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THE STRUCTURE OF METHYL ISOLEUCOTYLATE, AN ACID ISOMERIZED PRODUCT OF METHYL LEUCOTYLATE

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In the previous paper[1], it was reported that an acid treatment of methyl leucotylate (II), obtained as a triterpenic acid from a lichen (Parmelia leucotyliza NYL.), yielded an isomeric compound named as methyl isoleucotylate (V) in addition to the diene (IV). Further investigation on the acid treatment (for instance, boiling methyl leucotylate in 5% ethanolic hydrogen chloride 20 min.) disclosed the relative yield of IV to V was 5 : 5 with another minor isomeric product* (yield ratio: 1). Present communication describes the structural study of methyl isoleucotylate (V).

Methyl isoleucotylate (V), $C_{31}H_{52}O_4$, mp. 222°, $[\alpha]_D$ +40.2°, showed negative to tetranitromethane, the presence of OH functions

* The ester was named tentatively as methyl neoleucotylate $C_{31}H_{52}O_4$, mp. 223°, $[\alpha]_D$ +46.5°, which will be discussed in the future paper.

(ν_{max} 3350 cm^{-1})*, and seven methyls (τ: 8.32 (Me), 8.78 (2Me), 8.98, 8.99, 9.13, 9.25 (Me respectively))*. On acetylation with acetic anhydride-pyridine, V gave a monoacetate (VI), $C_{33}H_{54}O_5$, mp. 220°, $[\alpha]_D$ +70°; ν_{max} 3550, 1735, 1715 cm^{-1}; τ: 7.98 (CH_3COO). Chromium trioxide oxidation of V in pyridine afforded a monoketone (VII), $C_{31}H_{50}O_4$, mp. 212°, $[\alpha]_D$ +25°; ν_{max} 3400, 1710, 1695 cm^{-1}, one hydroxyl left unattacked, thus suggesting the existence of one secondary and one tertiary hydroxyl groups in V. The ketone has been found very stable to either acid or alkaline.

The NMR spectra of V, VI, and VII, indicating two methyl signals appeared around τ 8.3-8.8, support the constitution of tertiary hydroxyl to be $-C(OH)(CH_3)_2$. Moreover, remarkable resemblance of NMR and IR spectra between methyl isoleucotylate (V) and methyl leucotylate (II) would agree to assume the similar carbon skeleton for both isomers, which has now been confirmed by the evidence below.

Elongated acid treatment of V (boiling in 5% ethanolic hydrogen chloride for 6 hrs.) produced the diene (IV) as II did. The fact is reminiscent of the relative position of two hydroxyl functions in V being at C-16 and C-22 similarly as II. The configuration of hydroxyl at C-16 was assigned to be retained as β-equatorial since the NMR spectra of V and VI showed diffused signals at τ 5.95 and 5.08 (1H at C-16 respectively).

It follows that the possible differences of II and V could now be ascribed to either/both D/E ring juncture or/and the configuration at C-21.

* IR spectra were taken in $CHCl_3$, NMR spectra in $CDCl_3$.

On chromium trioxide oxidation in pyridine, II afforded in quite low yield* a monoketone (XIII), $C_{31}H_{50}O_4$, mp. 190°, $[\alpha]_D$ +72°; ν_{max} 3350, 1710, 1650** cm^{-1}, which was easily converted with alkaline to an isomeric monoketone (XIV), $C_{31}H_{50}O_4$, mp. 208°; ν_{max} 3480, 1710, 1695 cm^{-1}. As being widely known in the hydrindanones, the more stable configuration is with cis ring juncture[2], therefore the monoketone (XIV) probably has cis D/E ring fusion.

It has been suggested that the hydroxyisopropyl side chain at C-21 of II has α-configuration[1]. Since the ketone (VII) derived from V was identical neither with XIII nor XIV, the possible difference among them could consequently be the side chain configuration, i.e. β-side chain in VII. Being stable to acid and alkaline, VII must be in a stable form***. If D/E ring juncture of VII is trans, it would reasonably be understood that bulky β-side chain at C-21 could cause significant resistance for D/E ring inversion (trans⟶cis) because of marked interaction between C-21 side chain and C-15 in D/E cis structure****.

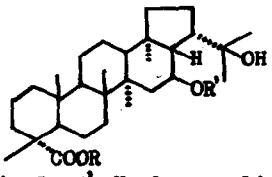
Treatment of VI with $POCl_3$ in pyridine yielded a monoene $C_{33}H_{52}O_4$, mp. 221°, $[\alpha]_D$ +61.5°; ν_{max} 1715, 1640, 890 cm^{-1}; τ:

* On the contrary, as described earlier, V gave a monoketone (VII) smoothly, suggesting fairly hindered hydroxyl location of II for oxidising reagent.

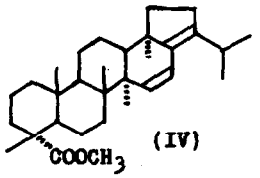
** The absorption band of hydrogen bonded carbonyl at C-16 was in accord with the deshielded signal of C-18 methyl probably caused by the tertiary hydroxyl at C-22, which will be discussed in detail in our full paper.

*** Even a treatment of VII with alkaline in boiling ethyleneglycol caused only the hydrlysis of $COOCH_3$ at C-4 without any juncture isomerization.

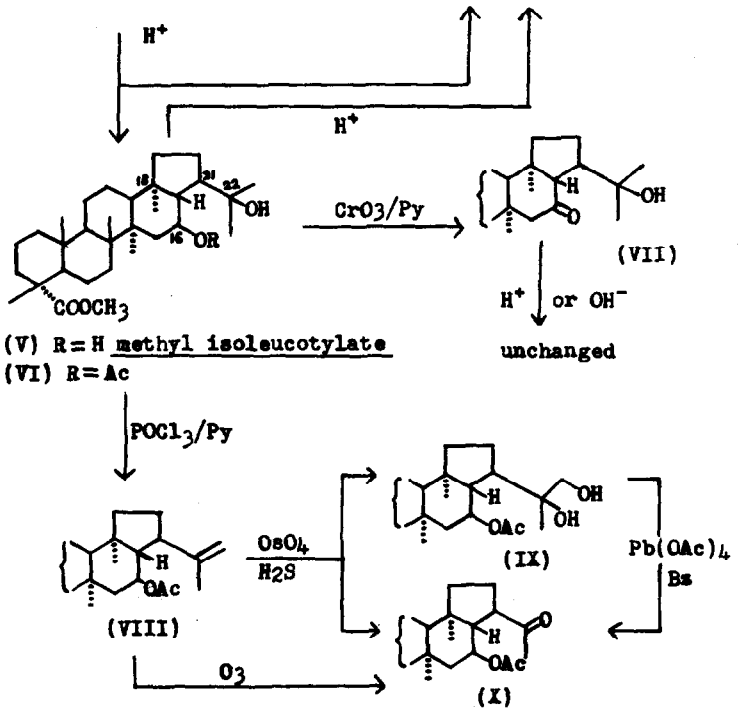
**** It has been reviewed in detail concerning relative stability of cis and trans hydrindanones that a trans isomer could be more stable in some cases than cis where steric interactions exist[3].

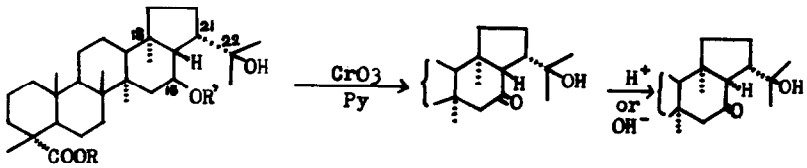


(I) R=R'=H leucotylic acid
(II) R=CH_3, R'=H methyl leucotylate
(III) R=CH_3, R'=Ac



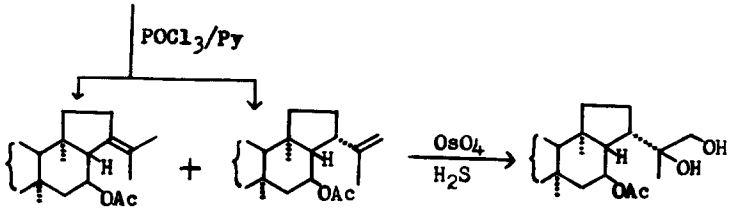
(IV)
methyl
leucotylidienate



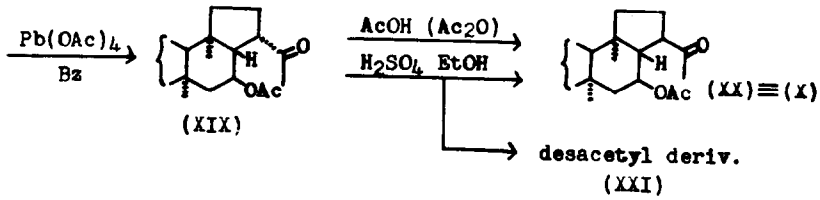


(II) R = CH_3, R' = H
methyl leucotylate
(III) R = CH_3, R' = Ac

(XIII) (XIV)

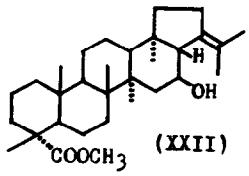


(XVI) (2 : 1) (XV) (XVII)

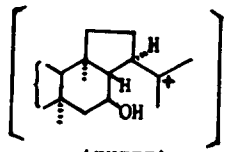


(XIX) (XX)≡(X)

desacetyl deriv.
(XXI)

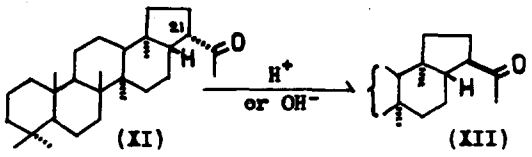


(XXII)
methyl leucotylininate



(XXIII)

5.37 (=C$\underline{H}_2$), 8.30 (=$\dot{C}$-C$\underline{H}_3$), which on osmium tetroxide oxidation followed by H_2S treatment afforded a glycol (IX) and a methylketone (X)*, $C_{32}H_{50}O_5$, mp. 183.5-185°, $[\alpha]_D$ +33.8°; ν_{max} 1715 cm^{-1}; τ: 7.87 (-COC$\underline{H}_3$). The latter was also obtained either by ozonolysis of VIII or by oxidation of IX with $Pb(OAc)_4$ in benzene[6], thus proving the retention of C-21 configuration in X. As was already reported by Jones et al.[6] and Ourisson et al.[7], 21α-H methylketone (XII) is more stable than 21β-H isomer (XI). In analogy, the methylketone (X) which was stable to acid and alkaline could be assigned 21α-H type.



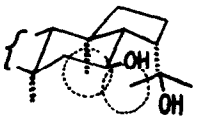
(XI) adiantone (XII) isoadiantone

The above mentioned evidences agree to assign methyl isoleucotylate as V (≡methyl 21α-H leucotylate).

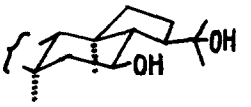
The difference of C-21 configuration between II and V was shown by comparing the dehydration reaction of III and VI with $POCl_3$ in pyridine, where III produced a mixture of XV and XVI (yield ratio 1 : 2), whereas VI gave VIII as a sole product. It would be reasonable to mention that a 1:3 steric interaction between C-18 methyl and C-21 α-side chain (cf. II') is quite large, which has become responsible for main dehydration path of III towards XVI, thus releasing interaction. These features have

* Formation of the ketonic compounds under these conditions has been demonstrated in the case of dehydrozeorinin[4] and hopa-15,17(21)-diene[5].

been known among other hopane derivatives such as zeorin[4], hydroxyhopanone[8], and leucotylin[9] having 21β-H configuration. In case of VI, such an interaction could not be observed (cf. V*), so that the dehydration proceeded preferentially to VIII with isopropenyl function.



(II')



(V')

Finally, the derivation of III into a common ketonic compound (XX) was performed as follows. As mentioned above, the dehydration of III gave a mixture of XV, $C_{33}H_{52}O_4$, mp. 187.5-189°; ν_{max} 1727, 892 cm^{-1}; τ: 8.26 ($H_2C{=}\overset{|}{C}\text{-}C\underline{H}_3$), 5.30 ($\text{-}\overset{|}{C}{=}C\underline{H}_2$), and (XVI), $C_{33}H_{52}O_4$, mp. 178-179°; ν_{max} 1728 cm^{-1}, which were successfully separated by $AgNO_3$ impregnated silica gel column chromatography[10]. The former was then submitted to osmium tetroxide oxidation followed by H_2S treatment yielding a glycol (XVII), $C_{33}H_{54}O_6$, mp. 219-221°; ν_{max} 3520, 3410(sh.), 1740(sh.), 1717 cm^{-1}; τ: 8.82 ($HO\text{-}\overset{|}{C}\text{-}C\underline{H}_3$), 6.62 (AB quartet, $\text{-}\overset{|}{C}\text{-}C\underline{H}_2OH$). By the action of $Pb(OAc)_4$ in benzene, XVII produced a methylketone (XIX), $C_{32}H_{50}O_5$, mp. 158-160°; ν_{max} 1717 cm^{-1} (br.); τ: 7.90 ($\text{-}COC\underline{H}_3$). The methylketone exhibited unstable under acidic condition* giving XX, $C_{32}H_{50}O_5$, mp. 185.5-187°, and the identity of which with X was achieved by mixed mp. (183.5-185°), IR spectra

* Under a similar condition (H_2SO_4-EtOH)[6] as for the isomerization of XI to XII, the methylketone (XIX) yielded a considerable amount of desacetyl derivative (XXI), whereas in boiling glacial acetic acid containing small amount of Ac_2O, the isomerization proceeded preferentially to XX.

($CHCl_3$), and TLC, thus confirming methyl isoleucotylate (V) is a C-21 side chain isomer of methyl leucotylate (II).

With mild acid treatment (1% HCl-EtOH, 5 min.), II yielded methyl leucotylininate (XXII), $C_{31}H_{48}O_3$, mp. 183°, $[\alpha]_D$ +58.2°; ν_{max} 3400, 1710 cm^{-1}, which on further acid treatment, was transformed into IV and V by the ratio of 1 to 1. The evidence would make it probable that XXII is an intermediate from II to IV and V. Namely, at first, XXII was formed by dehydration of II, then IV or V was formed either by further dehydration, double bond migration, or hydration via a probable intermediate XXIII giving a more stable isohopane skeleton. Such a hydration procedure has never been found in the hopane derivatives, however, similar pathway has been known in case of ring contraction of ring A of the triterpenoids* ((a)⟶(c)).

The isomerization mentioned here (21α→21β side chain) concerning hopane derivatives has now been extensively under study in our laboratory.

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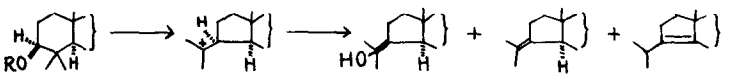
* It was reported by Biellmann and Ourisson[11] that a sulfonate (a, R=tosyl or mesyl) gave a mixture of (c), (d), and (e), on treatment with $CaCO_3$ in acetone via (b).



(a) (b) (c) (d) (e)

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