Studies on the Synthese of Heterocyclic Compounds. Part DXCV (1). The Stereochemistry of Methyl *O*-(4-Hydroxy-3-methoxycinnamoyl)reserpate

Tetsuji Kametani (2), Terumi Higa, Masataka Ihara, Keiichiro Fukumoto, and Masahiro Kajiwara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

and

Yasuo Fujimoto and Yoshihiro Tanaka

Research Laboratories, Nippon Chemipha Co., Ltd., Honkomagome, Bunkyo-ku, Tokyo, Japan

Received October 10, 1974

The stereochemistry of the title compound (I), which has an antihypertensive activity, was confirmed by chemical and spectroscopical evidences.

Previously we reported the synthesis of several rescinamine-like compounds. Among them, methyl *O*-(4-hydroxy-3-methoxycinnamoyl)reserpate (I) showed the strongest antihypertensive activity and lower side effects (3). This compound which was synthesized from reserpine (II) is sensitive to light and oxygen, and it was reported that reserpine (II) was oxidized with molecular oxygen in air to 3-dehydroreserpine (III) (4) and epimerized at C-3, C-16 and C-17 positions with acid and alkali treatments (5,6,7 and 8). Therefore the stereochemistry of the product (I) was further elucidated and we wish to report the confirmation of the configuration of I.

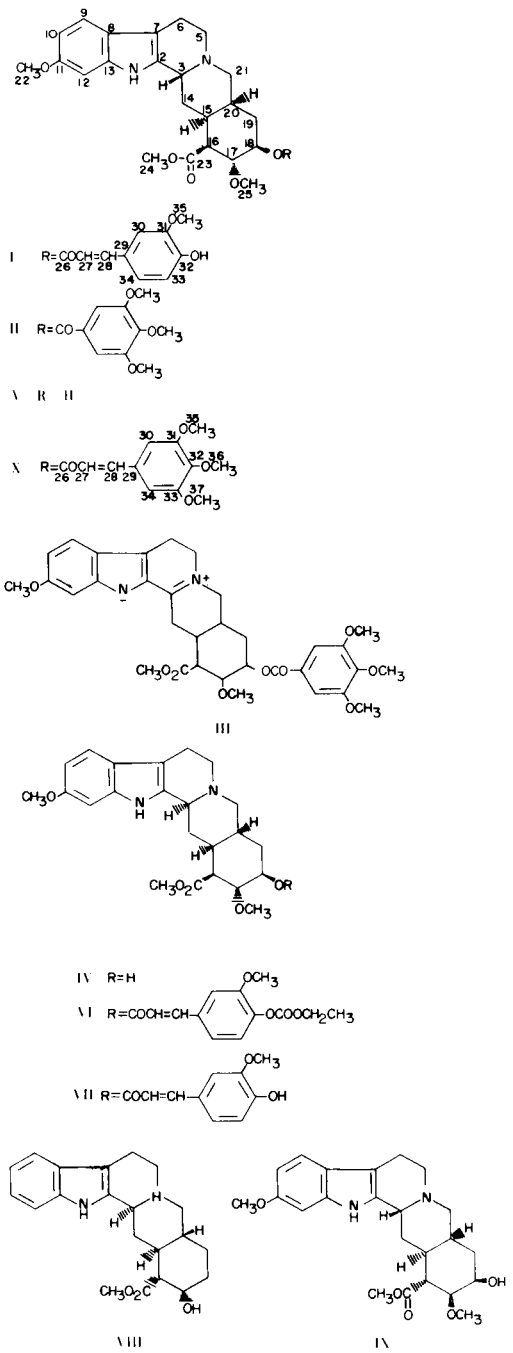
Methyl 3-isoreserpate (IV) synthesized from methyl reserpate (V) by the reported method (5) was condensed with 4-ethoxycarbonyloxy-3-methoxycinnamoyl chloride to give methyl *O*-(4-ethoxycarbonyloxy-3-methoxycinnamoyl)-3-isoreserpate (VI), m.p. 176-178°. The nitrate of the base (VI) was treated with a hot mixture of methanol and concentrated ammonia to methyl *O*-(4-hydroxy-3-methoxycinnamoyl)-3-isoreserpate (VII), m.p. 196-199°, whose ir spectrum showed Bohlmann-Wenkert bands, ν max (potassium bromide) 2850, 2800 and 2750 cm^{-1}, while the compound (I) did not show these absorptions, these facts are consistent with the *cis*-quinolizidine form of I. The nmr spectrum of VII was different from that of compound I.

The *cis* ring junction between C and D in compound I was further proved by reaction with mercuric acetate. Namely, following the procedure (9), compound I and reserpine (II) did not react with mercuric acetate, while yohimbine (VIII) having the *trans* form reacted with mercuric acetate. The reaction was followed by precipitation of mercurous acetate and change in the uv spectrum.

When compound I was refluxed for 4 hours with methanolic sodium methoxide, methyl reserpate (V) was obtained in 50% yield. On the other hand, refluxing the 3-isoreserpate derivative (VII) with the same reagent for 35 hours afforded the 3-isomer (IV) in 78% yield. Rosen and Sheppard reported that refluxing of methyl reserpate (V) with methanolic sodium methoxide for 4 hours did not cause any significant inversion at the C-16 and C-17. These conditions resulted in a mixture of methyl neoreserpate (IX) and the normal compound V in 1:99 ratio (8). Thus it was established that the configurations of all the chiral centers of compound I were identical with those of methyl reserpate (V), reserpine (II) and rescinamine (X).

Furthermore, the carbon-13 nmr (cmr) spectrum of the compound (I) was compared with those of reserpine (II), methyl reserpate (V) and rescinamine (X). The signals of the cmr of compound I, methyl reserpate (V) and rescinamine (X), were largely assigned in Table I using Roberts' assignments for other *Rauwolfia* alkaloids (10). Wenkert (11) and van Binst (12) assigned the C-3 carbon in the *cis*-quinolizidine form to the signal at higher field (54.5 or 51.7 ppm from TMS) as compared with that in *trans*-quinolizidine form at *ca.* 60 ppm. On the other hand, according to Roberts' assignment, the chemical shift of the C-3 carbon of reserpine (II) in *cis*-quinolizidine, 61.2 ppm, was nearly the same as that of yohimbine (VIII) in *trans*-quinolizidine, 60.6 ppm. Although the assignments of the signals in this region were not made clear from the present measurements, the chemical shifts of all the carbons of the reserpane part except the C-17, 18 and 19 carbons of compound I are similar to those of the *cis*-isomers (V), (II) and (X), suggesting the normal configuration of compound I.

Chart I



EXPERIMENTAL

All melting points are uncorrected. The cmr spectra were taken with a JEOL-PS-100 spectrometer using TMS as an external reference.

Methyl *O*-(4-Ethoxycarbonyloxy-3-methoxycinnamoyl)-3-isoreserpate (VI).

To a solution of 5.0 g. of methyl 3-isoreserpate (IV) (5) in a mixture of 20 ml. of dimethylformamide and 2 ml. of pyridine, 10.5 g. of 4-ethoxycarbonyloxy-3-methoxycinnamoyl chloride was added and the mixture was stirred overnight at room temperature. After addition of benzene, the resulting mixture was washed with water, 0.1 *N* aqueous sodium hydroxide solution, saturated aqueous sodium chloride solution, 0.1 *N* hydrochloric acid and water, and dried over sodium sulfate. Evaporation of the solvent gave a residue which was dissolved in ethanol and adjusted to pH 3-4 with nitric acid. The precipitated solid was recrystallized from water-ethanol to afford 6.4 g. (73%) of the nitrate of VI, m.p. 206-209°; ir ν max (potassium bromide) cm^{-1}: 1780 (OCO_2), 1740 (CO_2CH_3), 1720 (COCH=CH).

Anal. Calcd. for $C_{36}H_{42}N_2O_{10}.HNO_3$: C, 59.57; H, 5.97; N, 5.79. Found: C, 59.38; H, 6.10; N, 6.21.

A solution of 1.0 g. of the nitrate of VI in dimethylformamide was basified with 5% aqueous sodium bicarbonate solution and the free base was extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated to give 700 mg. of base VI as colorless needles; m.p. 176-178°, after washing with hot methanol, ir ν max (potassium bromide) cm^{-1}: 3400 (NH), 2850, 2800, 2750 (Bohlmann bands), 1770 (OCO_2), 1740 (CO_2CH_3), 1720 (COCH=CH); nmr δ (deuteriochloroform): 1.33 (3H, t, J = 8 Hz, OCH_2CH_3), 3.44 (3H, s, C_{17}-OCH_3), 3.70, 3.78, 3.80 (each 3H, each s, 3 X OCH_3), 4.23 (2H, q, J = 8 Hz, OCH_2CH_3), 6.24 (1H, d, J = 16 Hz, CH=CH-Ar), 6.60-6.80 (2H, m, C_{10}-H and C_{12}-H), 7.40 (3H, s, ArH), 7.24 (1H, d, J = 8 Hz, C_9-H), 7.54 (1H, d, J = 16 Hz, CH=CH-Ar), 7.90 (1H, s, NH); m/e 662 (M^+).

Anal. Calcd. for $C_{36}H_{42}N_2O_{10}\cdot0.5H_2O$: C, 64.36; H, 6.45; N, 4.17. Found: C, 64.51; H, 6.41; N, 3.94.

Methyl *O*-(4-Hydroxy-3-methoxycinnamoyl)-3-isoreserpate (VII).

A mixture of 1.5 g. of the nitrate of (VI), 15 ml. of methanol and 3 ml. of concentrated ammonia was shaken for 1.5 hour at 60°. After evaporation of the solvent, the resulting solid was recrystallized from methanol to afford 880 mg. of compound VII as pale yellowish needles, m.p. 176-178° (72%); ir ν max (potassium bromide) cm^{-1}: 3600-3400 (OH and NH), 2830, 2800, 2750 (Bohlmann bands), 1730 (CO_2CH_3), 1700 (COCH=CH); nmr δ (deuteriochloroform): 3.44 (3H, s, C_{17}-OCH_3), 3.76 and 3.80 (6H and 3H, each s, 3 X OCH_3), 6.16 (1H, d, J = 16 Hz, CH=CHAr), 6.58-7.40 (5H, m, C_{10}- and C_{12}-H, and ArH), 7.22 (1H, d, J = 8 Hz, C_9-H), 7.84 (1H, s, NH).

Anal. Calcd. for $C_{33}H_{38}N_2O_8$: C, 67.10; H, 6.49; N, 4.74. Found: C, 67.00; H, 6.64; N, 4.31.

Hydrolysis of Methyl *O*-(4-Hydroxy-3-methoxycinnamoyl)-3-isoreserpate (VII).

To a mixture of 40 mg. of sodium and 13 ml. of methanol, 295 mg. of the base (VII) was added and the mixture was refluxed for 35 hours. After acidification with diluted hydrochloric acid, the mixture was washed with benzene. The aqueous layer was basified with ammonia and extracted with ethyl acetate. The extract was dried over sodium sulfate and evaporated to afford 162 mg. of methyl 3-isoreserpate (IV) (78%), which was identified by mixed melting point test and comparisons by tlc behavior and ir with those of the authentic sample (IV).

Hydrolysis of Methyl *O*-(4-Hydroxy-3-methoxycinnamoyl)reserpate (I).

To a mixture of 320 mg. of sodium and 40 ml. of methanol, 2.36 g. of compound I was added and the mixture was refluxed for 4 hours. After acidification of the mixture with diluted hydrochloric acid, the mixture was extracted with ethyl acetate. The

Table I

Carbon-13 Chemical Shifts of the Compound (I), Methyl Reserpate (V) and Rescinamine (X) (a).

Solvent	The compound (I) DMSO-d_6		Methyl reserpate (V) DMSO-d_6		Rescinamine (X) Deuteriochloroform	
Molarity	0.17		0.30		0.315	
Carbon						
2	132.7	ST (b)	132.9	ST	131.9	ST
3	61.5*	DQ (c)	61.7*	DQ	61.8*	DQ
5	50.1	ST	50.5	ST	50.1	ST
6	17.8	ST	17.9	ST	18.0	ST
7	107.4	ST	107.4	ST	108.9	ST
8	123.2	ST	123.2	ST	123.4	ST
9	119.3	DQ	119.2	DQ	119.5	DQ
10	109.6	DQ	109.4	DQ	110.0	DQ
11	156.5	ST	156.4	ST	157.3	ST
12	96.3	DQ	96.2	DQ	96.5	DQ
13	137.8	ST	137.8	ST	137.7	ST
14	25.1^{+}	ST	25.2^{+}	ST	25.2^{+}	ST
15	33.7°	DQ	33.9°	DQ	33.5°	DQ
16	54.7*	DQ	54.8*	DQ	55.0*	DQ
17	79.0$^{\triangle}$	DQ	82.2$^{\triangle}$	DQ	79.7$^{\triangle}$	DQ
18	78.0$^{\triangle}$	DQ	75.5$^{\triangle}$	DQ	78.7$^{\triangle}$	DQ
19	31.1^{+}	ST	34.7^{+}	ST	31.0^{+}	ST
20	34.8°	DQ	35.3°	DQ	35.2°	DQ
21	52.1	ST	52.5	ST	52.5	ST
22	56.6*	DQ	56.6*	DQ	56.9*	DQ
23	173.1	ST	173.7	ST	173.9	ST
24	52.6*	DQ	52.9*	DQ	52.9*	DQ
25	53.2*	DQ	52.9*	DQ	52.9*	DQ
26	167.5	ST			167.5	ST
27	124.5	DQ			118.4	DQ
28	146.7	DQ			146.3	DQ
29	127.0	ST			130.9	ST
30	116.0$^{\square}$	DQ			106.8	DQ
31	150.8	ST			154.6	ST
32	149.4	ST			141.6	ST
33	112.8$^{\square}$	DQ			154.6	ST
34	117.0$^{\square}$	DQ			106.8	DQ
35	57.2	DQ			57.3	DQ
36					62.1*	DQ
37					57.3	DQ

(a) All shifts are in parts per million from TMS; (b) ST = singlet or triplet; (c) DQ = doublet or quartet in the single frequency off-resonance spectrum; *, +, ○, △, □ represent signals where the assignments may be reversed.

extract was washed with water, dried over sodium sulfate and evaporated to afford an oily syrup, which was chromatographed on silica gel. The chloroform eluate gave 55 mg. of methyl 4-hydroxy-3-methoxycinnamate as a syrup (67%), ir and nmr of which were identical with those of the authentic sample.

The above aqueous layer isolated during extraction was basified with ammonia and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated to give a crude product, which was chromatographed on silica gel using methanol-chloroform (1:50) to afford 832 mg. of methyl reserpate (V) (50%), which was identified by mixed melting point test and comparisons by tlc behaviour and ir with those of the authentic sample.

Acknowledgment.

We thank President A. Yamaguchi, Nippon Chemipha Co. Ltd., for his encouragement. We are indebted to Miss R. Kato, Miss R. Suenaga, and Miss H. Koizumi for spectral measurements and microanalysis.

REFERENCES

(1) Part DXCIV, T. Kametani, M. Takemura, K. Takahashi, M. Ihara, and K. Fukumoto, *Heterocycles*, 3, 139 (1975).

(2) Communication concerning this paper should be directed to Professor Tetsuji Kametani.

(3) T. Kametani, M. Ihara, T. Suzuki, T. Takahashi, R. Iwaki, H. Takei, N. Miyake, M. Yoshida, Y. Hasegawa, and H. Kitagawa, *J. Med. Chem.*, **15**, 686 (1972).

(4) K. G. Krebs and N. Futscher, *Arzneim.-Forsch.*, **10**, 75 (1960).

(5) H. B. MacPhillamy, C. F. Huebner, E. Schlittler, A. F. St. André, and P. R. Ulshafer, *J. Am. Chem. Soc.*, 77, 4335 (1955).

(6) C. F. Huebner, M. E. Kuehne, B. Korzeen, and E. Schlittler, *Experienta*, **12**, 249 (1956).

(7) W. E. Rosen and J. M. O'Connor, *J. Org. Chem.*, **26**, 3051 (1961).

(8) W. E. Rosen and H. Sheppard, *J. Am. Chem. Soc.*, **83**, 4240 (1961).

(9) P. G. Philpott and A. M. Parsons, *J. Chem. Soc.*, 3018 (1958).

(10) R. H. Levin, J.-Y. Lallemand, and J. D. Roberts, *J. Org. Chem.*, **38**, 1983 (1973).

(11) E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Accounts Chem. Res.*, **7**, 46 (1974).

(12) G. van Binst and C. Tourwe, *Heterocycles*, **1**, 257 (1973).