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Robert V. Hoffman
Department of Chemistry, New Mexico State University
Las Cruces, New Mexico 88003
Received June 15, 1976

The Structure of Xylomollin, a Secoiridoid Hemiacetal Acetal

Sir:

During the course of studies on *Xylocarpus molluscensis* (Meliaceae),[1] a tree widely used in folk medicine in East Africa, we had occasions to study its unripe and bitter fruits. The fruits (each weighing ca. 200 g) are used as aphrodisiacs[2] while young, but with ripening the bitterness is rapidly lost and the fruits become edible. We have isolated the bitter principle "xylomollin", which besides being an antifeedant against the African army worm *Spodoptera exempta*, strongly inhibits the respiratory reactions of mitochondria from rat liver.[3] Spectral data lead to the unusual monoterpenoid secoiridoid structure **1** having a nonglycosidic hemiacetal function at C-1 and an acetal function at C-3.

Xylomollin was readily obtained by extraction of the fruit flesh with aqueous methanol, removal of methanol, extraction of residual aqueous concentrate with ether and concentration; yield 0.1% of wet weight.

The physical constants of xylomollin **1** are as follows: mp 138–139 °C (ethanol), high resolution MS 275.1529 (M + H) (calculated for $C_{12}H_{19}O_7$ M + H, 275.1533);[4] chemical ionization MS[5] 275 (M + 1), 243 (275 − CH_3OH); ir (dilute $CHCl_3$) 3600, 1733, 1720 cm^{-1}. The nature of all carbon atoms was clarified by ^{13}C NMR (JEOL PS-100) with the techniques of PND, PRFT,[6] and off-resonance decoupling. The undecoupled ^{13}C NMR (Figure 1) was very revealing in that the doublet of quartets at 56.1 ppm (J = 6 and 0.5 Hz) showed for the first time that one of the two methoxyl peaks in the ^1H NMR (**1a**) was due to a methoxyl group attached to a methine carbon (C-3) with a J value of 0.5 Hz. All the protons attached to the skeleton, which contains no quaternary carbon and hence consists of one continuous proton system, was clarified by 100-MHz and 220-MHz (Varian) ^1H NMR as shown in **1a**; pyridine-d_5 was used as solvent owing to poor solubility of xylomollin in $CDCl_3$. An unusual feature was that all coupling constants were large, the smallest being the 3 Hz value for $J_{1,9}$. In addition, in spite of numerous attempts, no W type couplings or NOE's could be detected. Combination of these data leads uniquely to the structure shown in **1a** (or **1**). The structure is corroborated by the shifts seen in the ^1H NMR (pyridine-d_5) of the benzoate, mp 188 °C. Namely, as expected, the two protons in 1,3-diaxial relations to the 1-benzoate group were shifted from 5.45 to 5.00 ppm (3-H) and from 3.00 to 2.75 ppm (5-H), respectively.

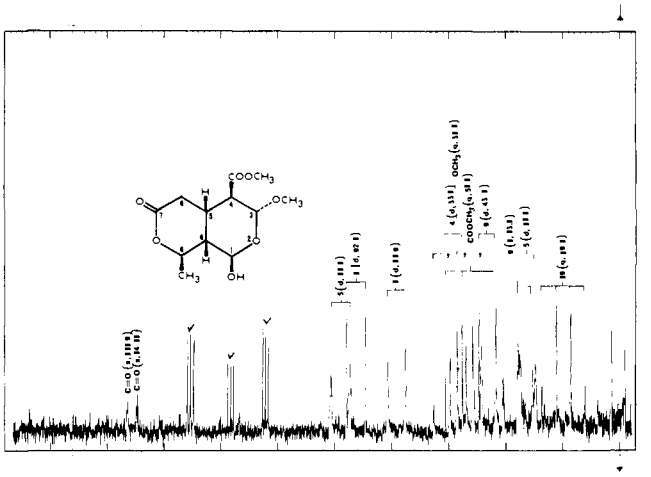


Figure 1. Undecoupled ^{13}C NMR of xyllomolin in pyridine-d_5, JEOL PS-100. The numerals outside the parentheses denote carbon atoms, and those inside the ppm and J values (Hz). The solvent peaks are indicated by check marks.

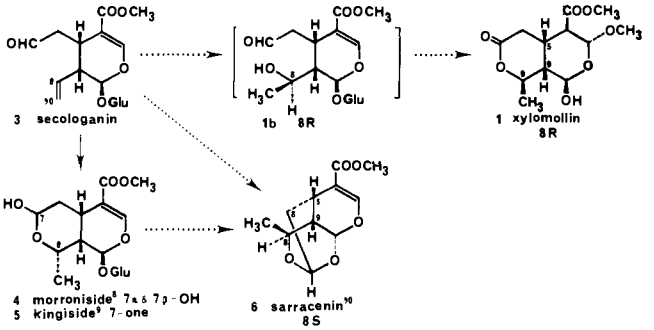
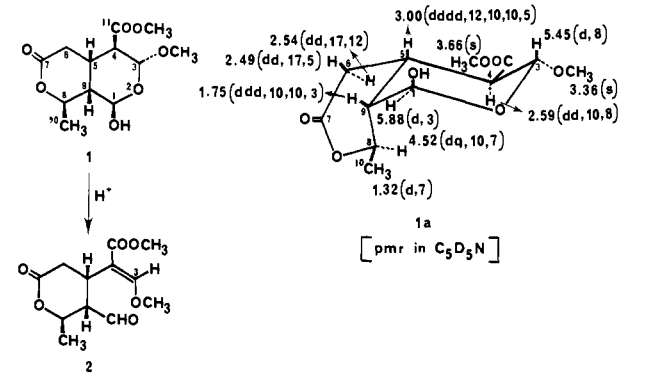


Figure 2. Biogenetic relationships. The transformation **3** → **4** has been proven experimentally.



Repeated chromatography of the ethereal mother liquid of the extract (vide supra) afforded numerous compounds, the major product being the enol ether aldehydes **2**, oil, mixture of cis and trans 3-ene isomers. The uv(MeOH) 238.5 nm (ε 12 000) and other spectral data, e.g., 3-H at 7.58 and 7.52 ppm, were in full agreement with structure **2**. The cis and trans mixture was also readily obtainable by leaving xylomollin in 1 N HCl/50% eq. MeOH at room temperature for 1 h (100% conversion).

As shown in Figure 2, xylomollin can be derived from secologanin **3** via the hydrated intermediate **1b** having an 8*R* configuration; the absolute configuration **1** is based on biogenetic considerations that all iridoids known to date have 5β,9β-H configurations. Hydration of the secologanin[7] 8,10-ene from the opposite side of the 8-ene leads to morroniside **4**[8] and kingiside[9] with 8S configuration; another related

secologanin derivative is the diacetal sarracenin **6**.[10] In view of the rapid disappearance of bitterness upon ripening of fruits, it is clear that xylomollin is transformed into other product(s), the hemiacetal acetal moiety being ideally suited for further transformations. It is conceivable that xylomollin is a key intermediate subsequent to secologanin in the biosynthesis of indole alkaloids.[11,12]

Acknowledgments. The authors are grateful to Mr. V. Saltamach for mass spectral measurements.[13]

References and Notes

(1) The plant was collected near Mombasa. The studies of other bioactive principles are in progress.
(2) This was not the reason for studying the unripe fruits.
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(4) Probe temperatures 120 °C, 14 eV. The M^+ peak was generally very weak under a variety of conditions on both the GlC and Finnigan instruments. One condition under which the M^+ could be detected (one-half the intensity of the M + 1 peak) was at 130 °C, 15 eV.
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(13) The work was initiated during the stay of I.K. at the International Center of Insect Physiology and Ecology, Nairobi, Kenya. The work was supported by grants from the United Nations Development Program (to ICIPE) and NIH AI 10187 (to K.N.).
(14) Japan Society for the Promotion of Science Research Fellow, 1974–1975.

Isao Kubo,* [14] Iwao Miura, Koji Nakanishi
Department of Chemistry, Columbia University
New York, New York 10027
Received June 11, 1976

Thermal Isomerization of (+)-(1*S*,2*S*)-*trans*,*trans*-2-Methyl-1-propenylcyclopropane: Quantification of Four Stereochemical Paths in a Vinylcyclopropane Rearrangement

Sir:

Since discovery of the vinylcyclopropane rearrangement in 1959 and 1960,[1] considerable effort has been expended in unsuccessful efforts to define the stereochemical characteristics of the cyclopentene-forming reaction; not a single unconstrained monocyclic vinylcyclopropane derivative has been studied so as to define the quantitative importance of the four possible stereochemical rearrangement modes. Molecules conceptually suitable for stereochemical investigations have been synthesized, but rapid enantiomerization and diastereomerization reactions of the judiciously labeled substrates have vitiated the work: product distributions from a single starting material have not been gained.[2]

The most complete solution to the vinylcyclopropane stereochemical problem to date has been derived from the rearrangements of *trans*-1-cyano-2-isopropenylcyclopropane (**1**) and its cis isomer (**2**).[3] The absence of stereochemical markers on the double bond termini makes the values of 69% inversion for *trans*-**1** and 39% inversion for *cis*-**2** the maximum information which can be gained from these systems.

The work we now report solves this long-standing problem. The key to our simplified kinetic analysis is appreciation of the kinetic behavior of *trans*- and *cis*-2-methyl-1-vinylcyclopropane (**3** and **4**).[4,5] *trans*-2-Methyl-1-vinylcyclopropane (**3**) was shown to rearrange to a 13 to 1 mixture of *cis*-1,4-hexadiene (**5**) and 4-methylcyclopentene (**6**), the former presumably arising from *cis*-**4** which rearranges to diene **5** via a concerted retro-ene reaction nearly three orders of magnitude faster than it is formed from *trans*-**3**. One consequence of these rate differences is that the 4-methylcyclopentene is formed only from **3**; diasteriomerization of **3** to **4** does not lead to complications in the kinetic scheme governing formation of 4-methylcyclopentene. Thus with optically active *trans*,*trans*-2-methyl-1-propenylcyclopropane (**7**)[6] as substrate, all four stereochemical paths could be traced quantitatively.

Table I. Isomeric Composition of Hydrocarbons Recovered from Pyrolysis of (+)-**7**

Time (min)	(product mole fraction ± standard deviation)[a] 7	8	9	8/9
60	0.527 ± 0.004	0.0225 ± 0.0005	0.00825 ± 0.00052	2.73 ± 0.11
120	0.280 ± 0.001	0.0301 ± 0.0003	0.0118 ± 0.0002	2.56 ± 0.03

[a] The remainder of the C_7H_{12} hydrocarbons consisted of *cis*-1,4-heptadiene (the heptadiene to **8** + **9** ratio was 12.4 ± 0.5) and other heptadiene isomers which increased with decreasing pressure.

Optically pure (+)-(1*S*,2*S*)-*trans*,*trans*-2-methyl-1-propenylcyclopropane (**7**) was prepared from optically pure (+)-(1*S*,2*S*)-2-phenylcyclopropanecarboxylic acid, $[\alpha]_D$ +303°. The phenyl acid was converted, by esterification, lithium aluminum hydride (LAH) reduction, mesylation, LAH reduction, and destructive ozonolysis, to (+)-(1*S*,2*S*)-*trans*-2-methylcyclopropanecarboxylic acid, $[\alpha]_D$ +95.8°.[7,8] Both carboxylic acids were shown to be optically pure by NMR analysis of the derived methyl esters with added Eu-Opt (tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]-europium(III)), an optically active NMR shift reagent. The methyl acid was converted to **7** by LAH reduction, Collins oxidation,[9] and Wittig-Schlosser reaction.[10] The optically pure (+)-(1*S*,2*S*)-**7** had $[\alpha]^{25}_{250}$ +586 ± 18° and $[\alpha]^{25}_{280}$ +528 ± 18°.

Synthesis of optically pure *trans*- and *cis*-3,4-dimethylcyclopentenes (**8**) and (**9**) began with (+)-(*R*)-3-methylcyclopentanone, $[\alpha]_D$ +153°. The ketone was converted to its hydroxymethylene derivatives and thence to a mixture of the corresponding butylthiomethylene compounds.[11] These were reduced to the ketones with Raney nickel[11] and converted to the six isomers of dimethylcyclopentene by LAH reduction, xanthate ester formation, and pyrolysis. Assurance of the geometrical relationships in **8** and **9** was obtained through alternative syntheses from commercial samples of *dl* and *meso*-3,4-dimethylcyclopentanone, and a racemic sample of **8** was reduced to give *trans*-1,2-dimethylcyclopentane identical with an optically active sample.[12] Assurance of the optical purities of **8** an **9** was secured as follows. The (+)-(*S*)-1,4-dimethylcyclopentene had $[\alpha]^{28}_{365}$ +16.21° (lit.[3] $[\alpha]^{27}_{365}$ −16.02° for the *R* enantiomer). Epoxidation of the (+)-(*R*)-1,5-dimethylcyclopentene and NMR analysis with added Eu-Opt under conditions known to resolve the enantiomeric epoxide methine protons demonstrated its optical purity. The (−)-(3*S*,4*R*)-*trans*-3,4-dimethylcyclopentene (**8**) had $[\alpha]^{25}_{223}$ −2850 ± 160° and $[\alpha]^{25}_{250}$ − 1720 ± 70°, and the (+)-(3*R*,4*R*)-*cis*-3,4-dimethylcyclopentene (**9**) had $[\alpha]^{25}_{223}$ + 1220° and $[\alpha]^{25}_{250}$ +900°. Pyrolyses of 500-mg samples of (+)-(1*S*,2*S*)-**7** were carried out at 60 and 120 min at 296.5 °C, in the gas phase at about 40 mm, corresponding to one and two half-lives for the disappearance of **7**. Combination of these disappearance rates with two sealed tube kinetic runs (temperature range: 58 °C) leads to a calculated activation energy of 47.1 + 2.3 kcal/mol and log *A* 14.3 ± 0.8; the corresponding