Methyl Transfer: the Mass Spectra of Reserpine Derivatives

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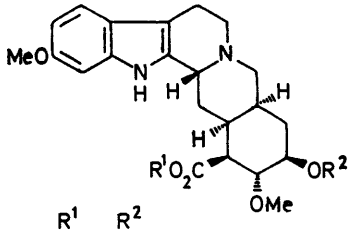
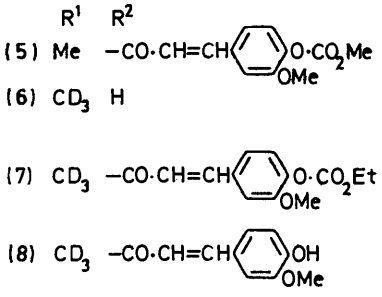
The mass spectrum of methyl 18β-(4-hydroxy-3-methoxycinnamoyloxy)-11,17α-dimethoxy-3β,20α-yohimban-16β-carboxylate (3) [methyl *O*-(4-hydroxy-3-methoxycinnamoyl)reserpate] shows that the ester methyl group is transferred intermolecularly to the basic nitrogen of the yohimban system; this was confirmed by studies on the [^{2}H]methyl ester (8), the ethyl ester homologue (4), and the quaternary salt of (3).

THE mass spectrum of methyl *O*-(4-hydroxy-3-methoxycinnamoyl)reserpate (3),[1] synthesized from methyl reserpate (1) by way of methyl *O*-(4-ethoxycarbonyloxy-3-methoxycinnamoyl)reserpate (2), shows a peak of 14 mass units greater (*m/e* 604) than the expected molecular weight (590). Considering that this must be due to either a higher homologue or a ketonic impurity, we examined the high-resolution mass spectrum and found that the former explanation was correct (Found: 604·2798. Calc. for $C_{34}H_{40}N_2O_8$: 604·2782). A chromatographically pure sample of (3) prepared by recrystallization from benzene–methanol or acetone still showed the peak at *m/e* 604. Moreover a sample synthesized *via* methyl *O*-(4-methoxycarbonyloxy-3-methoxycinnamoyl)reserpate (5) [in order to prevent contamination from the ethyl ester (4) formed by transesterification] also revealed the high mass peak. This suggested that the peak at *m/e* 604 was not due to a higher homologue contaminating our sample of (3).

Biemann [2] has reported a thermally induced intermolecular methyl transfer which can lead to the appearance of higher homologues in the mass spectra of voacamine and related compounds, and states that this phenomenon depends on the vaporisation temperature of the sample. We therefore assumed that we were observing an intermolecular methyl transfer to a basic nitrogen atom followed by Hofmann elimination [of (9)] to give the ion (10), *m/e* 604, and verified this as follows.



	R^1	R^2
(1)	Me	H
(2)	Me	–CO·CH=CH–(4-OMe, 3-O·CO$_2$Et)–C$_6$H$_3$
(3)	Me	–CO·CH=CH–(4-OH, 3-OMe)–C$_6$H$_3$
(4)	Et	–CO·CH=CH–(4-OH, 3-OMe)–C$_6$H$_3$



	R^1	R^2
(5)	Me	–CO·CH=CH–(4-O·CO$_2$Me, 3-OMe)–C$_6$H$_3$
(6)	CD_3	H
(7)	CD_3	–CO·CH=CH–(4-O·CO$_2$Et, 3-OMe)–C$_6$H$_3$
(8)	CD_3	–CO·CH=CH–(4-OH, 3-OMe)–C$_6$H$_3$

The mass spectrum of (3) taken at various vaporisation temperatures (130, 140, and 150°) showed an increase in relative intensity of the *m/e* 604 peak with increase in temperature (Table). Moreover, the mass spectrum revealed peaks at *m/e* 589 [$(M^+ + 14) - Me$], 573 [$(M^+ + 14) - OMe$], and 545 [$(M^+ + 14) - CO_2Me$] derived from the ion (10) at *m/e* 604 (10).

Intensities of the peak at *m/e* 604 relative to the molecular ion peak (*m/e* 590) at various temperatures*

Vaporisation temp. (°C)	130	140	150
Intensity	1·8%	2·9%	6·5%

* Ionising voltage 70 eV; chamber temp. 150°; target current 85 μA; total current 100 μA; scanning speed 3.

Secondly, the high resolution spectrum of [$^2H_3$]methyl *O*-(4-hydroxy-3-methoxycinnamoyl)reserpate (8) [prepared from reserpic acid lactone *via* [$^2H_3$]methyl reserpate (6) and its *O*-ethoxycarbonylferulate (7)] showed the highest mass peak at *m/e* 610·3149 ($C_{34}H_{34}D_6N_2O_8$) instead of *m/e* 604 and characteristic ions at *m/e* 592 [$(M^+ + 17) - CD_3$], 576 [$(M^+ + 17) - OCD_3$], and 548 [$(M^+ + 17) - CO_2CD_3$] as well as a molecular ion at *m/e* 593. This showed that the migrating methyl group was derived from the methoxycarbonyl group.

Thirdly, the methiodide ($C_{24}H_{41}IN_2O_8$) of (3) revealed a highest mass peak at *m/e* 605 ($C_{38}H_{41}IN_2O_8$ – I) but no peak at *m/e* 619 corresponding to the methyl transfer ion. Thus, it is likely that the methyl group in (3) is trans-

[1] T. Kametani, M. Ihara, T. Suzuki, T. Takahashi, R. Inoki, H. Takei, N. Miyake, M. Yoshida, Y. Hasegawa, and H. Kitagawa, *J. Medicin. Chem.*, 1972, **15**, 686.

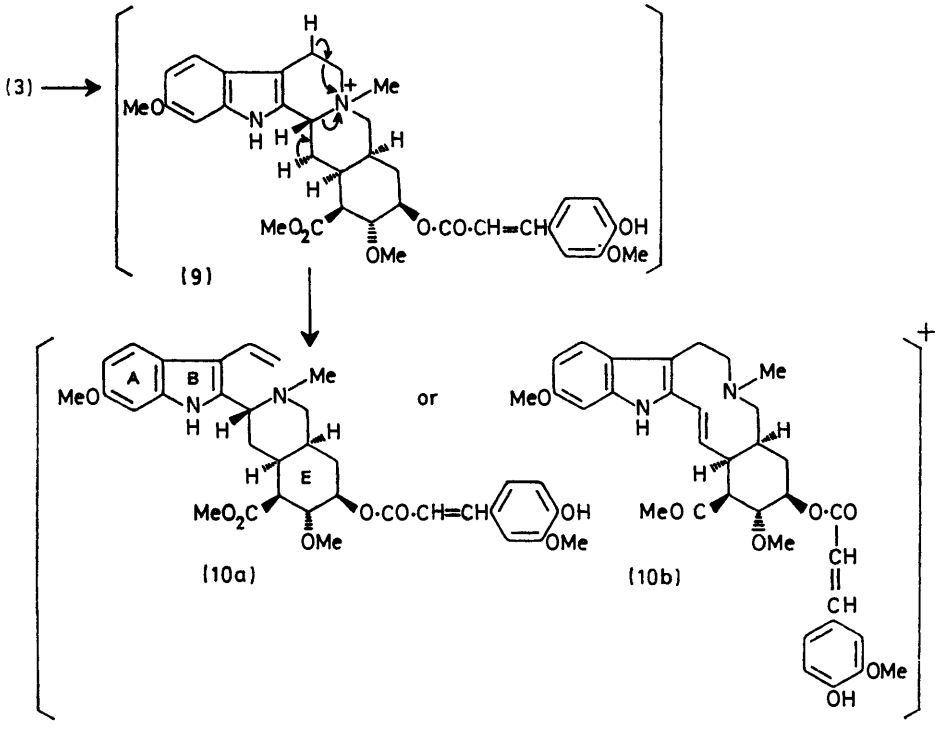
[2] D. W. Thomas and K. Biemann, *J. Amer. Chem. Soc.*, 1965, **87**, 5447.

ferred to the basic nitrogen atom of the yohimban ring system [see (9)]. Moreover, the methiodide spectrum showed ions at *m/e* 604 (Hofmann elimination of *m/e* 605), 589 (605 — CH_3), 573 (605 — OCH_3), and 545 (605 — CO_2CH_3), which were stronger than those of (3).[3]

Similarly, ethyl reserpate (4),[4] methyl reserpate (1),[1] and [$^2H_3$]methyl reserpate (6) showed thermally induced methyl transfer peaks at *m/e* 632, 428, and 434, respectively.

EXPERIMENTAL

Mass spectra were measured with JEOL JMS-OISG-2, Hitachi RMU-7L, and Hitachi RMU-7M spectrometers.



Methyl O-(3-*Methoxy*-4-*methoxycarbonyloxycinnamoyl*)-*reserpate* (5).—Methyl chlorocarbonate (1·0 g) was added dropwise to a mixture of methyl *O*-(4-hydroxy-3-methoxycinnamoyl)reserpate (3) (2 g) and dry pyridine (30 ml) with stirring below 10°; the mixture was stirred for 3 h at room temperature and then poured into water (400 ml). The separated oil was extracted with benzene and the extract was washed with water, dilute hydrochloric acid, water, N-sodium hydroxide, and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give the *ester* (5) (1·7 g, 77·3%) as pale yellow crystals, m.p. 210—211° (decomp.) (from methanol) (Found: C, 64·85; H, 6·2; N, 4·2. $C_{35}H_{40}N_2O_{10}$ requires C, 64·8; H, 6·2; N, 4·3%), $\nu_{max.}$ (KBr) 1780 cm^{-1} (O·CO·CH_3), δ ($CDCl_3$) 3·98 (3H, s, CO_2·CH_3).

Methyl O-(4-*Hydroxy*-3-*methoxycinnamoyl*)*reserpate* (3).—A mixture of the ester (5) (1 g), 2·8% ammonia (5 ml), and methanol (200 ml) was heated at 60° for 2 h with stirring in a current of nitrogen, and then evaporated to 5 ml to give the phenol (3) (0·9 g) as needles, m.p. 260—262° (decomp.) (from methanol–benzene) (Found: C, 67·1; H, 6·45; N, 4·55. Calc. for $C_{33}H_{38}N_2O_8$: C, 67·1; H, 6·5; N, 4·75%), *m/e* 590 (M^+) and 604 (M^+ + 14), identical with an authentic sample.[1]

The methiodide, prepared by methylation with methyl iodide in acetone, gave *pale yellow cubes*, m.p. 244—245° (decomp.) (from methanol–ether) (Found: C, 55·2; H, 5·4; N, 3·95. $C_{34}H_{41}IN_2O_8$ requires C, 55·75; H, 5·65; N, 3·85%), *m/e* 604 (M^+ — I) and 590 (M^+ — I — CH_3).

Ethyl O-(4-*Hydroxy*-3-*methoxycinnamoyl*)*reserpate* (4).—To a solution of ethyl reserpate [4] (3·8 g) in dry dimethylformamide (20 ml) and dry pyridine (2·4 g) were added dropwise *O*-ethoxycarbonyferuloyl chloride (6·8 g) and dry dimethylformamide (30 ml) with stirring below 10° in a current of nitrogen. After stirring overnight at room temperature, 1% sodium hydroxide (200 ml) was added, and the mixture was extracted with benzene. The extract was washed with saturated aqueous sodium chloride, 1% hydrochloric acid, and saturated sodium chloride solution again, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel [elution with benzene–ethanol (5 : 1)] to give the *O*-(4-ethoxycarbonyloxycinnamoyl)reserpate (2·9 g, 50%) as a brown powder, $\lambda_{max.}$ (EtOH) 306sh, 278, 225, and 216 nm; $\nu_{max.}$ (KBr) 1710 cm^{-1} (O·CO·CH=CH); δ ($CDCl_3$) 1·37 (6H, t, *J* 7·6 Hz, CH_3·CH_2) and 4·30 (4H, q, *J* 7·6 Hz, CH_3·CH_2).

A mixture of the crude *O*-(4-ethoxycarbonyloxycinnamoyl)reserpate (2 g), ethanol (20 ml), and 28% ammonia (10 ml) was stirred at 60° for 1·5 h in a current of nitrogen and then evaporated to 10 ml. The separated material was extracted with chloroform, and the extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and

[3] M. Hesse and H. Schmid, *Annalen*, 1966, **696**, 85; M. Hesse, *Helv. Chim. Acta*, 1967, **50**, 42.

[4] M. Hesse and U. Renner, *Helv. Chim. Acta*, 1966, **49**, 1875.

evaporated *in vacuo* to leave a syrup. This was subjected to alumina chromatography with benzene–ethanol (5 : 1). The resulting material was rechromatographed on silica gel [elution with chloroform–methanol (50 : 1)] to give the *product* (4) (0·4 g, 22·2%) as pale yellow cubes, m.p. 159—161° (decomp.) (from chloroform–petroleum) (Found: C, 67·65; H, 6·6; N, 4·2. $C_{34}H_{40}N_2O_8$ requires C, 67·55; H, 6·65; N, 4·65%), $\lambda_{max.}$ (EtOH) 330, 300, and 225 nm; $\nu_{max.}$ (KBr) 1740 (CO_2Et), 1710 (O·CO·CH=CH), and 1600 cm (CH=CH), δ [$(CD_3)_2SO$] 1·28 (3H, t, *J* 7·6 Hz, CH_2·CH_3), 3·44 (3H, s, CH·OCH_3), 3·75 (3H, s, ArOCH_3), 3·84 (3H, s, ArOCH_3), 4·32 (2H, q, *J* 7·6 Hz, CH_2·CH_3), 6·44 (1H, d, *J* 16·7 Hz, CH=C*H*·CO), and 7·60 (1H, d, *J* 16·7 Hz, C*H*=CH·CO), *m/e* 604 (M^+), 618 ($M^+ + 14$), and 632 ($M^+ + 28$).

[$^2H_3$]*Methyl Reserpate* (6).—Sodium (138 mg) was dissolved in [$^2H_4$]methanol (3·2 g) and dry tetrahydrofuran (10 ml), and reserpic acid lactone [4] (764 mg) was added. After stirring for 18 h at room temperature, the separated material was filtered off, and the filtrate was diluted with water (60 ml) and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated *in vacuo*. The pale yellow residue was chromatographed on silica gel (40 g) with benzene–methanol (10 : 1 and 5 : 1) as eluant to give the [$^2H_3$]ester (6) (465 mg) as a pale yellow powder, $\nu_{max.}$ (KBr) 1720 cm^{-1} (CO_2·CD_3), *m/e* 417 (M^+) and 434 ($M^+ + 17$).

[$^2H_3$]*Methyl* O-(4-*Hydroxy*-3-*methoxycinnamoyl*)*reserpate* (8).—*O*-Ethoxycarbonylferuloyl chloride (855 mg) was added to a solution of [$^2H_3$]methyl reserpate (6) (414 mg) in dry dimethylformamide (2 ml) and dry pyridine (0·5 ml), and the mixture was stirred for 4·5 h at room temperature. Sodium hydroxide (1%) was then added and the mixture was extracted with benzene. The extract was worked up as in the case of (5) to give crude compound (7) (999 mg), which was dissolved in tetrahydrofuran (4 ml) and 28% ammonia. After stirring for 2 h at 60° and evaporation of the solvent *in vacuo*, the product was diluted with water and extracted with chloroform. The extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was subjected to silica gel (20 g) chromatography [elution with tetrahydrofuran–benzene (1 : 1)] to give the product (8) (566 mg) as yellow needles, m.p. 260—262° (decomp.) (from tetrahydrofuran–dioxan), $\nu_{max.}$ (KBr) 1720 (CO_2·CD_3) and 1700 cm^{-1} (CO·CH=CH), *m/e* 593 (M^+) and 610 ($M^+ + 17$).

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