In all that follows, it is assumed that only the first term need be kept, i.e., that "first order" ionizations will lead to wave functions

$$\psi_s^{N-1} = \sum_i C_{si} a_i \psi^N = A_s \psi^N \qquad A_s = \sum_i C_{is} a_i \tag{1}$$

It is the retention of only the first-order term which is in analogy to Koopmans' theorem for an independent particle model.[40]

From (1) it is noted that the energy of the state ψ_s^{N-1} is

$$E_S^{N-1} = \langle \psi_s^{N-1} | \bar{\mathcal{H}} | \psi_s^{N-1} \rangle / \langle \psi_s^{N-1} | \psi_s^{N-1} \rangle$$

$$E_S^{N-1} = \langle \psi^N | A_s^+ \bar{\mathcal{H}} A_s | \psi^N \rangle / \langle \psi^N | A_s^+ A_s | \psi^N \rangle$$

It has been assumed that $\bar{\mathcal{H}}\psi^N = E\psi^N$, and therefore the first-order ionization potential of state s is given by eq 2.

$$E_S^{N-1} - E^N = \frac{\langle \psi^N | A_s^+ \bar{\mathcal{H}} A_s | \psi^N \rangle - \langle \psi^N | A_s^+ A_s \bar{\mathcal{H}} | \psi^N \rangle}{\langle \psi^N | A_s^+ A_s | \psi^N \rangle} = \frac{\langle \psi^N | A_s^+ [\bar{\mathcal{H}}, A_s] | \psi^N \rangle}{\langle \psi^N | A_s^+ A_s | \psi^N \rangle} \tag{2}$$

In order to simplify the problem further, it will be assumed that ψ^N based on a finite set of ϕ_i (in this case, the configurations used in the CI calculation) is an eigenfunction of model Hamiltonian $\bar{\mathcal{H}}$, which is the projection of $\mathcal{H}$ in the space spanned by the configurations $\{\phi_i\}$. ψ^N will be an eigenfunction of $\bar{\mathcal{H}}$ if a full CI has been done.

Substitution of (1) into (2) leads to

$$\sum_{ij} C_{si} C_{sj} \langle \psi^N | a_j^+ [\bar{\mathcal{H}}, a_i] | \psi^N \rangle = (E_S^{N-1} - E^N) \sum_{ij} C_{is} C_{js} \langle \psi^N | a_j^+ a_i | \psi^N \rangle \tag{3}$$

If we define

$$V_{ij} = -\langle \psi^N | a_j^+ [\bar{\mathcal{H}}, a_i] | \psi^N \rangle \tag{4}$$

and

$$D_{ij} = \langle \psi^N | a_j^+ a_i | \psi^N \rangle \tag{5}$$

and if we require E_S^{N-1} to be variationally stable with respect to the coefficients C, (3) reduces to a matrix equation

$$\mathbf{V}C = \mathbf{D}C\Delta \tag{6}$$

where $\Delta_{st} = (E^N - E_S^{N-1})\delta_{st}$. The solution of (6) yields the extended Koopmans' theorem ionization potentials. **V** is referred to as the one-particle potential and **D** is the first-order reduced density matrix. The **V** matrix elements may be obtained by recalling the second quantized form of $\bar{\mathcal{H}}$:

$$\bar{\mathcal{H}} = \sum_{ij} \mathbf{f}_{ij} a_i^+ a_j + \sum_{ijkl} \mathbf{g}_{ijkl} a_i^+ a_j^+ a_l a_k \tag{7}$$

where **f** and **g** matrices are the one- and two-electron integrals over configurations. Substitution of (7) into (4) leads to

$$V_{ij} = \sum_k \mathbf{f}_{ik} D_{kj} + \sum_{klm} \mathbf{g}_{iklm} \Gamma_{mlkj} \tag{8}$$

where Γ is the second-order reduced density matrix. In practice, since V_{ij} will only be Hermitian if ψ^N is a true eigenfunction of $\mathcal{H}$, V_{ij} is replaced by $^1/_2(V_{ij} + V_{ji})$ as has been done for atomic EKT calculations.[18] This replacement has been shown to be the best choice to the true self-adjoint matrix **V**.[41]

It is of interest to note that it has been recently proven[42] that if ψ^N is the exact ground-state wave function, then the first ionization potential as calculated by the EKT or MPL method will be exact, as will ψ^{N-1} for the ground state of the ion.

(40) See Slater[27] for a discussion of higher order terms in an independent particle model.

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Sch 18640. A New Thiostrepton-Type Antibiotic[1]

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Abstract: The structure of a new thiostrepton-type antibiotic, Sch 18640, is established on the basis of degradative and spectroscopic (^{13}C NMR and 600-MHz ^{1}H NMR) studies. In addition, for the first time, ^{252}CF plasma desorption mass spectrometry (^{252}CF-PDMS) has been applied to determine the molecular weight of this class of antibiotics.

Thiostrepton (**1**) produced by *Streptomyces aureus*[3-5] is active against gram-positive bacteria and has found application in veterinary medicine.[6] Its structure was elucidated by using extensive chemical degradations[7] and X-ray crystallographic analysis.[8] Several antibiotics which are closely related to **1** have been isolated, e.g., thiactin[9] bryamicin,[9] thiopeptins,[10] and siomycin.[11,12] Other sulfur-containing antibiotics of similar type are nosiheptide,[13] multhiomycin,[14] and micrococcins.[15]

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(1) After the submission of our results, two reports[11,12] on the structures of similar antibiotics appeared.

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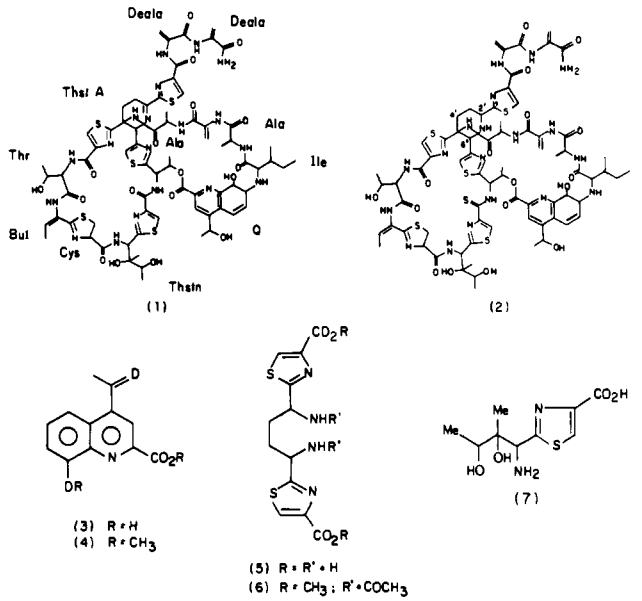
Table I. ^{13}C Chemical Shifts[a]

	thiostrepton (1)[b]	Sch 18640 (2)
C–CH_3	11.6 (Ile δ); 15.4, 15.9 (Ile α, Ala β), 16.5 (Ala β); 23.0 (Q2'); 18.8, 19.0, 19.2 × 3	11.8 (Ile δ), 15.7, 16.1 (Ile γ, Ala β); 16.3 (Ile β); 23.0 (Q2'); 18.9, 19.1 × 3, 19.3
C(S)–CH_2	25.0 (Thst A3'); 25.3 (Ile γ); 29.7 (Thst A4');	34.1 (Thst A3');[c] 24.5 (Ile γ); 29.1 (Thst A4');[c]
C–CH	35.2 (Cys β); 39.2 (Ile β)	35.3 (Cys β); 38.7 (Ile β)
N(O)–CH	49.9 (Ala α); 52.4, 53.7 (Ala α, Thst 1''); 56.2, 56.4 (Thr α, Thstn 1'); 59.6 (Ile α); 64.9 (Thst A6'); 66.2 (Q7); 67.1 (Thr β); 79.7 (Cys α); 64.9, 68.4, 68.6, 72.6 (Q8, Q1', Thstn 3', Thst A2'')	49.9 (Ala α); 52.4, 53.8 (Ala α, Thst 1''); 58.5,[c] 56.1 (Thr α, Thstn 1'); 59.1 (Ile α); 62.3 (Thst A6');[c] 65.6 (Q7); 66.7 (Thr β); 79.2 (Cys α); 64.8, 67.9, 68.2, 72.4 (Q8, Q1', Thstn 3', Thst A2''); 61.8 (Thst A2')[c]
N(O)–C	58.2 (Thst A5'); 77.7 (Thstn 2')	59.1 (Thst A5');[c] 77.4 (Thstn 2')
C=CH_2	103.0, 103.9, 104.8 (Deala β)	103.7, 104.0, 104.5 (Deala β)
C=CH	118.8 (But β); 122.9, 123.6, 125.4, 125.8, 127.8, 130.6, 133.0	118.5 (But β); 122.8, 123.7, 124.7, 125.4, 128.3, 130.3, 133.0
C=C	127.8, 129.2 (Q4, 10)	127.5, 128.7 (Q4, 10)
C=C–N	133.0, 133.9, 135.0 (Deala α); 144.2 (But α)	132.5, 133.2, 134.6 (Deala α); 143.9 (But α)
N=C	147.0, 150.6 × 2, 153.7, 155.3, 157.7, 160.0	146.2, 149.4, 154.0, 154.9, 155.5,[c] 156.6,[c] 160.1
C=O	169.5 (Ala CO); 161.5, 162.0, 162.4 × 2	169.3 (Ala CO); 161.0, 162.0, 162.4
N=C–S	162.7, 163.5, 166.1, 166.6, 167.3, 169.0, 170.5 × 2, 170.7, 172.1, 173.7, 174.2	163.1, 165.8,[c] 166.0, 166.3, 167.9, 170.7 × 2, 172.3, 173.0 × 2,[c] 173.7, 191.0[c]

[a] Varian XL-100-15 NMR spectrometer operating at a frequency of 25.2 MHz; solvent $CDCl_3$–CD_3OD (80:20). [b] Our data are identical with literature values.[11] [c] Chemical shift changes resulting from differences in structures.



Sch 18640 (2) is the major constituent of the antibiotic complex[16] (also referred as 68-1147 complex) produced by *Micromonospora arborensis*. It is extracted from the fermentation broth by using ethyl acetate and then further purified by column chromatography. Sch 18640 was differentiated from other related antibiotics by thin-layer chromatography. In this paper we wish to disclose the structure of Sch 18640 (2).

Experimental Section

Carbon-13 NMR spectra of a solution of 1 and 2 in $CDCl_3$–CD_3OD (80:20) were obtained by using Varian Associates XL-100-15 NMR spectrometer operating at a frequency of 25.2 MHz (^{13}C) and at ambient temperature. The spectrometer was internally locked to the deuterium frequency (15.4 MHz) of the solvent. The chemical shifts (δ, ppm) downfield from tetramethyl silane (Me_4Si) are presented in Table I. To facilitate assignments, we performed both fully decoupled and off-resonance experiments. Proton magnetic resonance data were obtained in $CDCl_3$, utilizing Carnegie Mellon high-field NMR spectrometer operating at a frequency of 600 MHz (^1H). The chemical shift assignments are listed in Table II.

Mass spectrometry (^{252}CF-PDMS) data were obtained at Texas A&M University. Thiostrepton (1) was obtained from SQUIBB Institute and was used without further purification. Sch 18640 was purified by preparative thin-layer chromatography on silica gel by using acetone–chloroform (50:50) as the developing system.

Results and Discussion

Sch 18640, $C_{72}H_{87}N_{19}O_{17}S_6$ (molecular formula is based on plasma desorption mass spectrometry; satisfactory elemental analysis could not be obtained because the compound crystallized with varying amounts of solvents): mp 225–229 °C; $[\alpha]^{26}_D$ 81.8° (0.3% in $CHCl_3$); IR ($CHCl_3$) 3350 (NH), 1732 (ester), 1695 and 1655 (amide), 1635 (C=N), 1515 (amide II) cm^{-1}; UV λ_{max} 245 nm (ε 49 980), 294 (18 030) and 306 nm (14,910). The amino acid analysis of Sch 18640 showed the presence of one isoleucine, two alanines, one threonine, and one cysteine residues. In connection with some other work, we became aware of the use of (^{252}CF-PDMS) for the elucidation of structures of complex antibiotics.[18,19] To the best of our knowledge, determination of molecular weight of thiostrepton class of antibiotics using mass

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Table II. Proton NMR Data (δ) in $CDCl_3$[a-c]

	assignts	1	2
Ala-1	$\beta(CH_3)$	1.48 d (6.5)	1.54 d (6.5)
	α(CH)	4.78 m	4.91 m
	CONH	6.56 d (6.3)	6.67 d (7.0)
Deala-1	β(=CH) (c)	5.23 b s	5.20 b s
	β(=CH) (t)	5.80 b s	5.80 b s
	CONH	7.83 b s	7.84 b s
Ala-2	$\beta(CH_3)$	1.21 d (6.5)	1.22 d (6.5)
	α(CH)	3.87 dq	3.86 dq (7.0, 6.5)
	CONH	7.60 d (6.0)	7.60 d (7.0)
Ile	$\delta(CH_3)$	0.96 t (6.5)	0.95 t (6.5)
	$\gamma(CH_3)$	0.91 d (6.5)	0.90 d (6.5)
	$\gamma(CH_2)$	1.26 m	1.26 m
	β(CH)	~1.5	~1.5
	α(CH)	3.01 d (5.5)	3.00 d (6.0)
	NH		
Q	3-CH	7.33 s	7.32 s
	5-CH	6.88 d (10.4)	6.89 d (10.0)
	6-CH	6.33 dd (10.5, 6.2)	6.32 dd (10.0, 4.5)
	7-CH	3.66 d (5.0)	3.64 d (5.0)
	8-CH	4.70 d (8.0)	4.66 d (8.0)
	11-CH	5.35 q (6.5)	5.34 q (6.0)
	11-CH_3	1.38 d (6.5)	1.37 d (6.5)
	8-OH	6.92 d (9.0)	6.85 d (8.0)
Thr-2	$\gamma(CH_3)$	1.78 d (6.5)	1.77 d (6.0)
	β(CH)	6.40 q (6.5)	6.54 q (6.0)
	α(CH)	5.85 d (8.3)	6.81 d (8.0)
	CONH	8.37 d (8.3)	9.82 d (8.0)
Thstn	$\gamma(CH_3)$	1.35 d (6.5)	1.35 d (6.0)
	γ(CH)	3.83 q (6.5)	3.81 q (6.0)
	$\beta(CH_3)$	1.20 s	1.20 s
	α(CH)	5.79 d (8.0)	5.77 d (10.0)
	CONH	7.58 d (8.0)	7.55 d (10.0)
	Thz-4=CH	8.30 s	8.54 s
(+)-Cys	β(CH)	3.13 dd (14.5, 10.5)	3.10 dd (12.0, 10.0)
	β'(CH)	3.72 dd (10.5, 10.5)	3.70 dd (10.0, 9.0)
	α(CH)	4.98 dd (14.5, 10.5)	4.95 dd (12.0, 9.0)
Debut	$\gamma(CH_3)$	1.64 d (6.5)	1.63 d (6.0)
	β(CH)	6.21 q (6.3)	6.19 q (6.0)
	CONH	8.53 b s	8.48 b s
Thr-1	$\gamma(CH_3)$	1.01 d (6.5)	0.97 d (6.5)
	β(CH)	1.08 m	1.10 m
	α(CH)	4.47 d (8.3)	4.43 d (8.0)
	CONH	6.90 d (9.0)	6.86 d (8.0)
Thst A	P2′CH		4.14 dd (7.0, 2.0)
	P3′$_a$CH	2.97 ddd	2.11 m
	P3′$_e$CH	3.50 ddd	2.11 m
	P4′$_a$CH	2.29 ddd	1.58 m
	P4′$_e$CH	4.11 ddd	2.35 m
	P6′$_a$CH	5.17 s	4.46 b s
	CONH	9.87 s	9.68 s
	Thz-1=CH	8.29 s	8.17 s
	Thz-2=CH	8.13 s	8.11 s
	Thz-3=CH	7.48 s	7.41 s
Deala-S-1	β(=CH) (c)	5.59 b s	5.56 b s
	β(=CH) (t)	6.81 b s	6.75 d (1.5)
	CONH	9.99 s	9.89 s
Deala-S-2	β(=CH) (c)	5.51 b s	5.45 b s
	β(=CH) (t)	6.68 b s	6.65 d (1.0)
	CONH	9.03 s	8.98 s

[a] 600-MHz spectrometer. Nomenclature is identical with the reported system.[12] [b] Unassigned resonances were δ 5.39 and 4.14 for 1 and δ 7.83, 5.41, 4.42, 4.09 d (4.0), and 4.03 d (2.0) for 2. All exchanged with D_2O in 2. [c] Coupling constants are in Hz in parentheses.

spectral techniques has not been achieved. We, therefore, investigated the use of the above technique to determine the molecular weight of thiostrepton[8] (1).

The ^{252}CF-PDMS of 1 showed isotopically averaged molecular weight to be 1665.2 ± 0.3 which corresponded well with the calculated value of 1664.89 for $C_{72}H_{85}N_{19}O_{18}S_5$. Sch 18640 showed molecular ion at m/e 1682.8 ± 0.2 corresponding to the molecular formula $C_{72}H_{87}N_{19}O_{17}S_6$ (calcd 1682.97).

Hydrolysis of 2 with aqueous acid (1 N HCl) yielded 3 which on methylation was converted to 4 (identical in all respects when compared with an authentic sample of 4 prepared from thiostrepton). Hydrolysis of compound 2 with concentrated HCl–HCO_2H, 1:1) yielded thiostreptoic acid (5) which was identified as its derivative (6) by comparison with an authentic sample.[17] The formation of thiostreptoic acid (5) from 2 is difficult to explain without involving an oxidation step. Comparison of ^{13}C NMR data of compound 2 indicated the close similarity of its structure with that of thiostrepton (1) (see Table I). However, two areas of major differences were observed. Specifically, carbons of the "Thst A" (thiostreptoic acid) portion of the molecule differed significantly; for example, see Chart I.

Chart I

	compd 1	compd 2	compd 2-TFA
2′	169.0 (C)	61.8 (CH)	61.2
3′	25.0 (CH_2)	34.1 (CH_2)	33.6
4′	29.7 (CH_2)	29.1 (CH_2)	26.8
5′	58.2 (C)	59.1 (C)	59.3
6′	64.9 (CH)	62.3 (CH)	62.0

On the basis of the above data, the presence of a piperidine moiety in the "Thst A" portion of the molecule in the structure of 2 became apparent. The assignment of C_2' in compound 2 at δ 61.8 is comparable to the expected value.[10] Protonation indicated small upfield changes in the chemical shift of the piperdine carbons similar to those observed in piperdine.[20b] In the thiostreptine part of the molecule, the C=O function at δ 162.7 in 1 shifted to δ 191.0 in 2 which is consistent with the proposed change[20a] of (C=O) in 1 to (C=S) in 2. It should be pointed out that thiostreptine (7) was not obtained by the hydrolysis of 2. In addition, carbon atom 2 in threonine portion (Thr-2) of the molecule appeared at δ 58.5 because of its close proximity and conformational influence of the (C=S) function. Other changes in ^{13}C NMR spectra associated with the aforementioned structural variations of 2 were δ 150.6 (155.5), 157.7 (156.6), 163.5 (165.8), and 170.7 (173.0). The figures in parentheses are those for compound 2.

Proton NMR data (600 MHz) presented in Table II also confirmed the presence of piperidine moiety in 2. The chemical shift values (δ, ppm) were H_2 (4.14, dd, J = 7 and 2 Hz), $H_{3'}$, (2.11, m), $H_{3'e}$ (2.11, m), $H_{4'a}$ (1.58, m), $H_{4'e}$ (2.35, m), and H_{6a} (4.46, s). Due to the presence of the thioamide function in 2 the chemical shifts of several protons in the immediate vicinity of C=S bond were affected. For example, the amide proton at δ 8.37 (Thr-2) in 1 shifted downfield to δ 9.82 in 2. Similar changes were observed for α(CH) of threonine (Thr-2) which changed from δ 5.85 in 1 to δ 6.81 in 2. In addition, the Thz-4 proton of the thiostreptine moiety suffered a small downfield shift (from δ 8.30 to δ 8.54). These changes are comparable to the differences in the proton shifts of methyl amide and thioamide.[20b]

On the basis of all the above observations, we wish to propose structure 2 for Sch 18640.

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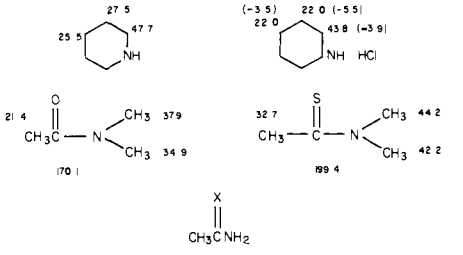
(20) (a) $\Delta\delta$ of 28.3 ppm is comparable to the $\Delta\delta$ value of 29.3 ppm between *N,N*-dimethylacetamide and thioamide. (b)



$\delta(NH_2)$ 6.4, 7.1 (X = O)
$\delta(NH_2)$ 9.1 (X = S)