Tetrahedron Letters,Vol.23,No.47,pp 4977-4980,1982 0040-4039/82/474977-04$03 00/0
Printed in Great Britain

STRUCTURE AND SYNTHESIS OF REDUCTILINE, A NOVEL METABOLITE FROM A VARIANT OF STREPTOMYCES ORIENTALIS

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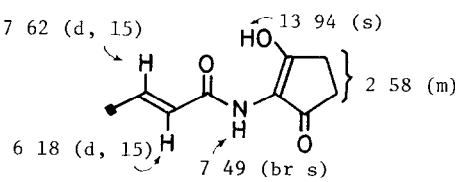
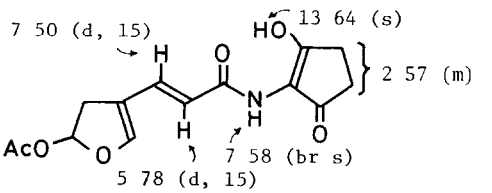
Abstract *The structure of reductiline, a metabolite of a variant of Streptomyces orientalis was elucidated as (1) based on chemical and spectroscopic evidence Transformation of an antitumor antibiotic reductiomycin (2) into reductiline (1) was carried out Synthesis of reductiline (1) was achieved starting from β-cyanopropionaldehyde dimethylacetal*

Reductiline (1) is a yellow crystalline compound isolated from a fermentation broth of a variant of Streptomyces orientalis.[1] Physical and spectral properties of reductiline (1) are as follows 1,[2] mp 203-204° (MeOH), $C_{16}H_{20}N_2O_3S$, UV (MeOH) nm (ε) 273 (16,000), 327 (28,700), IR (KBr) 3260, 2500 (broad), 1673 (weak), 1613 (strong), 1590 (strong), 1545 (shoulder), 1527 (medium), 1149, 982, 857 cm^{-1}, ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 2 04 (2H, quintet, J=7 Hz, H-9), 2 09 (3H, s, H-11), 2 44 (2H, t, J=7 Hz, H-10), 2 58 (4H, m, H-4', H-5'), 4 00 (2H, t, J=7 Hz, H-8), 6 18 (1H, d, J=15 Hz, H-2), 6 38 (1H, m, aromatic H), 6 66 (1H, m, aromatic H), 6 92 (1H, m, aromatic H), 7 49 (1H, br s, NH), 7 62 (1H, d, J=15 Hz, H-3), 13 94 (1H, s, OH), ^{13}C-NMR (DMSO-d_6, 22 5 MHz) δ 14 5 (q), ~30 (br signal),[3] 30 0 (t), 47 6 (t), 106 2 (d), 112 7 (d), 115 1 (s), 120 1 (s), 123 3 (d), 125 0 (d), 137 3 (d), 167 2 (s), MS (m/z) 320 (M^+), 208

Structure of reductiline (1) In the ^{1}H-NMR spectrum some signals of reductiline (1) were found to correspond well to those of an antitumor antibiotic, reductiomycin (2),[4] the structure of which was recently established in our laboratory,[5,6] and consequently the presence of the partial structure (A) in 1 was suggested as depicted below Conclusive evidence for the presence of the partial structure (A) in 1 was provided by the formation of an aldehyde (6) from 1 in three steps (vide post), the aldehyde (6) being also derived from reductiomycin (2)

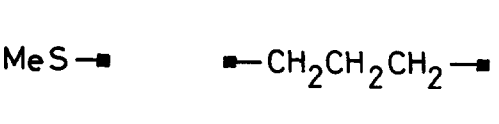


(A)

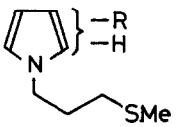


(2)

With the partial structure (A) in hand, the remaining problem was the determination of the structure corresponding to the formula $C_8H_{12}NS$ in 1. In the ^{1}H-NMR spectrum of 1 a signal at δ 2.09 (3H, s) was assigned to a methylthio group (B). Further a partial structure (C) was deduced to be present in 1 by three signals at δ 2.04 (2H, quintet, J=7 Hz), 2.44 (2H, t, J=7 Hz), and 4.00 (2H, t, J=7 Hz), and the presence of a pyrrole ring (D) substituted either at 1,2- or 1,3-positions by carbon atoms was suggested by signal patterns due to three aromatic protons at δ 6.38 (1H, m), 6.66 (1H, m), and 6.92 (1H, m) in the ^{1}H-NMR spectrum and by four signals at δ 106.2 (d), 120.1 (s), 123.3 (d), and 125.0 (d) in the ^{13}C-NMR spectrum. Since a signal arising from one of the methylene groups in the partial

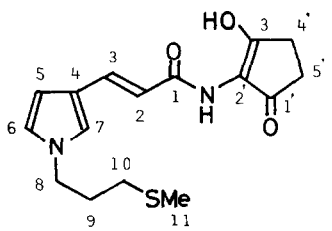


(B) (C) (D)

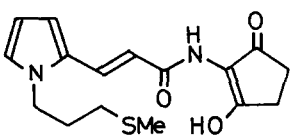


(E)

structure (C) appeared at δ 4.00, the methylene group was deduced to be attached to the nitrogen atom of the pyrrole ring (D). Further the methylthio group (B) was assigned to be connected with the other end of methylene groups in (C) in view of the fact that the β-carbon of the α,β-unsaturated amide group of the partial structure (A) must be bonded to a 2- or 3-position of the pyrrole moiety (D). Based on the above findings, correlation of the three partial structures, (B), (C), and (D) could be made, leading to the new partial structure (E), in which a group R stands for the partial structure (A). The whole structure of reductiline is, therefore represented by either 1 or 1a. The definite proof for the



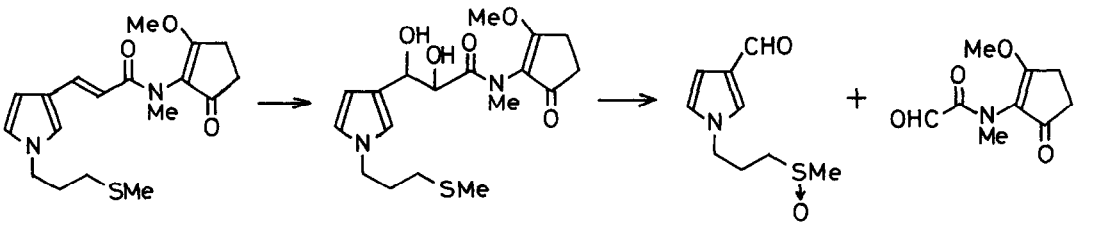
(1)



(1a)

structure (1) of reductiline was secured as follows. Treatment of 1 with methyl iodide in the presence of NaH (DMF, room temp., 30 min) afforded a dimethyl derivative (3),[2,7] $C_{18}H_{24}N_2O_3S$ (oil). Oxidation of the dimethyl derivative (3) with OsO_4 (THF-Py, room temp., 70 min) yielded a 1,2-diol (4),[2,8] $C_{18}H_{26}N_2O_5S$ (oil), the ^{1}H-NMR spectrum of which revealed that the double bond of the α,β-unsaturated amide group in 3 underwent oxidation to form the 1,2-diol grouping. The diol (4) was further oxidized with $NaIO_4$ (H_2O-EtOH, room temp., 90 min) to give a formylpyrrole (5) and an aldehyde (6), the latter (6) being found to be identical with the aldehyde derived from reductiomycin (2) by a series of reactions corresponding to those (1 → 3 → 4 → 6) described above. formylpyrrole (5),[2] (oil) $C_9H_{13}NO_2S$,

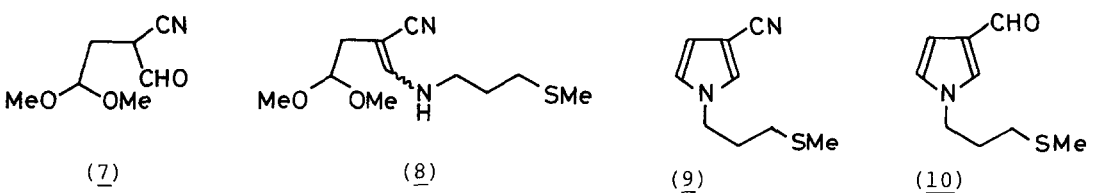
IR ($CHCl_3$) 1663, 1625, 1158 (strong) cm^{-1}, ^1H-NMR ($CDCl_3$, 100 MHz) δ 2 34 (2H, m), 2.58 (3H, s), 2.60 (2H, m), 4 16 (2H, t, J=7 Hz), 6 65 (2H, m), 7 33 (1H, m), 9 73 (1H, s), MS (m/z) 199 (M^+), 135, 106 The structure of the formylpyrrole (5) was unambiguously established by synthesis the formylpyrrole (5) was obtained by $NaIO_4$ oxidation of a sulfide (10), the synthesis of which is described below [see Section of synthesis of reductiline (1)]. Thus the structure of reductiline was determined to be 1



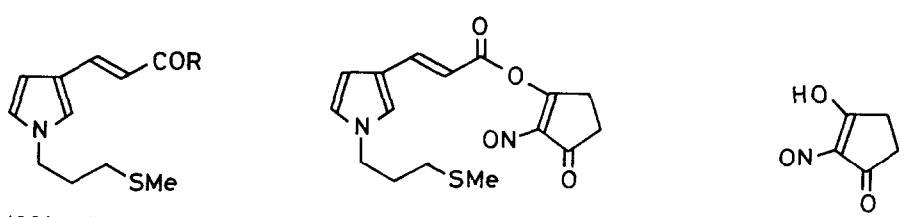
(3) (4) (5) (6)

Transformation of reductiomycin (2) into reductiline (1). Biogenetically reductiline (1) could be considered to originate from reductiomycin (2) and methionine Based on this biogenetic viewpoint, chemical conversion of reductiomycin (2) to reductiline (1) was attempted and actually executed on treatment with 3-(methylthio)propylamine (room temp , 17 h) 2 afforded 1 (79%) and the acetate of 3-(methylthio)propylamine

Synthesis of reductiline (1) The carbanion generated from β-cyanopropionaldehyde dimethylacetal[9] (LDA, THF, -30°) was formylated with HCOOMe (-20°∼ -15°, 2 h) to give an aldehyde (7)[10] (pale yellow oil), which was used in the next step without further purification On treatment of the aldehyde (7) with 3-(methylthio)propylamine (EtOH, room temp , 40 min) an enamine (8)[10] was obtained, which, without purification, was cyclized under acidic conditions (p-TsOH, benzene, room temp., 20 h) to afford a cyanopyrrole (9),[2,10] (colorless



(7) (8) (9) (10)



(11) R = OH
(12) R = Cl

(13) (14)

oil, 42% from β-cyanopropionaldehyde dimethylacetal after purification[11a]) Reduction of the cyanopyrrole (9) with DIBAL (toluene, 0° → room temp , 30 min) gave a formylpyrrole (10),[2,10] (colorless oil, 78% after purification[11b]) Condensation of the formylpyrrole (10) with malonic acid (piperidine, Py, 90°, 4 h) yielded a conjugated acid (11),[2,10] mp 81-82° (benzene-hexane) (50%) The acid (11) was converted [(i) n-BuLi, THF, -78° → room temp , 15 min , (ii) $(COCl)_2$, -40° → *room temp , 20 min.*] *to the acid chloride* (12), which was used immediately in the next step Acylation of 3-hydroxy-2-nitrosocyclopent-2-en-1-one (14)[12] with the acid chloride (12) [Py (2 molar equiv), acetone-THF, -30° → 0°, 20 min] yielded an enol ester (13), which, without isolation, was reduced by adding powdered zinc to the reaction mixture (-30° → room temp , 40 min), affording, *via* O → N acyl migration, reductiline (1),[10] mp 203-204° (*ca* 14% based on reacted 14) Identity of synthetic 1 with natural 1 was proved by mixed mp and by comparison of the spectral (IR, ^{1}H-NMR, MS) and chromatographic properties The rational synthesis of reductiline described herein has confirmed unambiguously the structure (1) of reductiline

Acknowledgment. Financial support from the Ministry of Education, Science, and Culture (Grant-in-aid for Scientific Research No 56540321) is gratefully acknowledged

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2. Satisfactory microanalyses or exact mass spectral data were obtained

3 The multiplicity could not be determined because of the broad shape of this signal

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7 3 IR ($CHCl_3$) 1697, 1643, 1617 cm^{-1}, ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 2 01 (2H, quintet, J=7 Hz), 2 08 (3H, s), 2.42 (2H, t, J=7 Hz), 2 64 (4H, m, AA'BB' type), 3 11 (3H, s), 3.96 (2H, t, J=7 Hz), 3 98 (3H, s), 6 09 (1H, d, J=15 Hz), 6 26 (1H, m), 6 60 (1H, m), 6 84 (1H, m), 7 58 (1H, d, J=15 Hz), MS (m/z) 348 (M^+), 208, 141

8 4 ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 2 01 (2H, quintet, J=7 Hz), 2 08 (3H, s), 2 44 (2H, br t, J=7 Hz), 2 60 (4H, m, AA'BB' type), 3 08 (3H, m), 3 93 (2H, t, J=7 Hz), 4 00 (3H, m), 4 13 (1H, br s), 4 72 (1H, br s), 6 02 (1H, m), 6 54 (1H, m), 6 66 (1H, m), MS (m/z) 382 (M^+), 364, 350

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10 The IR, ^{1}H-NMR, and mass spectral data for this compound were in accord with the structure assigned

11. By chromatography on silica gel with (a) $CHCl_3$, (b) $CHCl_3$-EtOAc (4 1)

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(Received in Japan 21 August 1982)