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# THE STRUCTURES OF EVONINE AND NEOEVONINE ALKALOIDS OBTAINED FROM *EUONYMUS SIEBOLDIANA* BLUME

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**Abstract**—Evonine (1) and neoevonine (2) were isolated from *Euonymus Sieboldiana* Blume. The structural studies of the principal alkaloid, evonine were carried out extensively by chemical and spectroscopic methods, resulting in the establishment of the structure of the alkaloid as 1: it is a highly oxygenated sesquiterpene of eudesman type, which is esterified with five moles of acetic acid and evoninic acid (33). The derivatives for the structure determination of 1 are summarized in Charts I–III. Interconversion of the two alkaloids, (1 and 2) was achieved and the structure of neoevonine was elucidated as 2.

## INTRODUCTION

The presence of alkaloids in the plants belonging to *Euonymus* genus (*Celastraceae* family) was reported in 1934.[1] Since then, studies on alkaloids in *Celastraceae* family have been made by several groups of investigators.[2–6]

Evonine, one of the principal alkaloids was isolated in crystalline form from *Euonymus europaea* L. first by Doebel and Reichstein[3] and later by Pailer and Libiseller,[6a] and was formulated as $C_{31}H_{39}NO_{14}$[3] (the trivial name, Alkaloid C in the original report) and $C_{36}H_{43-45}NO_{17}$[6c] by the respective groups. Pailer and Libiseller carried out the investigation on the constitution of evonine and obtained evoninic acid (33), whose structure was established as (2*S*; 3*S*)-2-methyl-3-methyl-3-(β-carboxy-α-pyridyl)-propionic acid by alkaline hydrolysis of evonine. The results of the Pailer's group, which are summarized below clearly demonstrate that evonine (1) is a $C_{15}$-polyhydroxy compound, whose OH groups form seven ester linkages with evoninic acid (33) and five moles of acetic acid.

We have been engaged in the studies of alkaloids in *Euonymus Sieboldiana* Blume (Japanese name, Mayumi) and isolated evonine (1) and neoevonine (2). The structural studies on both alkaloids were carried out by chemical and spectroscopic means, and the structural problems of evonine (1) and neoevonine (2) were completely settled, the results of which were reported as short communications.[7] In the present paper the full details on structural investigations of evonine (1) and neoevonine (2) are described. After our reports[7] were published, two papers on evonine (1) and related alkaloids appeared.[8,9] The Santavy and Reichstein's group published the result that Alkaloid A (evorine: i.e. desacetyl evonine), Alkaloid B (evozine; i.e. didesacetyl evonine), and Alkaloid C (evonine) were chemically correlated.[8] Pailer's group presented the structures of evonine (1) and evonoline, largely on the basis of spectral observations.[9] Kupchan *et al.* isolated two amorphous alkaloids, maytoline (3) and maytine (4) from *Maytenus ovatus* Loes., the structures of which were established by X-ray crystallography.[10] It should be noted that the structures of evonine (1) and maytoline (3) are closely related.

## ISOLATION AND CHARACTERIZATION

Dried and powdered fruits of *Euonymus Sieboldiana* Blume were extracted first with n-hexane and subsequently with ether. The n-hexane and ether extracts, concentrated to a small volume, were shaken with a 2·5% HCl. The aqueous phase was made alkaline (pH 9) with solid $K_2CO_3$ and extracted with AcOEt. The mixture of alkaloids obtained as amorphous powder from the AcOEt

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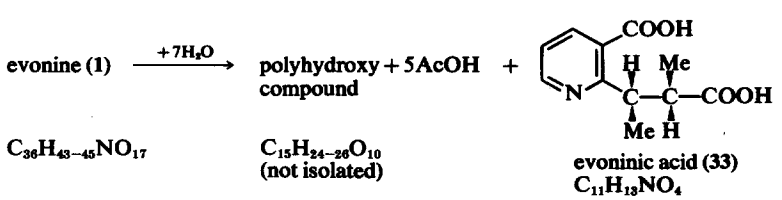
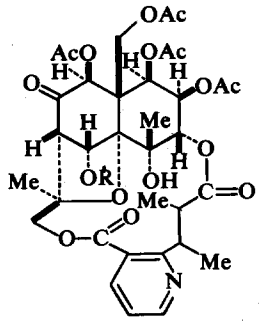
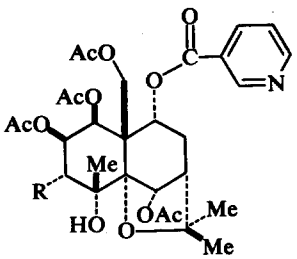


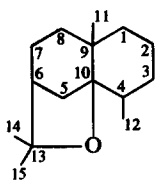


1: R = Ac (evonine)*
2: R = H (neoevonine)



3: R = OH (maytoline)
4: R = H (maytine)

*The numbering system shown here is used throughout the present paper.



†The identity of our alkaloid with evonine obtained from *Euonymus europaea* L., kindly provided by Prof. M. Pailer (Wien Univ., Austria), was proved by mixed melting point and spectral comparison (solution IR and mass).

solution was dissolved in EtOH. A crystalline mixture of evonine (1) and neoevonine (2) were precipitated from the EtOH solution within several days. Repeated fractional recrystallization from EtOH afforded pure evonine (1).† Recrystallization of the crystalline residue obtained on evaporation of the mother liquor from MeOH gave neoevonine (2).

The physical and spectral properties of the two alkaloids are as follows.

*Evonine* (1): $C_{36}H_{43}NO_{17}$; m.p. 184–190°; $[\alpha]_D$ +8·4° ($CHCl_3$, *c* 1·5); UV, $\lambda_{max}$ (EtOH), nm ($\epsilon$) 267 (3,200), 227 (6,200); IR, Fig 1; NMR, Fig 3; Mass, 761 (molecular ion peak).

*Neoevonine* (2): $C_{34}H_{41}NO_{16}$; m.p. 264–265°; $[\alpha]_D$ +24·9° ($CHCl_3$, *c* 1·27); UV, $\lambda_{max}$ (EtOH), nm ($\epsilon$) 265 (3,200), 224 (5,500); IR, Fig 2; NMR, Fig 4; Mass, 719 (molecular ion peak).

*Evonine*

The Pailer's result[6] that evonine (1) is a $C_{15}$-polyhydroxy compound which is esterified with evoninic acid (33) and five moles of AcOH was confirmed by NMR spectrum and the hydrolysis experiments. As pointed out by Pailer,[6] alkaline hydrolysis of evonine (1) afforded a deeply coloured oily material, from which evoninic acid (33) was obtained as a sole crystalline compound. Since the molecular formula of evonine (1) was unambiguously determined as $C_{36}H_{43}NO_{17}$ by mass spectrometry and elemental analysis, the $C_{15}$-component was proved to have the molecular formula $C_{15}H_{24}O_{10}$, extensive structural studies of which were carried out.

*Functional groups and their relationship in the sesquiterpene part of evonine* (1). The NMR spectra of evonine (1) and the derivatives were particularly useful for obtaining the information about the structures of various parts of the alkaloid 1 (Fig 3 and Table 1). By comparison with the NMR spectrum of dimethyl evoninate (Fig 5), the signals due to the evoninic acid moiety could easily be distinguished from those of the $C_{15}$-part in the NMR spectrum of the alkaloid 1.

From the NMR spectra of evonine (1) and the

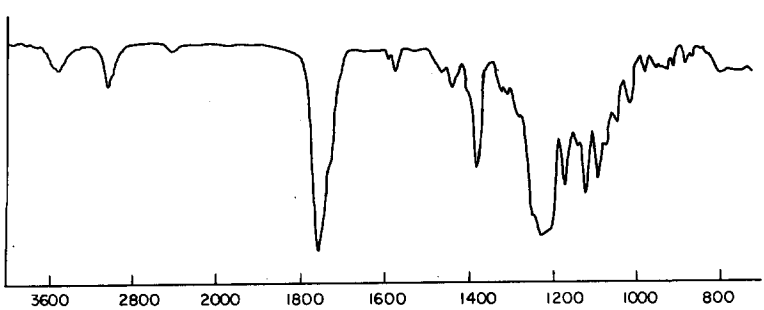



Fig 1. IR spectrum of evonine (1). ($CHCl_3$, $cm^{-1}$)

Table 1.* NMR spectral data of evonine (1), neoevonine (2) and the derivatives (δ in ppm)

| Compound | H-1 | H-2 | H-3 | H-5 | H-6 | H-7 | H-8 | H-11 ($CH_2$) | H-12 (Me) | H-14 (Me) | H-15 ($CH_2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1† | 5·71 (d 3·2) | 5·29 (t 3·2) | 4·78 (d 3·2) | 6·72 (d 1·0) | 3·04 (d 1·0) | | 5·57 (s) | 4·58 4·82 (ABq 13·0) | 1·61 (br.s) | 1·61 (br.s) | 3·76 (d 11·7) 6·04 (br.d 11·7) |
| 2 | 5·72 (d 3·2) | 5·34 (t 3·2) | 4·82 (d 3·2) | 5·41 (d 1·5) | 3·20 (d 1·5) | | 5·59 (s) | 4·47 4·92 (ABq 13·0) | 1·90 (br.s) | 1·64 (s) | 3·78 (d 12·0) 6·10 (br.d 12·0) |
| 6 | 4·24 (m) | 4·06 (t 3·0) | 4·85 (d 3·0) | 5·12 (s) | 3·13 (s) | | 4·45 (s) | 4·24 (m) | | | 3·73 (d 12·0) 6·04 (br.d 12·0) |
| 9 | 5·76 (d 3·8) | 5·20 (dd 3·0 3·8) | 4·75 (d 3·0) | 6·36 (br.s) | 2·99 (br.s) | | 4·25 (s) | 4·25 (s) | 1·60 (d 1·0) | | 3·75 5·92 (ABq 12·0) |
| 11 | 5·93 (d 3·8) | 5·30 (dd 3·8 4·5) | 4·63 (d 4·5) | 6·39 (d 10·5) | 4·22 (d 10·5) | | 9·73 (s) | 4·05 4·23 (ABq 12·3) | 1·59 (br.s) | 1·17 (s) | 4·15 4·84 (ABq 12·3) |
| 24† | 5·60 (d 3·8) | 5·27 (dd 2·8 3·8) | 4·81 (d 2·8) | 6·76 (d 0·8) | 2·34 (dd 0·8 4·0) | 5·50 (dd 4·0 6·0) | 5·34 (d 6·0) | 4·42 5·23 (ABq 13·7) | 1·48 (d 1·0) | 1·57 (s) | 3·96 4·90 (ABq 11·5) |
| 24-D | 5·65 (d 3·8) | 5·33 (dd 2·8 3·8) | 4·85 (d 2·8) | 6·81 (d 0·8) | 2·35 (d 0·8) | D | 5·28 (s) | 4·47 5·25 (ABq 13·7) | 1·50 (br.s) | 1·58 (s) | 4·03 4·90 (ABq 11·5) |
| 25† | 5·59 (d 3·6) | 5·27 (dd 2·7 3·6) | 4·79 (d 2·7) | 6·51 (d 1·0) | 2·45 (dd 1·0 2·6) | 5·57 (dd 2·6 10·0) | 5·69 (d 10·0) | 4·66 (s) | 1·49 (s) | 1·67 (s) | 3·95 4·89 (ABq 11·5) |
| 25-D | 5·62 (d 3·6) | 5·31 (dd 2·7 3·6) | 4·83 (d 2·7) | 6·55 (d 1·0) | 2·48 (d 1·0) | D | 5·69 (s) | 4·71 (s) | 1·50 (s) | 1·64 (s) | 4·03 4·88 (ABq 11·5) |

*Multiplicities and coupling constants (Hz) are given in parentheses. Spectra were taken in $CDCl_3$ at 100 MHz (**1**, **24**, **25**) and at 60 MHz (**2**, **6**, **9**, **11**, **24-D**, **25-D**).

†All the couplings were confirmed by double resonance experiments.

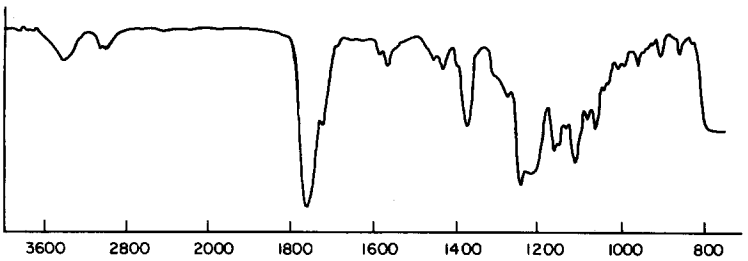



Fig 2. IR spectrum of neoevonine (2) ($CHCl_3$, $cm^{-1}$).

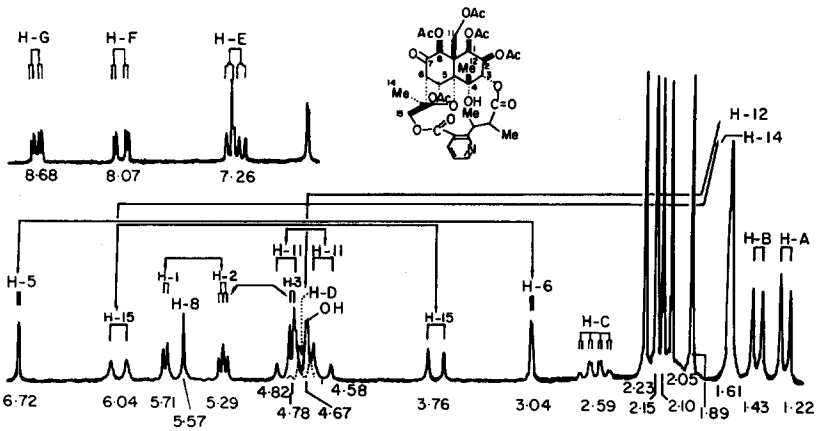
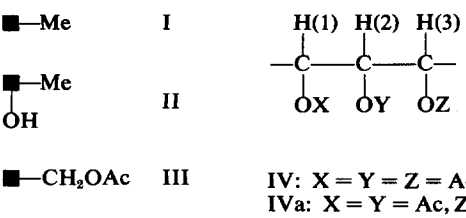



Fig 3. NMR spectrum of evonine (1) in $CDCl_3$ at 100 MHz ($\delta$ in ppm). Couplings confirmed by double resonance experiments are indicated by lines with arrows. Signals due to evoninic acid part are H—A, H—B, H—C, H—D, H—E, H—F and H—G (*cf.* Fig 5).

derivatives (Fig 3 and Table 1) the presence of the following groups (I, II, III, IV) is evident. There are two tertiary methyls (I and II; H-12 and H-14 in Fig 3), five acetate groups and an acetoxymethyl group (III; H-11 in Fig 3), the signals of which appeared as an AB quartet or a singlet in the derivatives of 1 (Table 1). There exists only one OH (II), which was shown to be attached to carbon bearing the tertiary Me by the double resonance experiment (Figs 3 and 6). The finding that the doublet due to the tertiary Me became a singlet on addition of $D_2O$ in the NMR spectra of various derivatives (e.g. **9**, **24**) is an additional evidence for the partial structure, II.




Further, the presence of a 1,2,3-triol grouping (H-1, H-2, H-3) as shown in IV was indicated by NMDR experiment (Fig 3). In accord with Pailer's observation, evonine (1) is unstable under a variety of basic conditions for hydrolysis, giving a deep brown oily material. However by means of NaOMe in MeOH at low temperatures with exclusion of oxygen in the reaction system, evonine (1) underwent methanolysis to give pentadesacetyl evonine (5), $C_{26}H_{33}NO_{12}$. The derivative (5), whose solubility to various organic solvents is quite low, formed an acetonide, pentadesacetyl evonine acetonide (6), $C_{29}H_{37}NO_{12}$ on treatment with 2,2-dimethoxypropane in the presence of camphorsulphonic acid in DMF. While pentadesacetyl evonine (5) consumed two molar equivalents of $NaIO_4$, the corresponding acetonide 6 reacted with one mole of the reagent. Comparison of the NMR spectra of 1 and 6 indicates that the Me signals due to five acetate groups in 1 were missing in 6 and the signals designated as H-1, H-2, H-5, H-8 and H-11 underwent upfield shifts by deacetylation reaction, 1 → 5 (Table 1 and Chart I). Thus the five acetate groups in 1 were

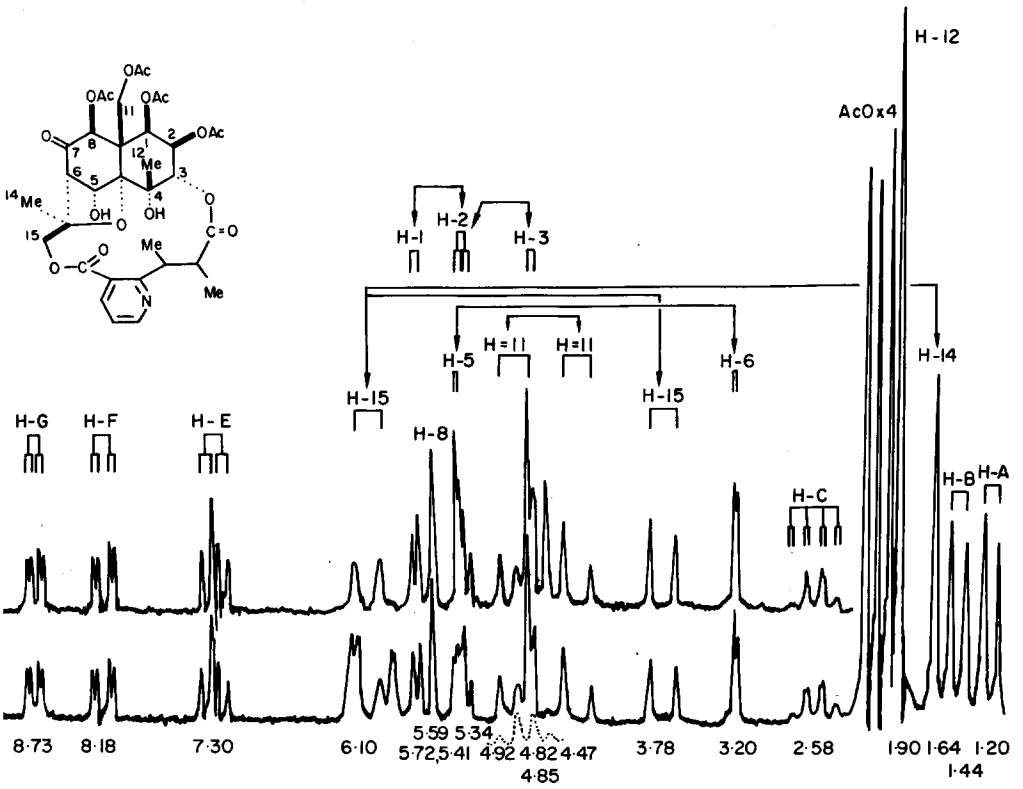



Fig 4. NMR spectra of neoevonine (2) in $CDCl_3$ at 60 MHz ($\delta$ in ppm). (The upper spectrum was obtained in the presence of $D_2O$).

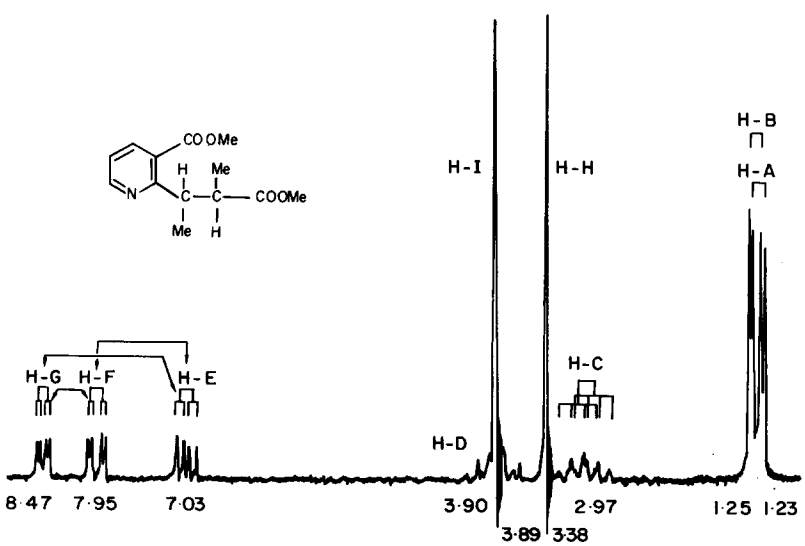
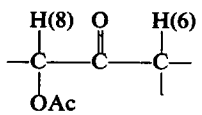



Fig 5. NMR spectrum of dimethyl evoninate (39) in $CCl_4$ at 60 MHz ($\delta$ in ppm).

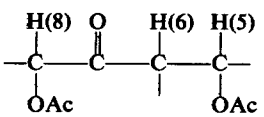
characterized: one primary (H-11) and four secondary (H-1, H-2, H-5, H-8) hydroxyls exist as acetates in **1**. The partial structure IV is therefore expressed by IVa.

Reduction of evonine (**1**) with LAH in ether–THF afforded a diol, **18**[8a] already prepared from evoninic acid by Pailer, and a mixture of two products (**19** and **20**), which was acetylated with $Ac_2O$ and pyridine at 60° (Chart II). The resulting mixture was separated by preparative TLC to afford euonyminol octaacetate, (**24**), $C_{31}H_{42}O_{18}$ (m.p. 192–193°) and isoeuonyminol octaacetate, (**25**), $C_{31}H_{42}O_{18}$ (m.p. 206–207°). Both octaacetates, **24** and **25** on treatment with NaOMe in MeOH afforded euonyminol, (**19**),* $C_{15}H_{26}O_{10}$ (m.p. 250° dec) and isoeuonyminol, (**20**), $C_{15}H_{26}O_{10}$ (amorphous), respectively. Formation of diastereoisomeric compounds, **19** and **20** from **1** implies that a keto group is present in **1**, which underwent reduction together with reductive cleavage of seven ester linkages. The presence of a keto group in **1** was further revealed by the fact that on reduction of **1** with $NaBH_4$ in EtOH, followed by acetylation a hexaacetate **36**, $C_{38}H_{47}NO_{18}$ corresponding to a dihydro derivative of **1** was formed (Chart III). The structural information about the keto group moiety was obtained from the NMR spectra of **1** and the reduction products, **24** and **25** (Figs 3, 6 and 7).

While H-6 and H-8 appeared as a doublet and a singlet, respectively in **1** (Fig 3 and Table 1), the corresponding protons in **24** (and **25**) were observed as a doublet of doublets and a doublet, and in addition, a new signal H-7 coupled to both H-6 and H-8 appeared at δ 5·50 as a doublet of doublets in **24**. As expected, no change of the multiplicity of H-6 and H-8 was observed in **24-D** obtained on reduction with LAD, followed by acetylation (Table 1). From these NMR spectral findings on **1** and **24** (and **25**), the relation of the two protons, H-6 and H-8 was made clear as shown in the partial structure V.




V




Va

Acetylation of pentadesacetyl evonine acetonide (**6**) with $Ac_2O$ and pyridine at 60° gave an acetonide triacetate (**9**), $C_{35}H_{43}NO_{15}$, which, for removal of the acetonide group, was treated with aqueous AcOH (1:1) to afford pentadesacetyl evonine triacetate (**7**), $C_{32}H_{39}NO_{15}$ (Chart I). From the NMR spectra of pentadesacetyl evonine acetonide (**6**) and its triacetate **9** (Table 1), the primary hydroxyl (H-11) and the secondary one (H-8)

*Since this polyhydroxy compound, **19** was proved to be identical with the one derived from euonymine, a minor alkaloid of *Euonymus Sieboldiana* Blume, a name euonyminol was given to the compound.

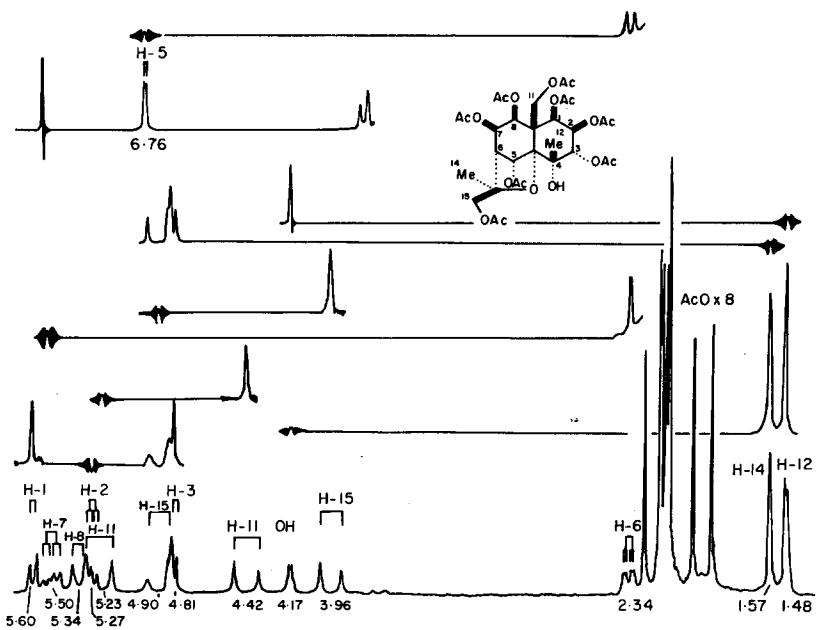



Fig 6. NMR and NMDR spectra of euonyminol octa-acetate (**24**) in $CDCl_3$ at 100 MHz (δ in ppm).

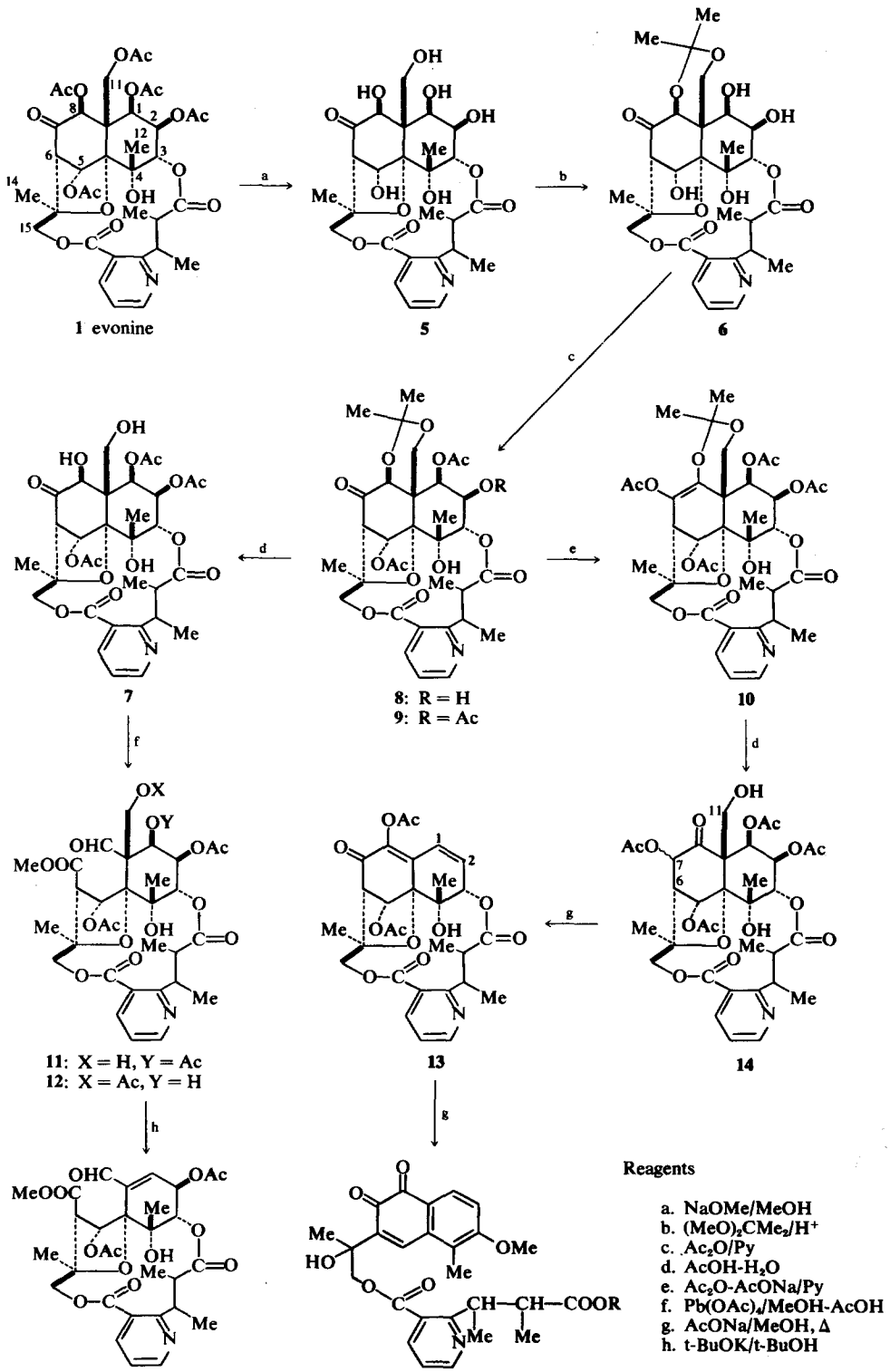

1 evonine
5
6
7
8: R = H
9: R = Ac
10
11: X = H, Y = Ac
12: X = Ac, Y = H
13
14
15
16: R = H
17: R = Me
a
b
c
d
e
f
g
h
Reagents
a. NaOMe/MeOH
b. (MeO)2CMe2/H+
c. Ac2O/Py
d. AcOH-H2O
e. Ac2O-AcONa/Py
f. Pb(OAc)4/MeOH-AcOH
g. AcONa/MeOH, Δ
h. t-BuOK/t-BuOH

CHART I

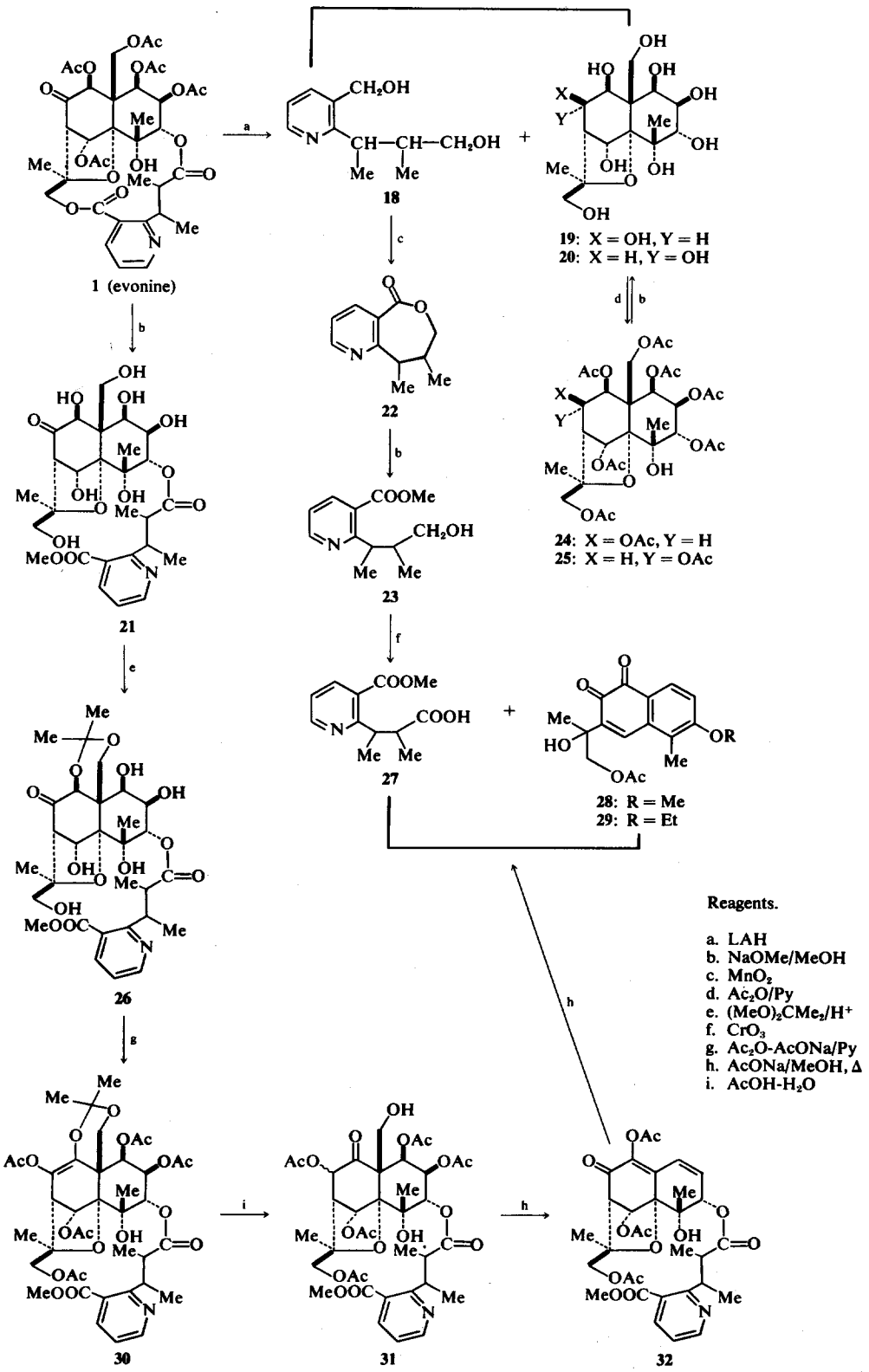

1 (evonine)
18
19: X = OH, Y = H
20: X = H, Y = OH
21
22
23
24: X = OAc, Y = H
25: X = H, Y = OAc
26
27
28: R = Me
29: R = Et
30
31
32
Reagents.
a. LAH
b. NaOMe/MeOH
c. $MnO_2$
d. $Ac_2O$/Py
e. $(MeO)_2CMe_2/H^+$
f. $CrO_3$
g. $Ac_2O$-AcONa/Py
h. AcONa/MeOH, Δ
i. AcOH-$H_2O$

CHART II

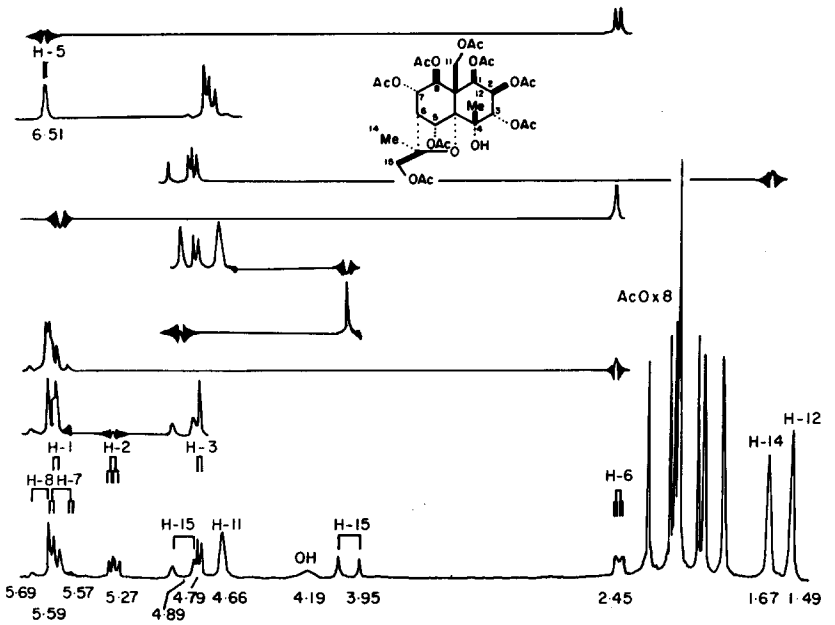


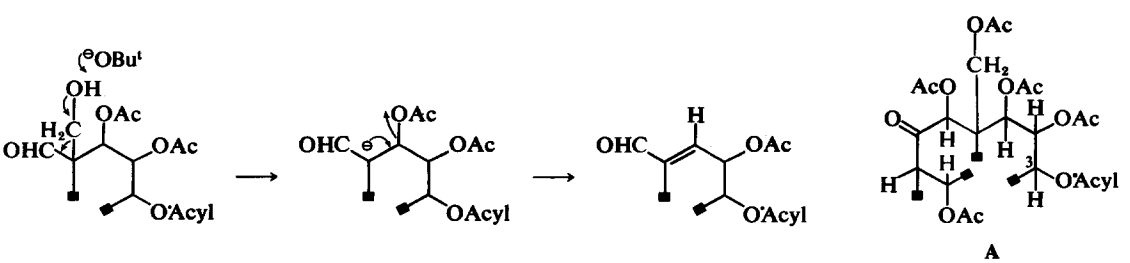

Fig 7. NMR and NMDR spectra of isoeuonyminol octa-acetate (**25**) in $CDCl_3$ at 100 MHz ($\delta$ in ppm).

of the $\alpha$-ketol moiety (partial structure, V) were shown to be involved in the formation of the acetonide. The result of the consumption of $NaIO_4$ by pentadesacetyl evonine (**5**) (two moles) and its acetonide **6** (one mole) suggests that the two hydroxyls involved in the acetonide formation are situated in 1,3-relationship, which was clearly established by a series of the following reactions.

For the cleavage of the $\alpha$-ketol grouping, pentadesacetyl evonine triacetate (**7**) was reacted with $Pb(OAc)_4$ in AcOH-MeOH to give an aldehyde ester triacetate (**11**), $C_{33}H_{41}NO_{16}$ and its isomer **12**, $C_{33}H_{41}NO_{16}$ (Chart I). While the major product **11** showed an expected NMR spectral pattern, the downfield shift (0·54 ppm) of the signal due to the hydroxymethyl group (H-11) was observed with the concomitant upfield shift (*ca* 1·1 ppm) of the signal of H-1 in the NMR spectrum of the minor isomer **12**, as compared with the corresponding signals in **11**. These findings indicate that the migration of the acetyl group from the OH on the terminal carbon (C-1) of the 1,2,3-triol system (partial structure, IVa) to the hydroxymethyl group (C-11, partial structure, III) took place during the $Pb(OAc)_4$ oxidation reaction.

The coupling constant between H-5 and H-6, which is small (1·0 Hz) in evonine (**1**) was found to be 10·5 Hz in **11**, indicating clearly that the two protons (H-5, H-6) are located on the two adjacent carbons. Thus the partial structure, Va in evonine (**1**) was established.

On treatment with t-BuOK in t-BuOH-DME, the aldehyde ester triacetate (**11**) afforded formaldehyde and an $\alpha\beta$-unsaturated aldehyde ester diacetate (**15**), $C_{30}H_{35}NO_{13}$ [UV (EtOH), $\lambda_{max}$ nm ($\epsilon$), 223 (7,700), 265 (3,100); NMR ($CDCl_3$) $\delta$ 2·03 (3H, s, AcO), 2·10 (3H, s, AcO), 6·59 (1H, dd, $J = 1·5$ and 4·5 Hz, vinyl H), 9·73 (1H, s, CHO)] (Chart I). This reaction, illustrated below, is retroaldolization of the hydroxymethyl group with subsequent elimination of one mole of AcOH, and made it possible to correlate three partial structures (III), (IVa) and (Va), leading to the new partial structure (A) for **1**.




A

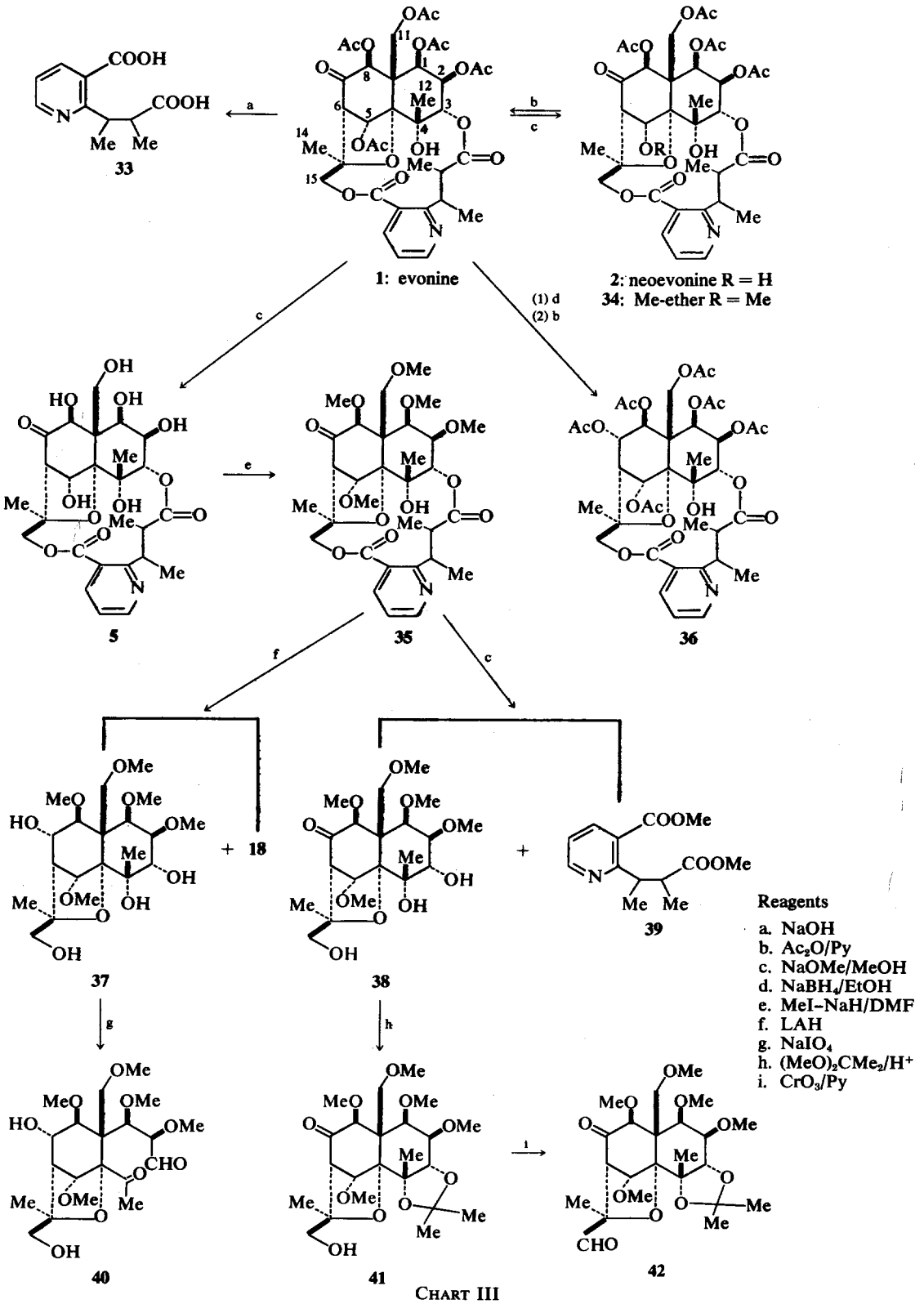
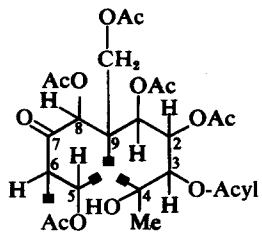

33
1: evonine
2: neoevonine R = H
34: Me-ether R = Me
5
35
36
37
38
39
40
41
42
+ 18
Reagents
a. NaOH
b. Ac2O/Py
c. NaOMe/MeOH
d. NaBH4/EtOH
e. MeI–NaH/DMF
f. LAH
g. NaIO4
h. (MeO)2CMe2/H+
i. CrO3/Py

CHART III

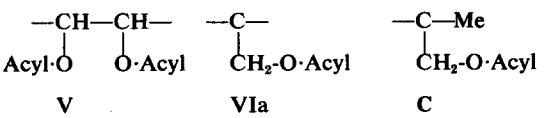
Further a series of the following reactions provided evidence correlating the two partial structures, II and A.

On treatment of pentadesacetyl evonine (5) with MeI and NaH in DMF, a pentamethyl ether (35), $C_{31}H_{43}NO_{12}$ was obtained, which was reduced with LAH in THF (Chart III). The resulting pentamethyl ether tetraol (37), $C_{20}H_{36}O_{10}$ was oxidized with $NaIO_4$ to give a methyl ketone aldehyde, 40, $C_{20}H_{34}O_{10}$ [IR ($CHCl_3$) 1735, 1708 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2·19 (3H, s, MeCO), 9·61 (1H, d, $J = 2·3$ Hz, CHO); mass 433 (M-1)]. Formation of 40 unambiguously demonstrates that the group (II) is adjacent to the terminal carbon (C-3) of the 1,2,3-triol grouping in the partial structure A, and evonine (1) is represented by the new partial structure B. The following result is consistent with the partial structure B: methanolysis of the pentamethyl ether (35) with NaOMe in MeOH gave dimethyl evoninate (39) and a pentamethyl ether triol (38), $C_{20}H_{34}O_{10}$, which, on treatment with 2,2-dimethoxy-propane–camphorsulphonic acid, afforded pentamethyl ether triol acetonide (41), $C_{23}H_{38}O_{10}$.




B

Among the protons of evonine (1) observed in the NMR spectrum (Fig 3), two protons (H-15) remained uncharacterized so far. Their signal pattern was remarkably affected by structural changes: the signals appeared as an AX type or an AB type (*cf* Table 1). From their chemical shifts it was expected that the structural unit (VI) would be responsible for these two protons. Contrary to this expectation these protons were proved to be methylene ones on carbon bearing an acyloxy group as indicated in VIa on the basis of the following reaction (Chart III). Pentamethyl ether triol acetonide (41) was oxidized with $CrO_3$ and pyridine to afford an aldehyde, 42, $C_{23}H_{36}O_{10}$ [NMR ($CDCl_3$) $\delta$ 9·80 (1H, s, CHO)].




V VIa C

Since the long range coupling ($J = ca$ 1 Hz) was observed between the tertiary Me group (H-14, partial structure I) and one of the methylene protons (H-15) in some compounds [e.g. 24 (Fig 6), 25, neoevonine methyl ether (34),* Fig 9], the partial structure C was proved to be present in evonine (1).

Characterization of functional groups and their correlation were almost achieved, the result of which can be summarized by the two partial structures, (B and C).

*Carbon skeleton of the sesquiterpene part of evonine* (1). At this stage of the structural analysis of the $C_{15}$-part of evonine (1), the information on the carbon skeleton is essential, which is described

*Since neoevonine (2) was shown to be desacetyl evonine (see later section), the NMR spectrum of the derivative of neoevonine was employed for the structural proof of evonine.

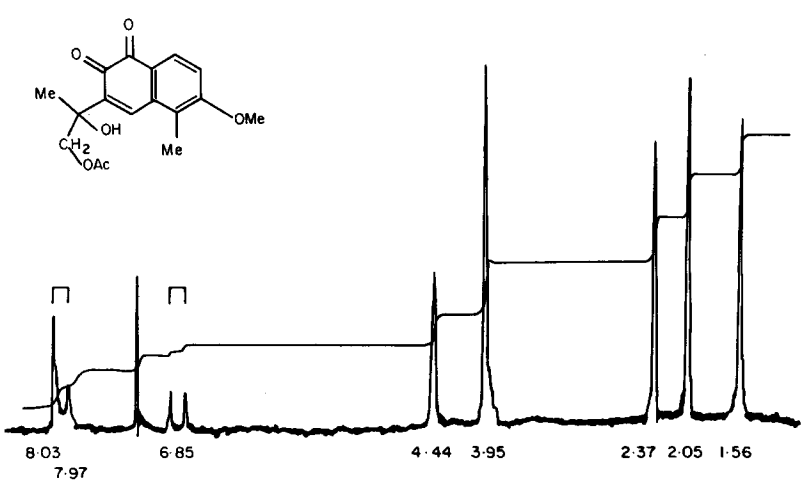



Fig 8. NMR spectrum of the 1,2-naphthoquinone (28) in $CDCl_3$ at 60 MHz ($\delta$ in ppm).

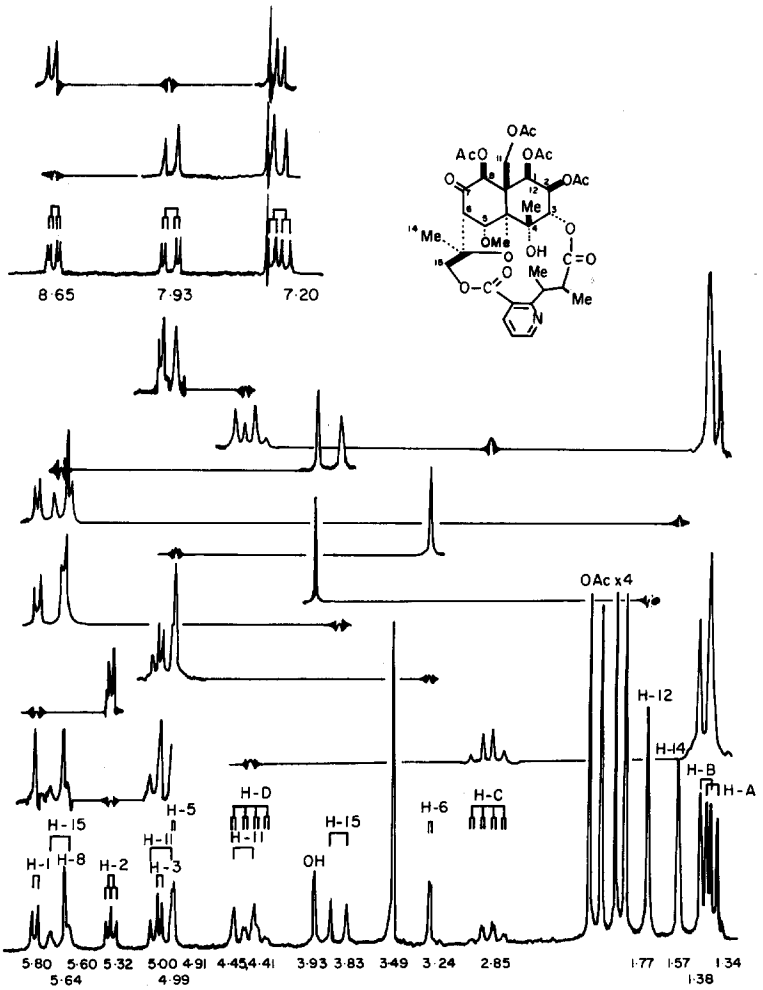
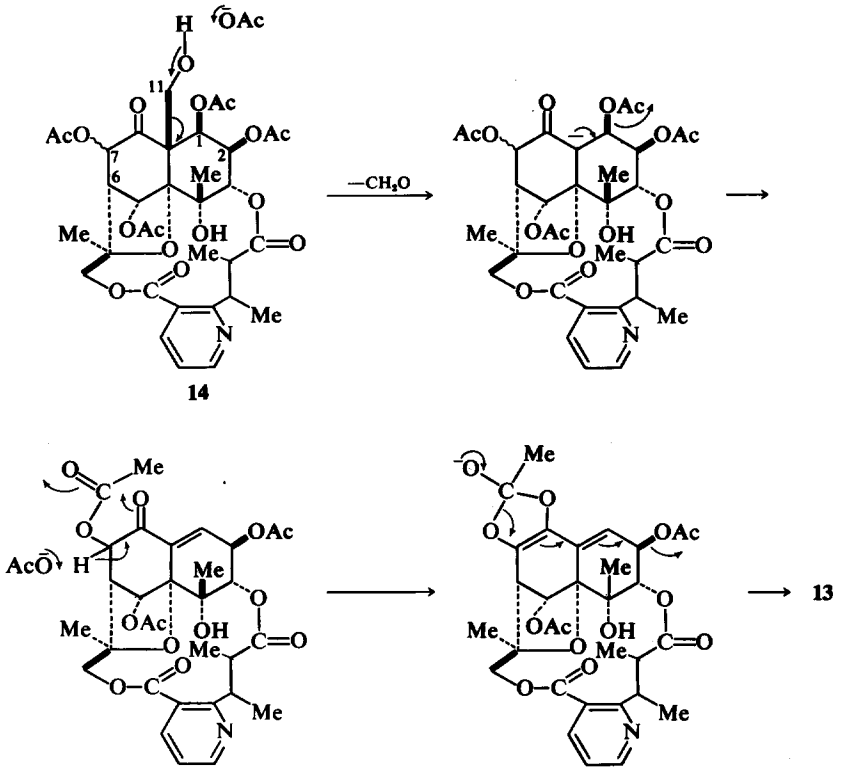



Fig 9. NMR and NMDR spectra of neoevonine methyl ether (**34**) in $CDCl_3$ at 100 MHz (δ in ppm).

here in detail. All the derivatives in this section are included in Charts I and II.

The acetonide triacetate **9** obtained from evonine (**1**) in three steps was further acetylated under forcing conditions ($Ac_2O$-AcONa in pyridine, 85–90°, 40 hr), giving an acetonide tetraacetate, **10** (Chart I). For removal of the isopropylidene group, the acetonide tetraacetate **10** was treated with aqueous AcOH to afford a tetraacetate, **14**, $C_{34}H_{41}NO_{16}$. In the NMR spectrum of **14**, two protons, H-6 and H-7 were observed as a doublet [δ 2·63 ($J = 3$ Hz)] and a doublet [δ 5·83 ($J = 3$ Hz)], respectively, indicating that the transposition between the CO and the OH of the α-ketol grouping in pentadesacetyl evonine (**5**) was achieved. In the derivative **14** a retroaldol reaction was expected to occur, considering the partial structure **B**. After the conditions for this reaction were extensively examined, the following conditions were found to give the best result: the tetraacetate **14** was treated with AcONa in EtOH at refluxing temperature for 25 min, affording a conjugated dienone, **13**, $C_{29}H_{31}NO_{11}$, the structure of which was firmly established by spectral evidence. In the NMR spectrum of **13**, signals due to the three protons, H-7 (methine) and H-11 (methylene) and due to two of the four acetate methyls originally present in **14** were missing and the signals of two protons, H-1 (δ 6·58, d, $J = 9{\cdot}8$ Hz) and H-2 (δ 6·35, dd, $J = 5{\cdot}3$ and 9·8 Hz) appeared in the vinyl proton region; the IR spectrum showed characteristic bands at 1700 and 1623 $cm^{-1}$ due to a conjugated ketone group in addition to a broad band of ester grouping at 1740 $cm^{-1}$; further in the UV spectrum, absorptions at 287 and 225 nm (ε 15,000 and 8,000) were observed, demonstrating the presence of an αβ,γδ-unsaturated keto group. These spectral

data indicate that the reaction (14→ 13) occurred with elimination of formaldehyde and two moles of AcOH, accompanied by acetyl migration in the α-ketol moiety. The reaction, 14→ 13 is illustrated as shown below.

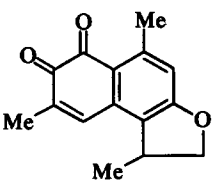



On further treatment of the dienone **13** with AcONa in MeOH at refluxing temperature, an orange red acidic compound, **16** was obtained in the amorphous state, which was esterified with HCl-MeOH, affording the methyl ester **17**, $C_{27}H_{29}NO_8$ [amorphous; mass 495 ($M^+$), 497 ($M+2$)] (Chart I). From the spectral data (*cf* Experimental), the methyl ester **17** was deduced to be a 1,2-naphthoquinone derivative. For the purpose of obtaining an aromatized compound in the crystalline state, various attempts were made, among which a series of the following reactions provided a crystalline aromatic compound (Chart II).

Upon treatment of evonine (**1**) with NaOMe in MeOH at 30°, methanolysis of one of the ester linkages of evoninic acid together with that of five acetate groups took place, affording pentadesacetyl evonine methyl ester (**21**), which formed an acetonide **26**, $C_{30}H_{41}NO_{13}$ with 2,2-dimethoxypropane in the presence of camphorsulphonic acid in DMF. In the NMR spectrum of **26**, the signal due to the methyl ester group appeared at δ 3·93 (3H, s); further it was observed that while there was no significant shift of a doublet of H-3, a doublet assigned to H-15 shifted to a higher field. From this NMR spectral evidence, one of the two ester linkages of evoninic acid attached to the hydroxymethyl group in the partial structure, (C) underwent methanolysis. The reactions already described for obtaining the amorphous orange red compound **16** (Chart I) were applied to pentadesacetyl evonine methyl ester acetonide (**26**) (Chart II).

Acetylation of **26** with $Ac_2O$-AcONa in pyridine (85–90°, 40 hr) gave a methyl ester acetonide pentaacetate, **30**. For removal of the isopropylident group, **30** was treated with aqueous AcOH. As in the case of the tetraacetate **14**, the resulting pentaacetate, **31** was treated with AcONa in MeOH at refluxing temperature for 25 min, giving a conjugated dienone methyl ester, **32**, $C_{32}H_{37}NO_{13}$ [mass 643 ($M^+$)]. The spectral evidence confirmed that the structural changes from **26** to **32** via the intermediates, **30** and **31** correspond exactly to those from **6** to **13** through **9**, **10** and **14**. Prolonged heating of the conjugated dienone methyl ester, **32** in the presence of AcONa in MeOH afforded, with expulsion of evoninic acid monomethyl ester (**27**), a crystalline orange red compound, **28**, $C_{17}H_{18}O_6$. The structure of the orange

red compound was proved to be a 1,2-naphthoquinone derivative as shown in **28**, on the basis of the following spectral data. From the NMR spectrum (Fig 8) and consideration of the partial structures, **B** and **C**, the presence of the following groups was evident: three aromatic protons (two vicinal ones and an isolated one), an acetoxymethyl, a tertiary Me, an aromatic Me, an OH and an OMe group. The OMe group in **28** was proved to originate from MeOH employed as solvent, since an OEt group was present in the naphthoquinone **29** obtained in the reaction using EtOH as solvent. This compound **28** showed the characteristic UV spectrum [$\lambda_{max}$ (EtOH) nm ($\epsilon$), 218 (17,000), 244 (12,000), 280 (16,000), 405 (6,700)], which was compared with those of various alkoxy-substituted 1,2-naphthoquinones. The UV spectrum of **28** was found to be quite similar to that of mansonone D [$\lambda_{max}$ (EtOH) nm (log $\epsilon$), 219 (4·30), 243 (4·10), 278 (4·11), 405 (3·88)].[11]

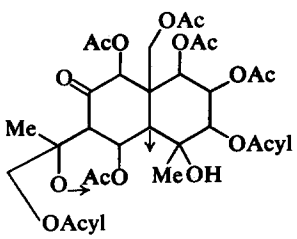



mansonone D

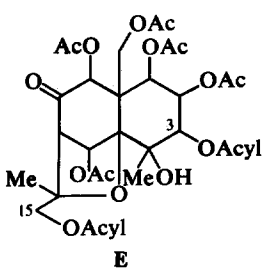
In the IR spectrum of **28**, bands characteristic of 1,2-naphthoquinones [1690, 1660 $cm^{-1}$ ($CHCl_3$)] were observed. Further, this compound showed a strong M+2 peak in the mass spectrum, which is a well-known feature of 1,2-naphthoquinones.[12] On the basis of these spectral data and the partial structures, **B** and **C** already established, the structure of the orange red 1,2-naphthoquinone was determined as **28**:* i.e., since the partial structures, **B** and **C** account for fourteen carbons, the remaining one is quaternary, which is evidently bonded to C-4, C-5 and C-9 in (**B**), and the three carbon unit (**C**) is attached to C-6 of (**B**).

Formation of **28** from **32** would be rationalized as shown in the next page.

*Planar structure of evonine* (**1**). Among ten oxygens in the $C_{15}$-component of evonine (**1**), nine ones were well characterized (one keto carbonyl, and eight hydroxyls), and the remaining one was deduced to be ethereal. A tertiary OH present in the 1,2-naphthoquinone **28** must originate from the ethereal oxygen of evonine (**1**) so far undetected. Considering the partial structures, **B** and **C**, and the formation of the aromatic compound **28**, the structure of the $C_{15}$-part of evonine (**1**) is represented by **D**, which, by making a bond between two atoms bearing an arrow mark is led to the structure **E**.




**D**



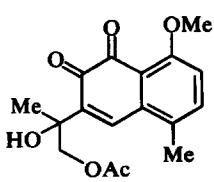

**E**

In the structure **E**, evoninic acid (**33**) is connected at C-3 and C-15 through ester linkage.

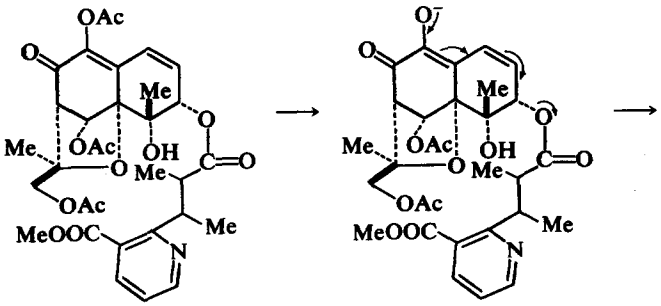
The remaining problem to be settled is the one regarding the two ester linkages formed between evoninic acid (**33**) and the sesquiterpene group **E**.

As described above, in the reaction of forming the 1,2-naphthoquinone **28** from the conjugated dienone methyl ester, **32**, evoninic acid monomethyl ester was formed, the structure of which was proved to be **27** from the following evidence (Chart II). The diol, **18**[6b] obtained by LAH reduction of evonine (**1**) was oxidized with $MnO_2$ in benzene, affording a lactone, **22**, $C_{11}H_{13}NO_2$ [IR ($CHCl_3$) 1720 $cm^{-1}$ (conjugated $\epsilon$-lactone)], which was converted to a hydroxy ester, **23** on treatment with NaOMe in MeOH. Oxidation of the hydroxy ester, **23** with $CrO_3$ in pyridine at 50° gave an ester acid, which evidently possesses the structure, **27**, considering the mode of preparation and was found to be identical with the ester acid obtained in the reaction, **32**→**28**. These findings unequivocally established that the aromatic carboxyl group of evoninic acid (**33**) was connected with the primary OH (C-15) of the sesquiterpene part (**E**). Further, supporting evidence that the

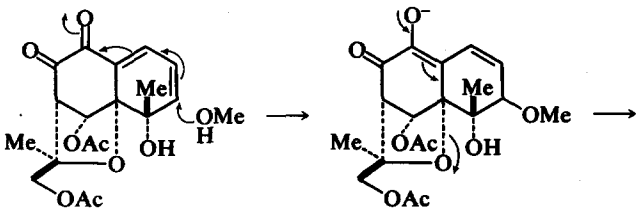
*An alternative structure **28a** conceivable from the possible mechanism of the aromatization reaction of the conjugated dienone methyl ester, **32** was excluded by the UV spectrum of the similarly substituted compound, 8-methoxy-1,2-naphthoquinone [$\lambda_{max}$ (EtOH) nm (log $\epsilon$), 243 (4·29), 418 (3·84)].

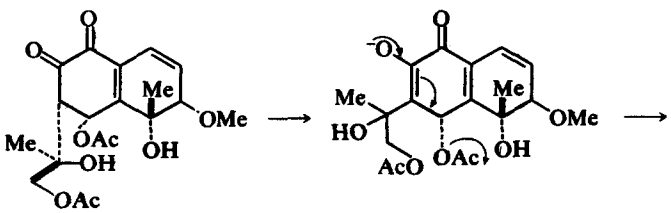


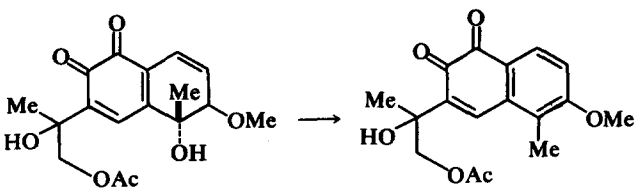

**28a**



32





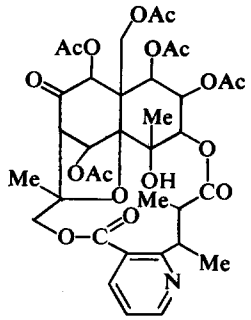


28

aromatic carboxyl group of evoninic acid is attached to C-15 of the sesquiterpene part (E) was obtained from the NMR spectra of pentadesacetyl evonine methyl ester (21) and methyl nicotinate. Since the Me signal of methyl nicotinate was observed at δ 3·93, two methyl ester singlets at δ 3·92 and 3·39 of dimethyl evoninate (39) (Chart III) were assigned to the aromatic one and the aliphatic one, respectively (*cf* Fig 5). The signal due to the methyl ester group of pentadesacetyl evonine methyl ester (21) and its derivatives (e.g. 26, 31, 32) appeared in the range of δ 3·89–3·94, indicating that it was the ester linkage between the aromatic carboxyl group of evoninic acid and the hydroxyl at C-15 of the sesquiterpene part (E) that underwent methanolysis in the reaction from evonine (1) to pentadesacetyl evonine methyl ester (21) (Chart II). The planar structure of evonine was thus determined, which is represented by F.

*Stereochemistry of evonine* (1). The configurations of two asymmetric centers in evoninic acid part were already determined by Pailer and Libiseller.[6b]

The stereochemistry of the sesquiterpene part was determined as follows. The C-ring is necessarily attached to the B-ring by two axial bonds at C-6 and C-10 of the B-ring on steric grounds (see the stereoformula of 1 in this section). Regarding the A/B ring juncture two configurations (*cis* and



F

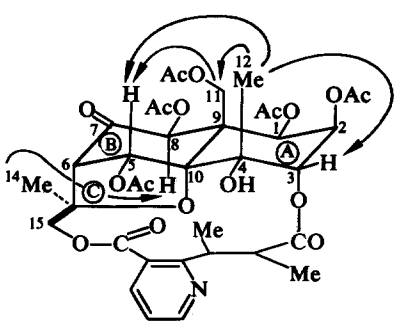
*trans*) are possible, and it was proved by the intramolecular nuclear Overhauser effects (NOE) on pentadesacetyl evonine acetonide diacetate (**8**) that the ring juncture is *trans*: (i) irradiation of H-11 (δ 4·27) caused an increase (20%) in the signal intensity of H-5 (δ 6·35), and (ii) an enhancement (8%) of the signal intensity of H-5 was detected on irradiation of H-12 (δ 1·67); (iii) further, the intensity of H-11 (δ 4·66) in isoeuonyminol octaacetate (**25**) was clearly increased (10%) on irradiation of H-12 (δ 1·67). These results of NOE indicate not only the *trans* nature of the A/B ring juncture, but that these three groups (the methine of C-5, the methylene of C-11, the Me of C-12) are axial in each cyclohexane ring.* Since the acetyl migration from C(1)-OH to C(11)-OH was observed during the $Pb(OAc)_4$ oxidation of **7**, as described earlier, the methylene group of C-11 and the hydroxyl at C-1 are in a *cis* arrangement. The *cis* relationship between H-3 and H-12 (the Me group on C-4) was deduced from the observation of the NOE between them in isoeuonyminol octaacetate (**25**): on irradiation of H-12 (δ 1·67) the intensity of the H-3 signal (δ 4·79) was increased (*ca* 15%).

The signal of H-1 was always observed in the significantly lower field region (δ 5·6–5·9) than those of H-2 (δ 5·2–5·3) and H-3 (δ 4·6–4·9), (Table 1). These results could be ascribed to the anisotropic effect of the ethereal oxygen at C-10 and the hydroxyl at C-3 situated in the 1,3-diaxial relations to H-1. Thus, H-1 must occupy the axial position in the A-ring. The coupling constant between H-1 and H-2 is in a range of 3·2–3·8 Hz in a variety of derivatives of **1** (Table 1), indicating that these vicinal hydrogens are *cis*.†

Formation of an acetonide linkage between C(8)-OH and C(11)-OH as exemplified by pentadesacetyl evonine acetonide (**6**) revealed that the methylene group of C-11 and the hydroxyl at C-8 are *cis*. The NOE was observed between H-8 and H-14: when the Me signal (H-14, δ 1·57) was irradiated in neoevonine methyl ether (**34**), an increase (30%) of the H-8 signal intensity (δ 5·60) occurred, demonstrating the configuration of the Me group (C-14) as shown in **1**. The complete structure including stereochemistry of evonine is thus unequivocally determined, which is represented by **1**. The results of NOE are summarized in Table 2.

Table 2. NOE on evonine derivatives ($CDCl_3$, 100 MHz)

| Compound | Irradiate | Observe | Percentage of enhancement |
|---|---|---|---|
| **8** | H-11 | H-5 | 20 |
| | H-12 | H-5 | 8 |
| **25** | H-12 | H-3 | 15 |
| | H-12 | H-11 | 10 |
| **34** | H-14 | H-8 | 30 |



**1** (evonine)

*Neoevonine*

Neoevonine (**2**) corresponds to a desacetyl compound of evonine (**1**), considering the molecular formulas of both alkaloids. Chemical correlation of both alkaloids was achieved: on acetylation of neoevonine (**2**) with $Ac_2O$ and pyridine at 45° evonine (**1**) was formed, while methanolysis of **1** under the carefully controlled conditions afforded **2**. Comparison of the NMR spectra of **1** and **2** made it possible to determine the locations of

*Santavy *et al.* cast a doubt on our stereochemical assignment at C-4 and C-5; A. Klasek, Z. Samek and F. Santavy, *Tetrahedron Letters* 941 (1972). It is surprising that they overlooked the result of NOE, which unequivocally established the stereochemical relation of the three groups, H-5, H-11 and H-12, and described explicitly in our communication.[7c]

†Definitive evidence that H-1 and H-2 are *cis* was obtained from the coupling constant ($J_{1,2}$) of H-1 and H-2 of the derivative possessing a new tetrahydrofurane ring formed by dehydration between C(2)-OH and C(11)-OH.[14] In this conformationally rigid derivative, H-1 appeared as a singlet, indicating that $J_{1,2}$ is virtually zero, owing to the fact that the dihedral angle between H-1 and H-2 is *ca* 90°; if H-1 and H-2 were *trans*, $J_{1,2}$ was expected to be *ca* 7 Hz. These phenomena observed in the bicyclo[3.2.1]-octane and the related systems containing oxygen were well documented in the literatures.[15,16]

four acetate groups in 2 (*cf* Figs 3 and 4); whereas chemical shifts of protons on carbon carrying the primary OH (H-11) and the three secondary OH's (H-1, H-2, H-8) were essentially the same in both 1 and 2, the signal, H-5, which appeared at δ 6·72 in 1 was observed at δ 5·41 in 2. The structure of neoevonine was therefore established as 2. Neoevonine (2) on treatment with MeI and $Ag_2O$ afforded the methyl ether, **34**, the NMR and NMDR spectra of which are shown in Fig 9.

## EXPERIMENTAL

All m.ps were uncorrected. UV spectra were measured in EtOH on a Perkin-Elmer Model 202 spectrophotometer. IR spectra were recorded with a JASCO Model IRS spectrophotometer and a JASCO DS-402G spectrophotometer. NMR spectra were determined on the following spectrometers, JNMC-60H, JNM 4H-100, and Varian HA-100; chemical shifts (δ) are given in ppm relative to internal TMS; signals arising from the sesquiterpene part are cited, unless otherwise stated. The mass spectra were determined on a Hitachi RMU-6C mass spectrometer equipped with a direct inlet system, and the high resolution mass spectra on a JEOLCO GMS-01SG mass spectrometer. Optical rotations were measured on an Oyo-denki Model MP-1 spectropolarimeter. A Hitachi K-53 gaschromatograph for analytical GLC was employed, equipped with 2 m × 3 mm columns packed with 5% SE-30 on Chromosorb W, and a Varian 1820-4 gas chromatograph was used for preparative GLC. For TLC silica gel $GF_{254}$, $PF_{254}$ and alumina $GF_{254}$, $PF_{254}$-Type T (E. Merck, A. G., Germany) were used: thickness employed was 0·25 mm for analytical purpose, and 1·00 mm for preparative purpose. For column chromatography, silicic acid (100 mesh, Mallinckrodt, U.S.A.) and alumina (activity, II–III, E. Merck, A. G., Germany) were used. The organic solns were dried over $Na_2SO_4$ and evaporated by vacuum rotary evaporator.

*Extraction of evonine* (1) *and neoevonine* (2). The seeds (*ca* 225 kg) of *Euonymus Sieboldiana* Blume collected in October–November at Mt. Ibuki (Shiga Prefecture), Mt. Fujiwara (Mie Prefecture), and Mt. Chausu (Aichi Prefecture) were dried and ground. To the powdered seeds n-hexane (60 l) was added. The mixture was left for several days at room temp and was filtered with suction. This procedure of n-hexane extraction was repeated twice. The combined n-hexane extracts were concentrated, affording an orange soln (*ca* 24 l), which was diluted with ether (*ca* 24 l). The n-hexane–ether soln was shaken with 2·5% HCl repeatedly. After the partly emulsifying mixture was filtered through Super Cel, the aqueous phase separated was washed with ether and was made alkaline (pH 9) with solid $K_2CO_3$. The resulting aqueous mixture was extracted with AcOEt 3 times. The AcOEt extracts were washed with saturated NaCl aq, dried, and concentrated, giving an oily alkaloidal mixture. After the treatment with n-hexane, the powdered seeds were further extracted with ether twice (60 l × 2). From these ethereal extracts an oily alkaloidal mixture was obtained by the same procedure as described in the extraction with n-hexane. The amount of the total alkaloidal mixture was 68 g. The mixture was dissolved in EtOH, and the soln was allowed to stand, giving crude crystals (23 g) of 1 and 2. Repeated fractional recrystallization of the crude crystals from EtOH afforded pure 1 (13 g). The crystalline residue obtained on evaporation of the mother liquor was recrystallized repeatedly from MeOH, affording pure 2 (7·2 g). After 1 and 2 were crystallized out, the mother liquor was evaporated, and the resulting amorphous powder (45 g) was chromatographed on silicic acid (1200 g) with benzene–AcOEt (v/v 1 : 1). Early fractions afforded crystalline 1 (9 g), and from the later fractions crystalline 2 (5 g) was obtained. The total amount of 1 and 2 was 22 g and 12·2 g, respectively. Physical and spectral data are recorded in the text. 1 (Found: C, 56·69; H, 5·63; N, 1·83. $C_{36}H_{43}NO_{17}$ requires: C, 56·76; H, 5·69; N, 1·84%). 2 (Found: C, 56·84; H, 5·56; N, 2·21. $C_{34}H_{41}NO_{16}$ requires: C, 56·79; H, 5·74; N, 1·95%).

*Pentadesacetyl evonine* (5). To a soln of 1 (2 g) in anhyd MeOH (55 ml) was added a soln (0·5 ml) of NaOMe in MeOH (prepared from 100 mg of Na and 10 ml of anhyd MeOH) at 5° under $N_2$. The soln was stirred at 5° for 5 hr, and added for neutralization of NaOMe with ion-exchange resin Amberlite IR-120 (H form). The ion-exchange resin was filtered with suction and the filtrate was concentrated. The resulting colourless powder was recrystallized from MeOH, affording crystalline 5 (1·03 g), m.p. 257° (dec); IR (KBr) 3440, 1740, 1718, 1702, 1585, 1568 $cm^{-1}$; Mass 551 ($M^+$). (Found: C, 56·47; H, 6·19; N, 2·21. $C_{26}H_{33}NO_{12}$ requires: C, 56·67; H, 6·04; N, 2·54%).

*Pentadesacetyl evonine acetonide* (6). A mixture of 5 (2·144 g), 2,2-dimethoxypropane (35 ml), and camphorsulphonic acid (1·3 g) in DMF (11 ml) was stirred at room temp for 4 hr. To this mixture, AcOEt and saturated $NaHCO_3$ aq were added. The AcOEt layer separated was washed with saturated NaCl aq, dried, and evaporated, to give an amorphous powder (2·21 g). Recrystallization from $CHCl_3$–$CCl_4$ afforded pure 6, m.p. 194–197°; NMR (Table 1). Mass 591 ($M^+$). (Found: C, 58·79; H, 6·35; N, 2·38. $C_{29}H_{37}NO_{12}$ requires: C, 58·88; H, 6·37; N, 2·37%).

*Reduction of* 1 *with* LAH: *diol* (18), *euonyminol* (19), *isoeuonyminol* (20), *and the octaacetates*, (24), (25). A soln of 1 (3 g) in dried THF (50 ml) was added dropwise to a soln of LAH (3·50 g) in dried THF (120 ml)–anhyd ether (50 ml) under ice-bath cooling. The mixture was stirred at room temp overnight. The excess reagent and the complex were decomposed by careful addition of $H_2O$ (16 ml). The mixture was filtered and the solid was washed with AcOEt thoroughly. The combined filtrate was evaporated to give a residue, which was purified by preparative TLC using silica gel $PF_{254}$ with benzene–AcOEt (1 : 1), affording crude 18.[6a] The solid was dissolved in 50% AcOH–$H_2O$ and the soln was passed through a column of ion-exchange resin Amberlite IR-120 (H form, 600 ml). The eluate was concentrated, to give a residue, which was dissolved in a small amount of $H_2O$. The aqueous soln was washed with AcOEt and concentrated to yield a resinous material (1·3 g, mixture of 19 and 20). A mixture of the resinous product (1·3 g) in $Ac_2O$ (10 ml) and pyridine (15 ml) was kept at 60° for 16 hr. The mixture was concentrated and diluted with AcOEt. The AcOEt soln was washed with sat $NaHCO_3$ aq and sat NaCl aq, dried, and evaporated, to give a resinous product (2·3 g). The product was chromatographed on silicic acid: fractions eluted with benzene gave 25 (*ca* 860 mg) and fractions obtained by using benzene–AcOEt (2 : 1) afforded 24 (*ca* 420 mg). Both octaacetates were recrystallized from EtOH. 24, m.p. 192–193°; IR (KBr) 3430, 1735 $cm^{-1}$; NMR (Fig 6).

Mass 702 ($M^+$). (Found: C, 53·08; H, 6·10. $C_{31}H_{42}O_{18}$ requires: C, 53·04; H, 6·03%). **25**, m.p. 206–207°; IR (KBr) 3430, 1745 $cm^{-1}$; NMR (Fig 7); Mass 685 (M-17). (Found: C, 53·08; H, 6·11. $C_{31}H_{42}O_{18}$ requires: C, 53·04; H, 6·03%).

A soln (1·5 ml) of NaOMe in MeOH (concentration, NaOMe 5 mg/ml) was added to a soln of **24** (1 g) in anhyd MeOH (100 ml). The mixture was allowed to stand at room temp overnight, concentrated to a small volume (*ca* 10 ml), and neutralized with ion-exchange resin Amberlite IR-120 (H form), which was filtered. The filtrate was evaporated, to give a resinous material (530 mg), which on recrystallization from MeOH–acetone afforded crystalline **19** (400 mg), m.p. 250° (dec). (Found: C, 49·11; H, 7·28. $C_{15}H_{26}O_{10}$ requires: C, 49·22; H, 7·16%). Under the same conditions as described above, **25** (1 g) underwent methanolysis to give amorphous **20** (512 mg).

*Reduction of* **1** *with* LAD. Reduction of **1** (1 g) with LAD (1·12 g), followed by acetylation was performed by the same procedure as used in LAH reduction; deutero-euonyminol octaacetate (**24-D**; 125 mg), m.p. 193°; NMR (Table 1). Mass 703 ($M^+$). (Found: C, 52·84; H, 6·10. $C_{31}H_{41}DO_{18}$ requires: C, 52·96; H, 6·19%): deutero-isoeuonyminol octaacetate (**25-D**; 196 mg), m.p. 206°; NMR (Table 1). (Found: C, 53·10; H, 5·99. $C_{31}H_{41}DO_{18}$ requires: C, 52·96; H, 5·99%).

*Reduction of* **1** *with* $NaBH_4$: (**36**). A soln of **1** (113 mg) and $NaBH_4$ (20 mg) in EtOH (2 ml) was stirred at room temp for 1 hr and diluted with $H_2O$. The mixture was extracted with four 30 ml portions of AcOEt. The AcOEt extracts were washed with sat NaCl aq, dried, and concentrated. The residue was purified by preparative TLC (silica gel $PF_{254}$) with AcOEt–benzene (1:1) to afford an amorphous powder (86 mg). A soln of this reduction product (80 mg) in $Ac_2O$ (2 ml) and pyridine (1·5 ml) was stirred at room temp for 12 hr and concentrated, giving a residue, which was extracted with three 20 ml portions of AcOEt. The combined AcOEt soln was washed with sat $NaHCO_3$ aq and sat NaCl aq, dried, and concentrated to afford amorphous **36** (82 mg); IR ($CHCl_3$) 3480, 1753, 1585, 1565 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 5·30 (1H, t, $J$ = 3·0 Hz, H-2), 4·77 (1H, d, $J$ = 3·0 Hz, H-3), 6·68 (1H, s, H-5), 1·60 and 1·72 (3H each, s, H-12 and H-14), 3·70 and 6·00 (2H, ABq, $J$ = 11·0 Hz, H-15), 1·89, 1·98, 2·02, 2·15, 2·22 and 2·32 (3H each, s, 6 × AcO); Mass 805 ($M^+$), 763, 746.

*Pentadesacetyl evonine acetonide triacetate* (**9**). A mixture of **6** (500 mg) in $Ac_2O$ (3 ml) and pyridine (3 ml) was kept at 60° for 15 hr, concentrated, and added with 5% $Na_2CO_3$ aq (10 ml). The mixture was extracted with three 20 ml portions of AcOEt. The AcOEt extracts were washed with sat NaCl aq, dried, and concentrated, to give a resinous material. Recrystallization from n-hexane–benzene afforded pure **9** (420 mg), m.p. 175–178°; NMR (Table 1); Mass 717 ($M^+$). (Found: C, 57·97; H, 6·00; N, 1·95. $C_{35}H_{43}NO_{15}$ requires: C, 58·57; H, 6·04; N, 1·95%).

*Pentadesacetyl evonine acetonide diacetate* (**8**). A mixture of **6** (150 mg) in $Ac_2O$ (2 ml) and pyridine (2 ml) was kept at 40° for 8 hr, concentrated, and added with 5% $Na_2CO_3$ aq. The mixture was extracted with AcOEt repeatedly. The combined AcOEt extracts were washed with sat NaCl aq, dried, and concentrated, affording a resinous product. Recrystallization from $CCl_4$ gave crystals of **8** (120 mg), m.p. 268°; NMR (60 MHz, $CDCl_3$) 5·61 (1H, d, $J$ = 3·0 Hz, H-1), 3·95 (1H, t, $J$ = 3·0 Hz, H-2), 4·76 (1H, d, $J$ = 3·0 Hz, H-3), 6·35 (1H, s, H-5), 4·43 (1H, s, H-8), 4·96 and 4·18 (2H, ABq, $J$ = 13·0 Hz, H-11), 1·35 (9H, complex pattern, 3 × Me including H-14), 1·67 (3H, s, H-12), 3·75 and 5·88 (2H, ABq, $J$ = 12·0 Hz, H-15), 2·10 (3H, s, AcO), 2·25 (3H, s, AcO). (Found: C, 57·97; H, 6·05; N, 2·05. $C_{33}H_{41}NO_{14}$ requires: C, 58·66; H, 6·10; N, 2·07%).

*Pentadesacetyl evonine triacetate* (**7**). A soln of **9** (100 mg) in 50% AcOH–$H_2O$ (2 ml) was kept at 80° for 4 hr and concentrated. The residue was chromatographed over alumina (1 g) with AcOEt to give crude **7**. Recrystallization from $CHCl_3$ afforded pure **7** (50 mg), m.p. 187–192°; IR (KBr) 3450, 1755, 1735, 1585, 1565 $cm^{-1}$; NMR (60 MHz, acetone-$d_6$) 5·81 (1H, d, $J$ = 3·8 Hz, H-1), 5·08 (1H, dd, $J$ = 3·8, 3·0 Hz, H-2), 4·73 (1H, d, $J$ = 3·0 Hz, H-3), 6·95 (1H, d, $J$ = 1·0 Hz, H-5), 3·23 (1H, d, $J$ = 1·0 Hz, H-6), 4·20 (1H, s, H-8), 4·10 and 4·48 (2H, ABq, $J$ = 12·8 Hz, H-11), 1·67 (3H, d, $J$ = 1·0 Hz, H-12), 1·47 (3H, s, H-14), 4·00 and 5·98 (2H, ABq, $J$ = 11·3 Hz, H-15). (Found: C, 56·68; H, 5·81; N, 1·98. $C_{32}H_{39}NO_{15}$ requires: C, 56·72; H, 5·80; N, 2·07%).

*Aldehyde ester triacetate* (**11**) *and its isomer* (**12**). A mixture of **7** (487 mg) and $Pb(OAc)_4$ (362 mg) in AcOH–MeOH (1:1) (30 ml) was allowed to stand at room temp for 14 hr, then added with ethylene glycol (2 drops), and concentrated. Water was added to the residue and the mixture was extracted with AcOEt repeatedly. The combined AcOEt soln was washed with sat NaCl aq, dried, and evaporated, giving an amorphous product. Recrystallization from $CHCl_3$ gave **11** (250 mg), m.p. 163–167°; IR ($CHCl_3$) 3580, 1760, 1590, 1570 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 5·93 (1H, d, $J$ = 3·8 Hz, H-1), 5·30 (1H, dd, $J$ = 3·8, 4·5 Hz, H-2), 4·63 (1H, d, $J$ = 4·5 Hz, H-3), 6·39 (1H, d, $J$ = 10·5 Hz, H-5), 4·22 (1H, d, $J$ = 10·5 Hz, H-6), 9·73 (1H, s, H-8), 4·05 and 4·23 (2H, ABq, $J$ = 12·3 Hz, H-11), 1·59 (3H, br.s, H-12), 1·17 (3H, s, H-14), 4·15 and 4·84 (2H, ABq, $J$ = 12·3 Hz, H-15), 3·82 (3H, s, COOMe). (Found: C, 56·05; H, 5·76; N, 1·99. $C_{33}H_{41}NO_{16}$ requires: C, 56·01; H, 5·84; N, 1·98%).

The mother liquor of **11** was concentrated to give a residue, which was dissolved in MeOH. From this MeOH soln the isomer **12** crystallized out and filtered. **12** (19 mg), m.p. 220–223°; IR (KBr) 3580, 1745, 1585, 1575 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 5·23 (1H, dd, $J$ = 4·5, 3·5 Hz, H-2), 6·61 (1H, d, $J$ = 10·5 Hz, H-5), 9·85 (1H, s, H-8), 4·52 and 4·83 (2H, ABq, $J$ = 12·3 Hz, H-11), 1·57 (3H, br.s, H-12), 1·15 (3H, s, H-14), 4·18 and 5·01 (2H, ABq, $J$ = 11·3 Hz, H-15), 3·85 (3H, s, COOMe); Mass 707 ($M^+$). (Found: C, 56·01; H, 5·78; N, 1·99. $C_{33}H_{41}NO_{16}$ requires: C, 56·01; H, 5·84; N, 1·98%).

*αβ-Unsaturated aldehyde ester diacetate* (**15**). To a soln of **11** (100 mg) in DME (2 ml) was added a soln (0·25 ml) of t-BuOK in t-BuOH (prepared from 183 mg of K and 8 ml of anhyd t-BuOH). The mixture was stirred at 75° for 3 hr under $N_2$ and neutralized by adding ion-exchange resin Amberlite IRC-50 (H form, 1 g). During the reaction, the $N_2$ stream from the reaction flask was introduced into a 2N HCl of 2,4-dinitrophenylhydrazine. The deposited 2,4-dinitrophenylhydrazone was collected by filtration, dried, weighed (17·5 mg, 0·46 molar equiv), and identified as that of HCHO by mixed m.p. with the authentic specimen and IR spectral data. The ion-exchange resin was filtered and washed with AcOEt (5 ml). The filtrate was concentrated giving a mixture, which was separated by preparative TLC (silica gel $GF_{254}$) with AcOEt–benzene (1:1). The product was

eluted from silica gel with AcOEt and the eluate was concentrated to give a residue, recrystallization of which from $CCl_4$ afforded **15** (48 mg), m.p. 224–225°; IR ($CHCl_3$) 3570, 1750, 1710, 1588, 1568 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 6·59 (1H, dd, $J = 4·5$, 1·5 Hz, H-1), 5·36 (1H, dd, $J = 4·5$, 1·0 Hz, H-2), 4·70 (1H, br.s, H-3), 7·06 (1H, d, $J = 11·0$ Hz, H-5), 4·08 (1H, d, $J = 11·0$ Hz, H-6), 9·73 (1H, s, H-8), 1·39 (3H, s, H-14), 4·48 and 4·85 (2H, ABq, $J = 12·0$ Hz, H-15), 3·80 (3H, s, COOMe), 2·03 (3H, s, AcO), 2·10 (3H, s, AcO); Mass 617 ($M^+$). (Found: C, 58·78; H, 5·79; N, 2·37. $C_{30}H_{35}NO_{13}$ requires: C, 58·34; H, 5·71; N, 2·27%).

*Pentamethyl ether* (**35**). Pentadesacetyl evonine (**5**) was dried at 100° for 2 hr *in vacuo* (1 mmHg). NaH (246 mg, 50% dispersion in mineral oil) was washed thoroughly with n-hexane. A mixture of dried **5** (141 mg), NaH, and MeI (7 ml) in anhyd DMF was stirred at room temp for 20 min and then at 45° overnight. After cooling the mixture was added with MeOH (1·5 ml) and subsequently $H_2O$ (100 ml), and extracted with four 45 ml portions of AcOEt. The combined organic layers were washed with sat NaCl aq, dried, and concentrated to give an amorphous powder, which was chromatographed on neutral alumina (4 g) with AcOEt for removal of a trace of DMF. On removal of the solvent, an amorphous powder (200 mg) was obtained, which was crystallized from n-hexane–ether to give **35** (86 mg). An additional amount (33 mg) of **35** was obtained by preparative TLC of the residue from the mother liquor using silica gel $GF_{254}$ with benzene–AcOEt (3 : 1). The total amount of **35** was 119 mg, m.p. 245–248°; IR ($CHCl_3$) 3520, 1730, 1588, 1565 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 1·45 (3H, s), 1·72 (3H, s), 3·21, 3·42, 3·43, 3·54, 3·56 (3H each, s, 5 × MeO); Mass 621 ($M^+$), 606, 589. (Found: C, 59·73; H, 7·10; N, 2·36. $C_{31}H_{43}NO_{12}$ requires: C, 59·89; H, 6·97; N, 2·25%).

*Pentamethyl ether tetraol* (**37**) *and methyl ketone aldehyde* (**40**). A mixture of **35** (25 mg) and LAH (20 mg) in anhyd ether (1 ml) was stirred at room temp overnight, and diluted with MeOH–$H_2O$. The resulting ppt was filtered with suction, washed with ether, and dissolved in AcOH–$H_2O$. The soln was passed through a column of ion-exchange resin Amberlite IR-120 (H form), and concentrated to give an oily product, **37** (12 mg). High resolution mass, $M^+$ 436·2306 ($C_{20}H_{36}O_{10}$ requires 436·2308). A soln of **37** (8 mg) and $NaIO_4$ (10 mg) in 50% MeOH–$H_2O$ (1 ml) was kept at room temp for 12 hr, and diluted with $H_2O$. The mixture was extracted with $CHCl_3$ repeatedly. The $CHCl_3$ extracts were washed with $H_2O$ and sat NaCl aq, dried, and evaporated, affording an amorphous powder, **40** (7 mg). IR ($CHCl_3$) 3400, 1735, 1708 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 9·61 (1H, d, $J = 2·3$ Hz, H-3), 2·51 (1H, dd, $J = 3·3$, 1·0 Hz, H-6), 2·19 (3H, s, H-12), 1·50 (3H, s, H-14). High resolution mass, M-1, 433·2077 ($C_{20}H_{33}O_{10}$ requires 433·2073).

*Pentamethyl ether triol* (**38**) *and dimethyl evoninate* (**39**). A soln (2 ml) of NaOMe in MeOH (prepared by dissolving 113 mg of Na in 20 ml of MeOH) was added to **35** (29 mg) and the mixture was stirred at room temp overnight, passed through a column of ion-exchange resin Amberlite IR-120 (H form), and evaporated to give an oily residue (17 mg), which was crystallized with ether–light petroleum. **38**, m.p. 116–121°; IR ($CHCl_3$) 3500, 1725 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 1·50 (3H, s), 1·72 (3H, s), 3·23 (3H, s, MeO), 3·42 (3H, s, MeO), 3·52 (6H, s, 2 × MeO), 3·62 (3H, s, MeO); Mass 402 (M-32), 384, 371. (Found: C, 54·63; H, 7·97. $C_{20}H_{34}O_{10}$ requires: C, 55·29; H, 7·89%). In a similar experiment without using the ion-exchange resin, a mixture of **38** and **39** was obtained, which was separated by preparative TLC (silica gel $GF_{254}$). For the preparation of **39** by Pailer's procedure,[6a] see later.

*Pentamethyl ether triol acetonide* (**41**). A soln of **38** (28 mg) and camphorsulphonic acid (10 mg) in 2,2-dimethoxypropane (4 ml) was kept at 50° for 3 hr. After cooling the soln was mixed with $NaHCO_3$ aq (20 ml) (prepared by diluting sat $NaHCO_3$ aq twice) and the resulting mixture was extracted with four 15 ml portions of AcOEt. The combined organic soln was dried and concentrated to give crude crystals, recrystallization of which from n-hexane–AcOEt afforded crystalline **41** (17 mg), m.p. 195–200°; IR ($CHCl_3$) 3460, 1725 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 1·40 (3H, s), 1·48 (3H, s), 1·53 (3H, s), 1·70 (3H, s), 3·22, 3·38, 3·51, 3·52, 3·61 (3H each, s, 5 × MeO), 4·17 (1H, d, $J = 2·0$ Hz, H-3), 5·02 (1H, s, H-5); Mass 459 (M-15), 443, 429. (Found: C, 58·33; H, 8·18. $C_{23}H_{38}O_{10}$ requires: C, 58·21; H, 8·07%).

*Aldehyde* (**42**). A mixture of $CrO_3$ (50 mg) in dried pyridine (2 ml) was added to a soln of **41** (21·6 mg) in dried pyridine (2 ml). The mixture was stirred at room temp overnight, concentrated, diluted with $H_2O$ (30 ml)–AcOEt (15 ml), and filtered through Super Cel with suction. After the organic layer was separated, the aqueous phase was extracted with four 15 ml portions of AcOEt. The combined organic soln was washed with sat NaCl aq, dried, and evaporated. The residue was recrystallized from ether–light petroleum, giving crystalline **42** (15 mg), m.p. 150–154°; IR ($CHCl_3$) 1725 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 1·28 (3H, s), 1·48 (3H, s), 1·59 (3H, s), 1·68 (3H, s), 3·08, 3·19, 3·51, 3·52, 3·62 (3H each, s, 5 × MeO), 9·80 (1H, s, H-15, i.e. CHO); Mass 457 (M-15), 401. (Found: C, 57·78; H, 7·75. $C_{23}H_{36}O_{10}$ requires: C, 58·46; H, 7·68%).

*Pentadesacetyl evonine acetonide tetraacetate* (**10**). A mixture of **9** (135 mg) and AcONa (55 mg) in $Ac_2O$ (3 ml)–pyridine (25 ml) was heated at 85–90° for 35 hr and concentrated to give a residue, which was dissolved in AcOEt. The AcOEt soln was washed with 5% $Na_2CO_3$ aq, $H_2O$, and sat NaCl aq, dried, and concentrated, affording an oily product, which was chromatographed over silicic acid with benzene. Evaporation of the fractions eluted with benzene–AcOEt afforded **10** (118 mg) as amorphous powder; IR ($CHCl_3$) 3550, 1755 (broad band), 1730, 1590, 1570 $cm^{-1}$.

*Pentadesacetyl evonine tetraacetate* (**14**). A soln of **10** (280 mg) in 50% AcOH–$H_2O$ (15 ml) was stirred at room temp for 12 hr and concentrated, giving an oily product, which was dissolved in AcOEt. The soln was passed through a column of alumina (2 g) for decolourization. The residue obtained on removal of the solvent was crystallized from n-hexane–AcOEt, affording **14** (210 mg), m.p. 196–198°; IR ($CHCl_3$) 3560, 1760 (broad band), 1590, 1570 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 5·71 (1H, d, $J = 4·5$ Hz, H-1), 5·20 (1H, dd, $J = 4·5$, 2·3 Hz, H-2), 5·69 (1H, d, $J = 2·3$ Hz, H-3), 6·85 (1H, br.s, H-5), 2·63 (1H, d, $J = 3·0$ Hz, H-6), 5·83 (1H, d, $J = 3·0$ Hz, H-7), 4·17 and 4·48 (2H, ABq, $J = 12·0$ Hz, H-11), 1·58 (3H, d, $J = 1·0$ Hz, H-12), 1·39 (3H, s, H-14), 3·63 and 5·93 (2H, ABq, $J = 11·5$ Hz, H-15). (Found: C, 56·78; H, 5·70; N, 1·90. $C_{34}H_{41}NO_{16}$ requires: C, 56·74; H, 5·74; N, 1·95%).

*Conjugated dienone* (**13**). A mixture of **14** (350 mg) and AcONa (80 mg) in EtOH (10 ml) was kept under reflux for 25 min and concentrated, giving a residue, which was extracted with AcOEt repeatedly. The com-

bined organic soln was washed with sat NaCl aq, dried, and concentrated, affording an oily product, which was chromatographed on silicic acid (20 g) with benzene. Evaporation of the fractions eluted with benzene–AcOEt (1:1) yielded crude **13**, recrystallization of which from n-hexane–benzene gave pure **13** (189 mg), m.p. 156–158°; UV $\lambda_{max}$ (EtOH) nm ($\epsilon$), 225 (8,000), 287 (15,000). IR ($CHCl_3$) 3550, 1775 (shoulder), 1740, 1700 (conjugated C=O), 1623 (conjugated C=C), 1585, 1570 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 6·58 (1H, d, $J$ = 9·8 Hz, H-1), 6·35 (1H, dd, $J$ = 9·8, 5·3 Hz, H-2), 5·13 (1H, d, $J$ = 5·3 Hz, H-3), 5·74 (1H, d, $J$ = 1·0 Hz, H-5), 3·13 (1H, d, $J$ = 1·0 Hz, H-6), 1·35 (3H, br.s, H-12), 1·35 (3H, br.s, H-14), 3·71 and 5·94 (2H, ABq, $J$ = 11·0 Hz, H-15), 2·25 (3H, s, AcO), 2·30 (3H, s, AcO); Mass 589 ($M^+$). (Found: C, 61·22; H, 5·46; N, 2·27. $C_{29}H_{31}NO_{11}$ requires: C, 61·16; H, 5·49; N, 2·46%).

*1,2-Naphthoquinone derivative* (**16**) *and its methyl ester* (**17**). A mixture of **13** (50 mg) and AcONa (50 mg) in MeOH (50 ml) was kept at refluxing temp for 8 hr and concentrated to afford a residue, which was extracted with four 15 ml portions of AcOEt–3% AcOH aq (1:1). The combined organic soln was washed with sat NaCl aq, dried, and concentrated. The resulting mixture was separated by preparative TLC (silica gel $PF_{254}$) with AcOEt–benzene (3:2), affording **16** (15 mg) as amorphous powder; UV (EtOH) $\lambda_{max}$ 223, 275, 320 (broad), 405 nm; IR ($CHCl_3$) 3480, 2800–2400, 1730 (broad band), 1660, 1655 (shoulder), 1580 (shoulder), 1575 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 8·00 (1H, d, $J$ = 9·0 Hz), 6·90 (1H, d, $J$ = 9·0 Hz), 8·21 (1H, s), 2·38 (3H, s), 1·68 (3H, s), 4·60 and 4·88 (2H, ABq, $J$ = 12·0 Hz), 4·00 (3H, s). A soln of **16** (15 mg) in MeOH (5 ml) was mixed with 0·5 ml of MeOH sat with HCl gas. The soln was kept at room temp for 8 hr and poured into sat $NaHCO_3$ aq. The mixture was extracted with four 15 ml portions of AcOEt. The combined organic soln was washed with sat NaCl aq, dried, and concentrated, giving amorphous **17** (15 mg); IR ($CHCl_3$) 3480, 1725 (broad band), 1660, 1650 (shoulder), 1585 (shoulder), 1575, 1565 $cm^{-1}$; Mass 495 ($M^+$), 497 ($M+2$).

*Pentadesacetyl evonine methyl ester* (**21**). To a soln of **1** (400 mg) in anhyd MeOH (18 ml) was added a soln (1·4 ml) of NaOMe in MeOH (prepared from 31 mg of Na and 10 ml of anhyd MeOH) under $N_2$. The soln was kept at 30° for 12 hr and added with ion-exchange resin Amberlite IRC-50 (H form) required for neutralization of NaOMe. The ion-exchange resin was filtered with suction and the filtrate was concentrated, affording an amorphous powder (315 mg), which was chromatographed on silicic acid (12 g). Evaporation of the fractions eluted with $CHCl_3$–MeOH (100:5) afforded **21** (184 mg) as amorphous powder; IR ($CHCl_3$) 3480, 1730 (broad band) $cm^{-1}$; NMR (60 MHz, MeOH-$d_4$) 4·71 (1H, d, $J$ = 3·5 Hz, H-3), 5·50 (1H, d, $J$ = 1·0 Hz, H-5), 3·01 (1H, d, $J$ = 1·0 Hz, H-6), 1·75 (3H, s, H-12), 1·40 (3H, s, H-14), 3·94 (3H, s, COOMe).

*Pentadesacetyl evonine methyl ester acetonide* (**26**). A soln of **21** (170 mg), camphorsulphonic acid (100 mg), and 2,2-dimethoxypropane (10 ml) in DMF (3 ml) was stirred at 0° for 4 hr and poured into $NaHCO_3$ aq. The mixture was extracted with AcOEt. The AcOEt extracts were washed with sat NaCl aq, dried, and evaporated to give resinous **26** (130 mg). IR ($CHCl_3$) 3450, 1730, 1580, 1565 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 4·83 (1H, d, $J$ = 3·0 Hz, H-3), 5·05 (1H, d, $J$ = 1·0 Hz, H-5), 3·04 (1H, d, $J$ = 1·0 Hz, H-6), 3·93 (3H, s, COOMe). High resolution mass, $M^+$ 623·2600 ($C_{30}H_{41}NO_{13}$ requires 623·2578).

*Methyl ester acetonide pentaacetate* (**30**). A mixture of **26** (130 mg) and AcONa (50 mg) in $Ac_2O$ (4 ml)–pyridine (3·5 ml) was heated at 85–90° for 40 hr and concentrated to give a residue, which was dissolved in AcOEt. The AcOEt soln was washed with $Na_2CO_3$ aq and sat NaCl aq, dried, and evaporated, affording oily **30** (140 mg); IR ($CHCl_3$) 3400, 1765 (shoulder), 1743 (broad band), 1585, 1570 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 5·86 (1H, d, $J$ = 3·2 Hz, H-1), 5·11 (1H, dd, $J$ = 3·2, 3·0 Hz, H-2), 4·77 (1H, d, $J$ = 3·0 Hz, H-3), 6·32 (1H, d, $J$ = 1·0 Hz, H-5), 3·12 (1H, d, $J$ = 1·0 Hz, H-6), 4·18 (2H, s, H-11), 1·23–1·51 [18H (6 × Me), complex pattern], 2·06 (3H, s, AcO), 2·09 (3H, s, AcO), 2·11 (6H, s, 2 × AcO), 2·18 (3H, s, AcO); Mass 833 ($M^+$).

*Methyl ester pentaacetate* (**31**). A soln of **30** (140 mg) in AcOH–$H_2O$ (1:1) (10 ml) was stirred at room temp for 12 hr and evaporated. The crude product was purified by preparative TLC (silica gel $PF_{254}$) with benzene–AcOEt (3:2), affording **31** (70 mg) as amorphous powder; IR ($CHCl_3$) 3500, 1750 (broad band), 1590, 1575 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 5·75 (1H, d, $J$ = 3·5 Hz, H-1), 5·17 (1H, dd, $J$ = 3·5, 3·0 Hz, H-2), 4·68 (1H, d, $J$ = 3·0 Hz, H-3), 6·58 (1H, d, $J$ = 1·0 Hz, H-5), 2·76 (1H, dd, $J$ = 1·0, 4·2 Hz, H-6), 5·87 (1H, d, $J$ = 4·2 Hz, H-7), 4·30 (2H, s, H-11), 1·47 (3H, d, $J$ = 1·0 Hz, H-12), 1·33 (3H, s, H-14), 3·91 (3H, s, COOMe).

*Conjugated dienone methyl ester* (**32**). A mixture of **31** (56 mg) and AcONa (15 mg) in MeOH (5 ml) was kept under reflux for 25 min and concentrated. The residue was dissolved in AcOEt and the AcOEt soln was washed with sat NaCl aq, dried, and evaporated, giving **32** (32 mg) as amorphous colourless powder; UV (EtOH) $\lambda_{max}$ 220, 272 (shoulder), 283 nm; IR ($CHCl_3$) 3450, 1725 (broad band), 1695 (conjugated C=O), 1620 (conjugated C=C), 1585, 1570 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 6·46 (1H, d, $J$ = 9·3 Hz, H-1), 6·21 (1H, dd, $J$ = 9·3, 6·0 Hz, H-2), 4·82 (1H, d, $J$ = 6·0 Hz, H-3), 5·43 (1H, d, $J$ = 1·0 Hz, H-5), 3·04 (1H, d, $J$ = 1·0 Hz, H-6), 1·30 (3H, br.s, H-12), 1·30 (3H, br.s, H-14), 4·22 and 4·46 (2H, ABq, $J$ = 11·3 Hz, H-15), 3·89 (3H, s, COOMe). High resolution mass, $M^+$ 643·2264 ($C_{32}H_{37}NO_{13}$ requires 643·2265).

*Evoninic acid monomethyl ester* (**27**) *and 1,2-naphthoquinone derivative* (**28**). A mixture of **32** (32 mg) and AcONa (45 mg) in MeOH (5 ml) was kept under reflux for 7·5 hr under $N_2$ and concentrated to afford a residue, which was extracted with AcOEt repeatedly. The combined AcOEt extracts were washed with sat NaCl aq, dried, and concentrated. The residue showed two main spots on TLC; one, (**27**) was positive to Dragendorff reaction and the other was dark red in colour. The mixture was separated by preparative TLC (alumina) with AcOEt–benzene (1:1), affording amorphous **27** (8 mg) and crystalline **28**, recrystallization of which from n-hexane–benzene yielded pure **28** (4·8 mg), m.p. 146–147·5°. **27**; IR ($CHCl_3$) 2800–2320, 1900, 1730 (broad band), 1585 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 8·31 (1H, dd, $J$ = 8·0, 1·5 Hz), 7·40 (1H, dd, $J$ = 8·0, 4·6 Hz), 8·67 (1H, dd, $J$ = 4·6, 1·5 Hz), 4·13 (1H, m), 3·12 (1H, m), 1·42 (3H, d, $J$ = 7·5 Hz), 1·16 (3H, d, $J$ = 7·5 Hz), 3·97 (3H, s, COOMe).

*Compound* **28**. UV (EtOH) $\lambda_{max}$ nm ($\epsilon$) 218 (17,000), 244 (12,000), 280 (16,000), 405 (6,700); IR ($CHCl_3$) 3450, 1740, 1660, 1575 $cm^{-1}$; NMR (60 MHz, $CDCl_3$)

7·97 (1H, d, $J = 8·3$ Hz), 6·85 (1H, d, $J = 8·3$ Hz), 8·03 (1H, s), 2·37 (3H, s), 1·56 (3H, s), 4·44 (2H, s), 3·95 (3H, s), 2·05 (3H, s). High resolution mass, $M^+$ 318·1103 ($C_{17}H_{18}O_6$ requires 318·1103).

1,2-*Naphthoquinone derivative* (**29**). A mixture of **32** (35 mg) and AcONa (30 mg) in anhyd EtOH (5 ml) was kept at refluxing temp for 7·5 hr and concentrated. The residue was mixed with a small amount of sat NaCl aq and the mixture was extracted with three 10 ml portions of AcOEt. The AcOEt extracts were washed with sat NaCl aq, dried, and concentrated. The residue was purified by preparative TLC (alumina) with AcOEt–benzene (1 : 1), affording oily **29** (8 mg); IR ($CHCl_3$) 3450, 1735 (broad band), 1655, 1575 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 1·50 (3H, t, $J = 7·0$ Hz), 1·54 (3H, s), 2·04 (3H, s), 2·37 (3H, s), 4·16 (2H, q, $J = 7·0$ Hz), 4·44 (2H, s), 6·83 (1H, d, $J = 8·3$ Hz), 7·95 (1H, d, $J = 8·3$ Hz), 8·03 (1H, s). High resolution mass, $M^+$ 332·1251 ($C_{18}H_{20}O_6$ requires 332·1259).

*Lactone* (**22**). A mixture of **18** (10 mg) and $MnO_2$ (150 mg; freshly prepared from $MnSO_4$, $KMnO_4$ and NaOH)[13] in benzene (5 ml) was stirred under reflux for 5 hr and filtered with suction. The filtrate was concentrated, affording a liquid product, **22** (5 mg). The sample for spectroscopic studies was obtained by preparative GLC (temp 220°); IR ($CHCl_3$) 1720, 1585, 1570 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 7·97 (1H, dd, $J =$ 8·0, 1·6 Hz), 7·30 (1H, dd, $J = 8·0$, 4·6 Hz), 8·69 (1H, dd, $J = 4·6$, 1·6 Hz), 3·00 (1H, m), 2·04 (1H, m), 1·47 (3H, d, $J = 7·0$ Hz), 1·23 (3H, d, $J = 7·0$ Hz), 4·06 (2H, m). High resolution mass, $M^+$ 192·0933 ($C_{11}H_{13}NO_2$ requires 192·0939).

*Hydroxy ester* (**23**). Lactone, **22** (5 mg) was dissolved in a soln (2 ml) of NaOMe in MeOH (prepared by dissolving 20 mg of Na into 59 ml of anhyd MeOH). The soln was kept at room temp for 15 hr and added with ion-exchange resin Amberlite IR-120 (H form) required for neutralization of NaOMe. The ion-exchange resin was filtered and the filtrate was concentrated, yielding a liquid product, **23** (4 mg); IR ($CHCl_3$) 3450, 1720, 1585, 1570 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) 8·01 (1H, dd, $J = 7·6$, 1·6 Hz), 7·15 (1H, dd, $J = 7·6$, 4·6 Hz), 8·64 (1H, dd, $J = 4·6$, 1·6 Hz), 3·81 (1H, m), 2·11 (1H, m), 1·29 (3H, d, $J = 7·2$ Hz), 1·04 (3H, d, $J = 7·2$ Hz), 3·40 (2H, m, $CH_2OH$), 3·92 (3H, s, COOMe).

*Oxidation of hydroxy ester* (**23**) *to evoninic acid monomethyl ester* (**27**). A mixture of **23** (4 mg) and $CrO_3$ (10 mg) in pyridine (1 ml) was kept at 50° for 14 hr and diluted with AcOEt (30 ml). The mixture was filtered with suction. The filtrate was washed with sat NaCl aq, dried, and concentrated, giving a residue, which was purified by preparative TLC (silica gel $PF_{254}$) with AcOEt–benzene (1 : 1). Elution from silica gel with AcOEt, followed by evaporation afforded **27** (2·5 mg); IR ($CHCl_3$) 2800–2320, 1900, 1730 (broad band), 1585 $cm^{-1}$. High resolution mass, $M^+$ 237·0979 ($C_{12}H_{15}NO_4$ requires 237·100).

*Neoevonine methyl ether* (**34**). A mixture of **2** (412 mg) and $Ag_2O$ (320 mg) in MeI (7 ml) was stirred at refluxing temp for 24 hr. Additional $Ag_2O$ (160 mg) was added to the mixture, which was kept under reflux for further 72 hr. The mixture was diluted with AcOEt and filtered with suction. Evaporation of the filtrate afforded crude **34**, which was recrystallized from EtOH to give pure **34** (364 mg), m.p. 309–310°; IR (KBr) 3560, 1750 $cm^{-1}$; NMR (Fig 9); Mass 733 ($M^+$). (Found: C, 57·79; H, 5·76; N, 2·14. $C_{35}H_{43}NO_{16}$ requires: C, 57·35; H, 5·94; N, 1·92%).

*Interconversion of evonine* (**1**) *and neoevonine* (**2**).

(a) A soln of **2** (106 mg) in $Ac_2O$ (3 ml) and pyridine (2 ml) was kept at 45° for 15 hr and concentrated. The residue was recrystallized from acetone–isopropyl ether, giving crystals (**1**, 84 mg), m.p. 178–186°, the spectral data (soln IR, NMR, and mass) of which were shown to be identical with those of evonine (**1**).

(b) To a soln of **1** (200 mg) in MeOH (4 ml) was added 0·1 M NaOMe in MeOH (0·05 ml). The soln was kept at −5° for 2 hr. During the reaction, a ppt appeared, which was dissolved by adding $CHCl_3$ (5 ml) after the reaction. The soln was neutralized with ion-exchange resin Amberlite IRC-50 (1 g) and filtered. The filtrate was concentrated and the residue was purified by preparative TLC (silica gel $PF_{254}$) with AcOEt–benzene (1 : 1), affording a residue. Recrystallization from MeOH gave pure **2** (126 mg), m.p. 264–265°, mixed m.p. 264–265°.

*Dimethyl evoninate* (**39**). Hydrolysis of **1** (1·3 g) with aq NaOH by Pailer's procedure[6a] afforded crude evoninic acid (**33**), which was methylated with $CH_2N_2$, giving crude **39** (230 mg). Distillation of crude **39** under reduced pressure afforded pure **39**; IR ($CCl_4$) 1738, 1585, 1565 $cm^{-1}$. NMR (Fig 5). Mass 251 ($M^+$). (Found: C, 62·50; H, 6·92; N, 5·53. $C_{13}H_{17}NO_4$ requires: C, 62·20; H, 6·83; N, 5·58%).

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