound, the α,β-unsaturated keto-ester (IX) which was characterized by its optical rotation, $[\alpha]_D$ +5.5°, infrared bands at 1740 (ester), 1669, and 1630 cm^{-1} (cyclohexenone), ultraviolet absorption at 237 mμ with log ε 4.18 (β,β-disubstituted enone), and nuclear magnetic resonance signals at 9.00 τ (3H, singlet, $C\underline{H}_3$-C≤CO-), 8.89 τ (6H, doublet, J=6.8 c.p.s., $(C\underline{H}_3)_2$CH-C=C), 6.42 τ (3H, singlet, $C\underline{H}_3$-O-CO-), and 4.38 τ (1H, unresolved band, -CO-C$\underline{H}$=C<).

On the other hand, the model compounds, the keto-esters (XV; X=H) and (XVI), were prepared in the following way: β-eudesmol (X; R=CH_2) on ozonolysis followed by dehydration with phosphorus oxychloride in pyridine gave the mixture of two isomeric unsaturated ketones (XI), the isopropenyl and the isopropylidene derivatives, from which the latter crystallized. This mixture (XI) was hydrogenated to yield 14-noreudesmanone (XII), whose homogeneity, shown by vapor phase chromatography and by nuclear magnetic resonance spectrum, confirmed that the side chain of XII at C-7 possessed the same (*i.e.*, β-) configuration as that of β-eudesmol (X; R=CH_2). On peracid oxidation, XII afforded the ε-lactone (XIII), which was hydrolyzed and successively methylated to the hydroxy-ester (XIV; R=CH_3). Chromic acid oxidation of XIV (R=CH_3) gave the first model compound, the keto-ester (XV; X=H), which displayed infrared band at 1739 (ester) and 1706 cm^{-1} (cyclohexanone), and nuclear magnetic resonance signals at 9.17 τ (6H, doublet, J=5.7 c.p.s., $(C\underline{H}_3)_2$CH-), 9.00 τ (3H, singlet, $C\underline{H}_3$-C≤CO-), and 6.43 τ (3H, singlet, $C\underline{H}_3$-O-CO-). Comparison of the physical data of VIII (R=O, X=H) and XV (X=H) revealed that the compounds were not identical. Bromination and subsequent dehydrobromination of XV (X=H) furnished the second model compound, the α,β-unsaturated keto-ester (XVI), which was characterized by its optical rotation, $[\alpha]_D$ −4.6°, infrared bands at 1740 (ester), 1669, and 1630 cm^{-1} (cyclohexenone), ultraviolet absorption at 236 mμ with log ε 4.19 (β,β-disubstituted enone), and nuclear magnetic resonance signals at 9.00 τ (3H, singlet, $C\underline{H}_3$-C≤CO-), 8.89 τ (6H, doublet, J=6.8 c.p.s., $(C\underline{H}_3)_2$CH-C=C), 6.42 τ (3H, singlet, $C\underline{H}_3$-O-CO-), and 4.38 τ (1H, unresolved band, -CO-C$\underline{H}$=C<).

The properties of XVI agreed in all respects with those of IX prepared from valeranone except for the rotation values, which were within experimental error, equal in magnitude, but opposite in sign. It is clear that IX is the enantiomer of XVI, a member of the natural eudesmane series, whose absolute stereochemistry is well established.[17] These results thus established not only the locations of the isopropyl group at C-7 and the methyl group at C-10, but also the absolute configuration of the isopropyl as being β-oriented and the methyl group α-oriented.

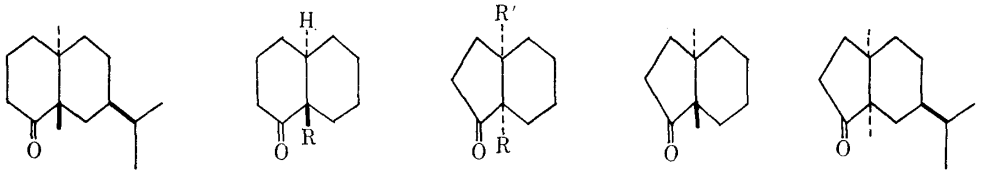
It now remains to decide which of the two possible formulae V and XVII represents valeranone depending on the absolute configuration of the C-5 methyl group.

The rotatory dispersion of valeranone has a negative Cotton effect, from which it was suggested[12] that the C-5 methyl group must be β-oriented. However, this is now shown to be incorrect by the following evidence.

trans-1-Decalone (XVIII; R=H) shows a positive Cotton effect,[18] while *trans*-9-methyl-1-decalone (XVIII; R=CH_3) exhibits a negative Cotton effect.[18] Although it is conceivable that in XVII the non-bonded 1,3-interaction between the axial isopropyl and methyl substitutions forces the non-oxygenated ring into a boat-like conformation, the ketone (XVII) would still be expected to possess a negative Cotton curve.

In the other possible representation V for valeranone, at least the two interchangable all chair conformations need to be considered due to the flexible nature of a *cis*-decalone. In these two conformations, however, the one with the axial isopropyl

17) cf. B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold, R. B. Woodward: J. Am. Chem. Soc., **76**, 313 (1954).
18) cf. W. Klyne: Experientia, **20**, 349 (1964) and the references cited therein.



XVII XVIII XIX XX XXI

Chart 3.

group is very unlikely owing to higher energy requirement for the axial orientation of the isopropyl and to a non-bonded interaction between the carbonyl and isopropyl groupings. The more probable conformation with the isopropyl group equatorial is anticipated to give a negative Cotton effect in analogy with methyl 1-oxo-5β-etianate,[19] the stereochemical environment of the two carbonyl groups being the same. However, other possible conformations with a twist form have also to be taken into consideration.

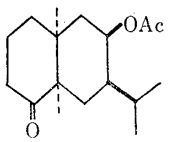
Therefore, no conclusion can be reached from the rotatory dispersion of the original ketone, valeranone, as to the absolute configuration on C-5.

Similarly, a positive Cotton effect show by dibromovaleranone[18] is not sufficient evidence to establish the absolute configuration on C-5.

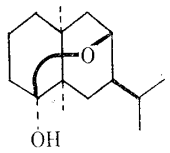
Although the rotatory dispersion of 4α,9α-dimethylhexahydro-1-indanone (XIX; R=R'=CH_3) seems not to have been described, it has been observed[20] that the compounds of the 9α-methyl-4α-hexahydro-1-indanone (XIX; R=CH_3, R'=H) series and the 4α-methyl-9α-hexahydro-1-indanone (XIX; R=H, R'=CH_3) series, both show a negative Cotton effect. Therefore, the sign of the Cotton curve is not essentially affected by angular methyl groups in the *cis*-hexahydro-1-indanone (XIX) series. Likewise, a prediction can be made that the 4α,9β-dimethylhexahydro-1-indanone (XX) series should show a positive Cotton effect.[20] From the above, it is apparent that the norketone derived from V should exhibit a negative Cotton effect, while the norketone from XVII should show a positive Cotton effect. Experimentally, there was observed a negative Cotton effect, whereupon it was established that norvaleranone has the *cis* ring junction as shown in formula XXI and consequently valeranone is correctly represented by formula V.

This conclusion was further supported by nuclear magnetic resonance evidence. A difference was noted in the chemical shifts of the C-5 methyl groups of valeranone and deoxovaleranone (valerane). An analogy for this can be found in steroid chemistry[21] where it is shown that in the cholestane skeleton the difference between the C-10 methyl signals of 1-oxo- and 1-deoxo-derivatives is 0.360~0.384 p.p.m., while in the coprostane skeleton it is 0.20~0.212 p.p.m. If valeranone has structure V, the more likely of the two all chair conformation appears to be with the isopropyl group in the equatorial orientation where the C-5 methyl corresponds stereochemically to the C-10 methyl in coprostan-1-one. Besides the all chair conformations, a number of conformations with a twist form can also be envisaged (*vide supra*) and thus the exact value of the difference of chemical shifts cannot be anticipated. On the other hand, if formula XVII is correct the C-5 methyl group should correspond to the C-10 methyl of cholestan-1-one, *i.e.* the difference should range between 0.35~0.4 p.p.m. Experimentally, the difference between the C-5 methyl groups of valeranone and deoxo-

19) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, Ch. Tamm : Helv. Chim. Acta, **41**, 250 (1958).
20) cf. W. Klyne : Tetrahedron, **13**, 29 (1961).
21) R.F. Zürcher : Helv. Chim. Acta, **44**, 1380 (1961), **46**, 2054 (1963); K. Tori, K. Aono : Ann. Repts. Shionogi Research Lab., **14**, 136 (1964).



XXII



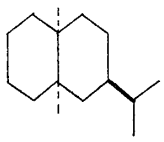
XXIII

Chart 4.

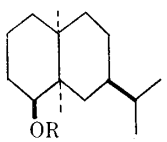
valeranone is 0.13 p.p.m., thus eliminating the postulated *trans* ring junction for valeranone as represented in formula XVII.

The most convincing evidence for a *cis* ring junction in valeranone is provided by the recently discovered sesquiterpenoid, fauronyl acetate (XXII).[7] Thus, it has been shown[22] that the substance (XXII) has the same carbon skeleton as valeranone and is hydrolyzed to yield the hemiketal, cryptofauronol (XXIII), instead of the free ketol, a result possible only with the *cis* ring juncture of the valerane skeleton.

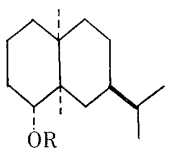
In the nuclear magnetic resonance spectrum of valerane (XXIV), two tertiary methyl groups appear at 9.15 τ. Reduction of valeranone with sodium and ethanol afforded 4-*epi*-valeranol (XXV; R=H) whose nuclear magnetic resonance spectrum exhibits peaks at 9.15 τ (C-15 methyl), 9.00 τ (C-14 methyl), and 6.41 τ (C-4methine). 4-*epi*-Valeranyl acetate (XXV; R=$COCH_3$) possesses nuclear magnetic resonance signals at 9.13 τ (C-15 methyl), 9.08 τ (C-14 methyl), and 5.20 τ (C-4 methine). The broad peak (half band width: 16 c.p.s. in XXV (R=H) and 13 c.p.s. in XXV (R=$COCH_3$)) due to the C-4 methine proton indicates the C-4 hydroxyl group to be equatorially disposed. Naturally, no influence is obserbed on the signal of the C-15 methyl protons from the C-4 hydroxyl group in 4-*epi*-valeranol (XXV; R=H). On the other hand, valeranone on lithium aluminum hydride reduction gave valeranol (XXVI; R=H) whose nuclear magnetic resonance spectrum displays an unresolved band at 6.75 τ (C-4 methine) with half band width of 6c.p.s. which shows the axial orientation of the C-4 hydroxyl group. The C-14 methyl proton signal is observed at 8.99 τ (or 8.98 τ) as in XXVI (R=H), whereas the C-15 methyl signal at 8.98 τ (or 8.99 τ) which has a down-field shift of 0.17 p.p.m. (or 0.16 p.p.m.) compared with that (9.15 τ) of XXIV or XXV (R=H). In the nuclear magnetic resonance spectrum of valeranyl acetate (XXVI; R=$COCH_3$) with the C-4 methine signal at 5.45 τ as an unresolved band (half band width: 5 c.p.s.), the chemical shift of the C-15 methyl protons moved upfield by 0.14 p.p.m. reappearing at 9.12 τ. This observation revealed the spatially close relation,[23] *viz.* 1,3-diaxial position, of the C-10 angular methyl group to the C-4 axially situated hydroxyl in XXVI (R=H). Application of the "benzoate rule"[24] to these alcohols and their benzoates ($\Delta[M]_D$ −217° for the valeranol series and $\Delta[M]_D$ +36° for the 4-*epi*-series) confirmed the *R*-configuration at C-4 of valeranol (XXVI) and *S*-configuration at C-4 of 4-*epi*-valeranol (XXV). The fact that the C-4 axial hydroxyl group of *R*-configuration is situated in a 1,3-diaxial relationship to the C-10 methyl group, also provided additional supporting evidence for the absolute configuration of valeranone as shown in formula V.



XXIV



XXV



XXVI

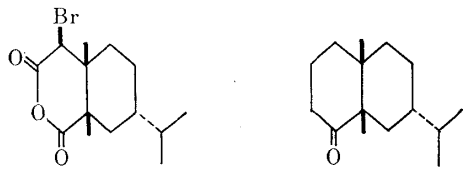
Chart 5.

It has been observed[25] that the axial proton absorbs at higher frequencies than its equatorial counterpart in cyclohexane. The above inversion of the chemical shifts between the C-4 axial and equatorial protons in the alcohols and their acetates as

22) H. Hikino, Y. Takeshita, Y. Hikino, T. Takemoto : This Bulletin, **13**, 631 (1965).
23) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, K. Tsuda : *Ibid.*, **10**, 338 (1962).
24) J. H. Brewster : Tetrahedron, **13**, 106 (1961).
25) L. M. Jackman : "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 116 (1959). Pergamon Press, London.

well as in their benzoates might be explained by a long range shielding effect associated with the diamagnetic anisotropy of the C-5 : C-6 single bond and some other factors which, however, are not clear at the moment. For an understanding of this phenomenon, further nuclear magnetic resonance study is required.

It is of interest that valeranone and kanokonol (15-hydroxyvaleranone) are found in the same plants together with maaliol,[26] kessane,[27] α-kessyl alcohol,[28] kessanol,[29] and kessyl glycol.[28] The co-occurrence of these substances having the same unusual configuration of the substituents must be biogenetically rationalized in terms of a common precursor.



XXVII XXVIII

Chart 6.

Subsequent to our preliminary communication,[16] Höhne[30] published the result of his X-ray analysis of monobromc-seconorvaleranoic anhydride for which the stereostructure XXVII was indicated. This work implies the stereoformula XXVIII or its mirror image (V) for valeranone in agreement with our conclusion. Simultaneously, Křepinský, *et al.*[31] deduced the absolute configuration at C-5 of the lactone (VI) to be *S* by applying Hudson-Klyne lactone rule extended to the case where a hydrogen atom on the asymmetric center is substituted by a methyl group,[32] and on this basis proposed the enantiomeric structure XXVIII for valeranone. However, in the reactions which they performed to obtain chemical evidence for the relative configuration of valeranone, the constitutions of the products were not well established and, therefore, their stereochemical argument failed to be supported by persuasive chemical evidence. Later, Herout,[33] on comparing the keto-ester (XVI) (supplied by us) with the keto-ester (IX) (prepared by them) with the aid of rotatory dispersion, confirmed our similar observation that the compounds were enantiomeric, and admitted that the extended lactone rule failed in this case, and that consequently the formula XXVIII for valeranone was incorrect. Recently, the rotatory dispersion curves of the keto-esters (IX) and (XVI) were reported.[34] Meanwhile, Kulkarni, *et al.*[35] discussed the stereochemistry of valeranone in connection with that of kanokonol (15-hydroxyvaleranone), however, since no proof of the conformations of the compounds in question was given, their stereochemical discussion was unconvincing.

Experimental*3

Valeranone——$C_{15}H_{26}O$, d_4^{25} 0.963, n_D^{25} 1.491, α_D −41.8°, ORD (c=0.189, MeOH) : $[M]_{316}^{trough}$ −6130°,

*3 Melting points are uncorrected. Specific rotations were measured in $CHCl_3$ solution. NMR spectra were determined at 60 Mc.p.s. in CCl_4 solution *vs.* Me_4Si as internal standard. Chemical shifts are given in τ-values and coupling constants (J) in c.p.s.

26) G. Büchi, M. Schach v. Wittenan, D. M. White : J. Am. Chem. Soc., **81**, 1968 (1959).
27) H. Hikino, Y. Hikino, Y. Takeshita, K. Shirata, T. Takemoto : This Bulletin, **11**, 547 (1963).
28) S. Ito, M. Kodama, T. Nozoe, H. Hikino, Y. Hikino, Y. Takeshita, T. Takemoto : Tetrahedron Letters, **1963**, 1787.
29) H. Hikino, Y. Hikino, Y. Takeshita, K. Shirata, T. Takemoto : This Bulletin, **11**, 952 (1963).
30) E. Höhne : Collection Czechoslov. Chem. Commums., **28**, 3128 (1963).
31) J. Křepinský, M. Romaňuk, V. Herout, F. Šorm : *Ibid.*, **28**, 3122 (1963).
32) M. Romaňuk, J. Křepinský : *Ibid.*, **29**, 830 (1964).
33) V. Herout : personal communication (February 14, 1964).
34) M. P. Hartshorn, D. N. Kirk, W. Klyne : Tetrahedron Letters, **1965**, 89. cf. Addendum by W. Klyne (p. 92); W. Klyne, S. C. Bhattacharyya, S. K. Paknikar, C. S. Narayanan, K. S. Kulkarni, J. Křepinský, M. Romaňuk, V. Herout, F. Šorm : *Ibid.*, **1964**, 1443.
35) K. S. Kulkarni, S. K. Paknikar, S. C. Bhattacharyya : Tetrahedron, **20**, 1289 (1964).

$[M]_{274}^{peak}$ +8010°, IR (liquid) cm^{-1} : 1702 (cyclohexanone), NMR : singlet (3H) at 9.21 τ ($C\underline{H}_3$-C$\leqslant$), doublet (6H) at 9.13 τ (J=7.1, $(C\underline{H}_3)_2CH$-), singlet (3H) at 9.02 τ ($C\underline{H}_3$-C$\leqslant$CO-).

Oxidation of Valeranone with Perbenzoic Acid——Valeranone (1.9 g.) was added to a solution of perbenzoic acid (1.0 g.) in $CHCl_3$ (20 ml.). The mixture was left standing at 25° for 10 days. The product was heated under reflux with *N* ethanolic NaOH (15 ml.) for 1 hr. and separated into acidic and neutral fractions : the former (1.3 g.) was treated with excess of redistilled CH_2N_2 in ether and the esterified product was chromatographed over neutral alumina (50 g.). Elution with benzene and distillation of the eluate gave the hydroxy-ester (Ⅶ; R=CH_3, R'=H) as a colorless oil, n_D^{25} 1.477, $[\alpha]_D$ +22.0° (c=10.8), *Anal.* Calcd. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found : C, 70.71; H, 10.96, IR (liquid) cm^{-1} : 3560 (hydroxyl), 1736 (ester).

Acetylation of the Hydroxy-ester——A mixture of the hydroxy-ester (Ⅶ; R=CH_3, R'=H) (1.3 g.), Ac_2O (15 ml.), and AcONa (5 g.) was heated under reflux for 2 hr. Chromatography on alumina (40 g.) of the product in light petroleum-benzene gave a fraction which on distillation under diminished pressure afforded the acetoxy-ester (Ⅶ; R=CH_3, R'=$COCH_3$) as a colorless oil, n_D^{25} 1.468, $[\alpha]_D$ −12.0° (c=10.3), *Anal.* Calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found : C, 69.78; H, 10.61, IR (liquid) cm^{-1} : 1740 (ester), 1730, 1247 (acetoxyl).

Pyrolysis of the Acetoxy-ester——The acetoxy-ester (Ⅶ; R=CH_3, R'=$COCH_3$) (1.48 g.) was refluxed under N_2 for 2 hr. The liquid obtained was purified by chromatography over neutral alumina (10 g.). Elution with light petroleum and distillation gave the unsaturated ester (Ⅷ; R=CH_2, X=H) as a colorless oil, n_D^{25} 1.470, $[\alpha]_D$ +34.6° (c=10.3), *Anal.* Calcd. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found : C, 76.23; H, 11.13, IR (liquid) cm^{-1} : 3090, 1634, 888 (vinylidene), 1740 (ester).

Ozonolysis of the Unsaturated Ester——To a solution of the unsaturated ester (Ⅷ; R=CH_2, X=H) (0.85 g.) in AcOEt (10 ml.), ozonized oxygen was passed at 0° until the $C(NO_2)_4$ test was negative. After addition of H_2O (10 ml.), the reaction mixture was heated on a steam-bath for 1 hr. The neutral product was chromatographed on neutral alumina (20 g.), eluted with light petroleum-benzene, and distilled under reduced pressure to give the keto-ester (Ⅷ; R=O, X=H) as a colorless oil, n_D^{25} 1.466, $[\alpha]_D$ +83.5° (c=8.3), *Anal.* Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found : C, 70.65; H, 10.37, IR (CCl_4) : described previously, NMR : described previously.

Bromination of the Keto-ester——A solution of Br_2 (70 mg.) in AcOH (0.5 ml.) was added to a solution of the keto-ester (Ⅷ; R=O, X=H) (111 mg.) in AcOH (0.5 ml.). The mixture was set aside for 15 hr., diluted with H_2O, and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography over silica gel to give the monobromoketo-ester (Ⅷ; R=O, X=Br) (146 mg.), IR (liquid) cm^{-1} : 1739 (ester), 1729 (α-bromocyclohexanone).

Dehydrobromination of the Monobromoketo-ester——The monobromoketo-ester (Ⅷ; R=O, X=Br) (130 mg.) in 2,6-lutidine (1 ml.) was heated under reflux for 3 hr. The reaction mixture was diluted with H_2O, acidified with dil. HCl, and extracted with ether. After removal of the solvent, the residue (96 mg.) was chromatographed on silica gel (3 g.). The combined benzene eluates were distilled *in vacuo* to give the α,β-unsaturated keto-ester (Ⅸ) as a colorless oil, n_D^{25} 1.487, $[\alpha]_D$ +5.5° (c=7.2), *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found : C, 71.08; H, 9.19, IR (CCl_4) : described previously, UV λ_{max}^{EtOH} mμ (log ε) : 237 (4.18), NMR : described previously.

Ozonolysis of β-Eudesmol——β-Eudesmol (Ⅹ; R=CH_2) (10.8 g.) in AcOEt (150 ml.) was treated with ozonized oxygen at 0° until the $C(NO_2)_4$ test was negative (6 hr.) and the ozonide was decomposed by heating under reflux with H_2O (70 ml.) for 2 hr. affording crude nor-β-eudesmolone (Ⅹ; R=O) (10.0 g.) as a viscous oil which was not further purified.

Dehydration of Nor-β-eudesmolone——A mixture of the nor-β-eudesmolone (Ⅹ; R=O) (10.0 g.) in pyridine (75 ml.) and $POCl_3$ (14.7 g.) was kept at 0° overnight and then at room temperature for 3 hr. The reaction product was worked up in the usual manner and distilled under reduced pressure to yield the isomers of 14-noreudesmenone (Ⅺ) as a colorless crystal paste, $[\alpha]_D$ +50.8° (c=10.0), *Anal.* Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found : C, 81.42; H, 10.78, IR (liquid) cm^{-1} : 1712 (cyclohexanone), 3096, 1643, 886 (vinylidene). Crystallization of the mixture from light petroleum gave 14-noreudesm-7 (11)-enone as colorless needles, m.p. 82~83°, $[\alpha]_D$ +66.7° (c=9.9), *Anal.* Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found : C, 81.12; H, 10.62, IR (KBr) cm^{-1} : 1710 (cyclohexanone), NMR : singlet (3H) at 9.17 τ ($C\underline{H}_3$-C$\leqslant$), singlet (6H) at 8.37 τ ($(C\underline{H}_3)_2C$=C$\langle$).

Catalytic Hydrogenation of the 14-Noreudesmenones——The mixture of the isomers of 14-noreudesmenone (Ⅺ) (5.5 g.) in MeOH (40 ml.) was hydrogenated over Pd-C (5%; 3.0 g.) at room temperature consuming 1.0 mole of H_2. The product was adsorbed on alumina (35 g.) from light petroleum. Elution with the same solvent and distillation under reduced pressure afforded 14-noreudesmanone (Ⅻ) as a colorless oil, d_4^{25} 0.956, n_D^{25} 1.486, $[\alpha]_D$ +15.6° (c=9.5), *Anal.* Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found : C, 80.62; H, 11.52, IR (liquid) cm^{-1} : 1710 (cyclohexanone), NMR : singlet (3H) at 9.25 τ ($C\underline{H}_3$-C$\leqslant$), doublet (6H) at 9.09 τ (J=5.7, $(C\underline{H}_3)_2CH$-).

The semicarbazone, prepared in the usual way ($NH_2NHCONH_2$·HCl-AcONa), crystallized from EtOH as colorless needles, m.p. 212~213.5°, *Anal.* Calcd. for $C_{15}H_{27}ON_3 \cdot \frac{1}{2}H_2O$: C, 65.65; H, 10.29; N, 15.31. Found : C, 65.94; H, 10.09; N, 15.16. This semihydrate, when dried at 100° *in vacuo* (pressure 0.02

mm. Hg) for 18 hr., lost 3.31% of its weight (theoretically 3.28%) to give the anhydrous derivative, m.p. 221~223°, *Anal.* Calcd. for $C_{15}H_{27}ON_3$: C, 67.88; H, 10.26; N, 15.83. Found: C, 67.63; H, 10.01; N, 15.63.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner ($NH_2NHC_6H_3(NO_2)_2$-H_2SO_4-EtOH), crystallized from EtOH as orange needles, m.p. 141~142°, *Anal.* Calcd. for $C_{20}H_{28}O_4N_4$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.83; H, 7.29; N, 14.52.

Oxidation of 14-Noreudesmanone with Perbenzoic Acid——A mixture of 14-noreudesmanone (XII) (4.3 g.) and perbenzoic acid (3.0 g.) in $CHCl_3$ (100 ml.) was kept at 25° for 9 days. The reaction mixture was washed ($NaHCO_3$ solution and H_2O), dried (Na_2SO_4), and evaporated to give the crude lactone (XIII), IR (liquid) cm^{-1}: 1727 (ε-lactone), which, without further purification, was hydrolyzed by heating under reflux with *N* ethanolic KOH (50 ml.) for 2 hr. The acidic product (4.4 g.) obtained in the usual way was treated with excess of redistilled CH_2N_2 in ether and distilled under diminished pressure to give the hydroxy-ester (XIV; R=CH_3) as a colorless oil, n_D^{25} 1.475, $[\alpha]_D$ +27.7°(c=5.5), *Anal.* Calcd. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.50; H, 11.28, IR (liquid) cm^{-1}: 3500 (hydroxyl), 1730 (ester).

The acetate, prepared in the usual manner (Ac_2O-AcONa), distilled as a colorless oil, n_D^{25} 1.489, $[\alpha]_D$ −53.8°(c=5.3), *Anal.* Calcd. for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.91; H, 10.02, IR (liquid) cm^{-1}: 1739, 1238 (ester and acetoxyl).

Oxidation of the Hydroxy-ester with Chromic Acid——The hydroxy-ester (XIV; R=CH_3) (4.6 g.) in ether (20 ml.) was stirred with $Na_2Cr_2O_7$ (2.1 g.) in H_2SO_4 (2.4 g.) and H_2O (20 ml.) at room temperature for 5 hr. The mixture was worked up in the customary manner and the neutral product was purified by chromatography over alumina (30 g.) in light petroleum and distillation under reduced pressure to afford the keto-ester (XV; X=H) (2.2 g.) as a colorless oil, n_D^{25} 1.474, $[\alpha]_D$ +45.7°(c=10.8), *Anal.* Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.45; H, 10.35, IR (CCl_4): described previously, NMR: described previously.

Bromination of the Keto-ester——To a solution of the keto-ester (XV; X=H) (0.47 g.) in AcOH (0.6 ml.), a solution of Br_2 (0.3 g.) in AcOH (0.6 ml.) was added and the mixture was left standing at room temperature overnight. The product was chromatographed over neutral alumina (6 g.) and subsequently over silica gel (6 g.) to give the monobromoketo-ester (XV; X=Br) (0.45 g.), n_D^{25} 1.496, $[\alpha]_D$ −7.0°(c=9.7), *Anal.* Calcd. for $C_{15}H_{25}O_3Br$: C, 54.06; H, 7.56. Found: C, 54.21; H, 7.56, IR (liquid) cm^{-1}: 1733 (broad, ester and α-bromocyclohexanone).

Dehydrobromination of the Monobromoketo-ester——The monobromoketo-ester (XV; X=Br) (0.79 g.) in 2,6-lutidine (3 ml.) was heated under reflux for 3 hr. The product (0.58 g.) obtained in the usual way was chromatographed over silica gel (6 g.). Elution with light petroleum-benzene and distillation *in vacuo* furnished the α,β-unsaturated keto-ester (XVI) as a colorless oil, n_D^{25} 1.487, $[\alpha]_D$ −4.6°(c=20.1), *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.49, IR (CCl_4): described previously, UV λ_{max}^{EtOH} mμ (log ε): 236 (4.19), NMR: described previously. The IR, UV, and NMR spectra were indistinguishable from those of IX.

Norvaleranone——Norvaleranone (XXI), prepared according to Govindachari, *et al.*,[12] distilled as a colorless oil, n_D^{25} 1.481, ORD (c=1.695, MeOH): $[M]_{307}^{trough}$ −3040°, $[M]_{266}^{peak}$ +4980°, *Anal.* Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.67; H, 11.68, IR (liquid) cm^{-1}: 1740 (cyclopentanone).

The semicarbazone, prepared in the customary manner ($NH_2NHCONH_2$·HCl-AcONa), crystallized from EtOH as colorless needles, m.p. 228~230°, *Anal.* Calcd. for $C_{15}H_{27}ON_3$: C, 67.88; H, 10.26; N, 15.83. Found: C, 67.89; H, 10.22; N, 16.16.

The 2,4-dinitrophenylhydrazone, prepared in the customary manner ($NH_2NHC_6H_3(NO_2)_2$-H_2SO_4-EtOH), crystallized from AcOEt as orange plates, m.p. 166.5~167°, *Anal.* Calcd. for $C_{20}H_{28}O_4N_4$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.76; H, 7.33; N, 14.72.

Huang-Minlon Reduction of Valeranone——A mixture of valeranone (225 mg.), KOH (0.3 g.), NH_2NH_2·H_2O (80%; 0.5 ml.), and triethylene glycol (3 ml.) was heated at 180~190° for 4 hr. The cooled solution was poured into H_2O and extracted with ether. The product in light petroleum was filtered through alumina and distilled to give valerane (XXIV) as a colorless mobile oil, n_D^{25} 1.483, $[\alpha]_D$ +76.0°(c=5.0), *Anal.* Calcd. for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found: C, 86.87; H, 13.39, NMR: singlet (6H) at 9.15 τ ($C\underline{H}_3$-C<), doublet (6H) at 9.13 τ (J=4.9, $(C\underline{H}_3)_2CH$-).

Reduction of Valeranone with Sodium and Ethanol——To a refluxing solution of valeranone (550 mg.) in EtOH (16 ml.), metallic Na (1.7 g.) was gradually added during 30 min. The mixture was left on a steam-bath for further 3.5 hr., diluted with H_2O and EtOH was distilled off. The residue was extracted with ether, washed, dried (Na_2SO_4), and evaporated to yield on crystallization from light petroleum 4-*epi*-valeranol (XXV; R=H) as colorless needles, m.p. 85~86.5°, $[\alpha]_D$ +62.5°(c=8.0), *Anal.* Calcd. for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.58; H, 12.40, IR (KBr) cm^{-1}: 3356 (hydroxyl), NMR: singlet (3H) at 9.15 τ ($C\underline{H}_3$-C<), doublet (6H) at 9.11 τ (J=5.0, $(C\underline{H}_3)_2CH$-), singlet (3H) at 9.00 τ ($C\underline{H}_3$-C<), broad peak (band width at half height: 16 c.p.s., 1H) at 6.41 τ ($\underline{H}$-C<OH).

The acetate (XXV; R=$COCH_3$), prepared in the usual manner (Ac_2O-AcONa), distilled as a colorless oil, n_D^{25} 1.481, $[\alpha]_D$ +39.2°(c=5.1), *Anal.* Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.37; H,

11.02, IR (liquid) cm^{-1} : 1733, 1239 (acetoxyl), NMR : singlet (3H) at 9.13 τ ($C\underline{H}_3$-C$\lessdot$), doublet (6H) at 9.13 τ (J=5.1, $(C\underline{H}_3)_2CH$-), singlet (3H) at 9.08 τ ($C\underline{H}_3$-C$\lessdot$), singlet (3H) at 8.06 τ ($C\underline{H}_3$-CO-O-), broad peak (band width at half height : 13 c.p.s., 1H) at 5.20 τ ($\underline{H}$-C$\lessdot$OAc).

The benzoate (XXV; R=COC_6H_5), prepared in the usual way (BzCl-pyridine), distilled as a colorless viscous oil, $[\alpha]_D$ +54.1°(c=10.4), *Anal.* Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found : C, 80.25; H, 9.67, IR (liquid) cm^{-1} : 1715, 1274 (ester), 3067, 1605, 710 (phenyl), NMR : broad peak (1H) at 4.97 τ ($\underline{H}$-C$\lessdot$OBz).

Reduction of Valeranone with Lithium Aluminum Hydride——Valeranone (2.0 g.) in ether (15 ml.) was stirred with excess $LiAlH_4$ for 1.5 hr. Working up in the usual way and crystallization from light petroleum gave valeranol (XXVI; R=H) as colorless prisms, m.p. 56.5~57°, $[\alpha]_D$ +51.6° (c=10.0), *Anal.* Calcd. for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found : C, 80.40; H, 12.38, IR (KBr) cm^{-1} : 3448 (hydroxyl), NMR : doublet (6H) at 9.13 τ (J=5.2, $(C\underline{H}_3)_2CH$-), singlet (3H) at 8.99 τ ($C\underline{H}_3$-C$\lessdot$), singlet (3H) at 8.98 τ ($C\underline{H}_3$-C$\lessdot$), unresolved band (band width at half height : 6 c.p.s., 1H) at 6.57 τ ($\underline{H}$-C$\lessdot$OH).

The acetate (XXVI; R=$COCH_3$), prepared in the usual manner (Ac_2O-AcONa), distilled as a colorless oil, n_D^{25} 1.480, $[\alpha]_D$ +28.0°(c=5.0), *Anal.* Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found : C, 76.86; H, 11.22, IR (liquid) cm^{-1} : 1736, 1238 (acetoxyl), NMR : doublet (6H) at 9.14 τ (J=5.0, $(C\underline{H}_3)_2CH$-), singlet (3H) at 9.12 τ ($C\underline{H}_3$-C$\lessdot$), singlet (3H) at 8.98 τ ($C\underline{H}_3$-C$\lessdot$), singlet (3H) at 8.00 τ ($C\underline{H}_3$-CO-O-), unresolved band (band width at half height : 5 c.p.s., 1H) at 5.45 τ ($\underline{H}$-C$\lessdot$OAc).

The benzoate (XXVI; R=COC_6H_5), prepared in the usual way (BzCl-pyridine), distilled as a colorless viscous oil, $[\alpha]_D$ −31.1°(c=10.3), *Anal.* Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found : C, 80.56; H, 9.68, IR (liquid) cm^{-1} : 1715, 1274 (ester), 3067, 1605, 711 (phenyl), NMR : unresolved band (1H) at 5.24 τ ($\underline{H}$-C$\lessdot$OBz).

The 3,5-dinitrobenzoate (XXVI; R=$COC_6H_3(NO_2)_2$), prepared in the usual way ($(NO_2)_2C_6H_3COCl$-pyridine), crystallized from EtOH as pale yellow needles, m.p. 128~128.5°, *Anal.* Calcd. for $C_{22}H_{30}O_6N_2$: C, 63.14; H, 7.23; N, 6.69. Found : C, 63.05; H, 7.21; N, 6.75.

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Summary

The structure and absolute configuration of valeranone have been established as V from the following evidence. Valeranone (V) was converted into IX *via* VIII (R=O, X=H), and β-eudesmol (X; R=CH_2) into XVI *via* XV (X=H). VIII (R=O, X=H) was shown to be a diastereomer of XV (X=H), and IX the enantiomer of XVI, thus establishing the absolute configuration of the C-10 methyl as α and that of the C-7 isopropyl group as β. The absolute configuration of the C-5 methyl was confirmed to be α by observing a negative Cotton effect of XXI, the difference of the nuclear magnetic resonance signals of the C-5 methyls of V and XXIV, and the conversion of XXII into XXIII. The absolute stereochemistry was also supported by the nuclear magnetic resonance spectra of XXVI (R=H and Ac) which revealed that the C-4 hydroxyl of *R*-configuration was located in a 1,3-diaxial relation to the C-10 methyl group.

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