STRUCTURE OF SIBIROMYCIN

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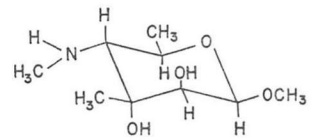
Sibiromycin, an antitumor antibiotic produced by *Streptosporangium sibiricum*, belongs to the group of pyrrolo-(1,4)-benzodiazepine antibiotics and contains an aminosugar.

The present paper is concerned with the structure elucidation of sibiromycin, an antitumor antibiotic produced by *Streptosporangium sibiricum*[1]. The isolation and properties of sibiromycin and some characteristics of its degradation products were reported previously[2,3].

We have found that under mild acidic conditions sibiromycin loses a molecule of water to form biologically inactive yellow crystalline anhydrosibiromycin, $C_{24}H_{29}N_3O_6$, λ_{max} 277,407 and 435 nm. Further investigation showed that both sibiromycin and anhydrosibiromycin are glycosides of a novel branched-chain aminosugar named sibirosamine. Methanolysis of sibiromycin and/or anhydrosibiromycin yielded a mixture of the anomeric methyl sibirosaminides, $C_9H_{19}NO_4$. One anomer accounting for 90 % of the mixture was obtained as a crystalline hydrochloride, m.p. 184~187°C, $[\alpha]_D^{20}$ −50° (water). The second anomer was obtained as an amorphous hydrochloride, m.p. 178~179°C, $[\alpha]_D^{20}$ +75° (water). The structure of the major, laevorotary anomer of methyl sibirosaminide was assigned as methyl 4-methylamino-4,6-dideoxy-3-C-methyl-β-D-altropyranoside[4] (Fig. 1).

Fig. 1. Methyl sibirosaminide.



Under conditions of drastic acidic hydrolysis anhydrosibiromycin lost the aminosugar moiety and gave anhydrosibiromycinone (**3**) as a bright yellow optically inactive crystalline substance, $C_{16}H_{14}N_2O_3$, λ_{max} 290, 375, 410 and 435 nm. In Table 1 are presented PMR spectral data of anhydrosibiromycinone and its derivatives.

Anhydrosibiromycinone was found to be very stable even during prolonged heating in concentrated hydrochloric acid. Acetylation of anhydrosibiromycinone with acetic anhydride in pyridine afforded the diacetate (**4**), $C_{20}H_{18}N_2O_5$, m.p. 225~226°C, ν_{max} (in chloroform) 1750, 1680, 1630, 1205 cm^{-1}. Mild hydrolysis of **4** with 2 N hydrochloric acid gave anhydrosibiromycinone, thus showing the presence of two phenolic hydroxyls in **3**. Anhydrosibiromycinone was very slowly methylated with diazomethane, yielding the monomethyl ether. The same mono-methylated product, $C_{17}H_{16}N_2O_3$, m.p. 200~202°C, δ 3.96 (3H, O-CH_3), was isolated after short-term methylation of anhydrosibiromycinone with dimethyl sulfate in acetone in the presence of potassium carbonate (2 hours in refluxing acetone). Prolonged methylation converted anhydrosibiromycinone in quantitative yield to the dimethyl ether (**5**), $C_{18}H_{18}N_2O_3$, m.p. 192~193°C.

Table 1. PMR spectral data of anhydro-sibiromycinone and its derivatives (δ ppm, 100 Mc).

3, 4, 5 6, 7, 8

Substance	Solvent	C(2″)-CH_3	C(8)-CH_3	H-I	H-2	H-2′	H-2″	H-3	H-II	H-IIa	H-6	R_1 R_2	R_3
Anhydrosibiromycinone (3) $R_1=R_2=H$	DMSO	1.89	2.16	2.27	←6.31→			8.06	8.28	—	7.51	—	—
Diacetate-3 (4) $R_1=R_2=COCH_3$	$CDCl_3$	1.89	2.15	7.07	←6.27→			8.07	8.37	—	8.24	2.34 2.41	—
Dimethyl-3 (5) $R_1=R_2=CH_3$	$CDCl_3$	1.88	2.29	7.07	←6.30→			8.07	8.48	—	7.88	3.89 3.96	—
Octahydro-3 (6) $R_1=R_2=R_3=H$	DMSO	0.87	1.97	←1.29→				←2.80–3.90→			6.92	—	—
Triacetate-6 (7) $R_1=R_2=R_3=COCH_3$	$CDCl_3$	0.90	2.05	←1.36→				←2.80–4.50→			7.40	2.29 2.33	1.80
N-acetyl-dimethyl-6 (8) $R_1=R_2=CH_3$, $R_3=COCH_3$	$CDCl_3$	1.01	2.26	←1.35→				←2.80–4.50→			7.15	3.74 3.92	1.86

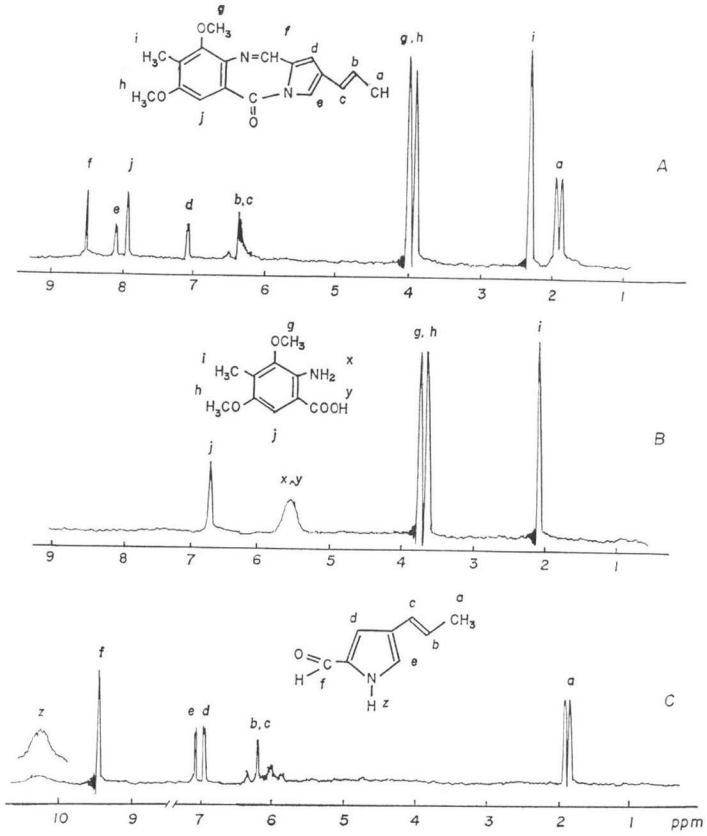
Catalytic hydrogenation of anhydrosibiromycinone over palladium charcoal resulted in the uptake of 4 equivalents of hydrogen to form the octahydro derivative (**6**), $C_{16}H_{22}N_2O_3$, λ_{max} (in methanol) 229, 260 (shoulder) and 350 nm (ε 34,000; 10,000 and 4,000). The hydrogenation product gave a stable hydrochloride and yielded on acetylation with acetic anhydride in pyridine the triacetate (**7**), $C_{22}H_{28}N_2O_6$, m.p. 131~133°C, ν_{max} (in chloroform) 1780, 1680~1665, 1208 cm^{-1}. Treatment of the hydrogenation product with diazomethane and subsequent acetylation with acetic anhydride in pyridine produced N-acetyl-dimethyl-6, **8**, $C_{20}H_{28}N_2O_4$, m.p. 161~162°C, ν_{max} (in chloroform) 1665~1640 cm^{-1}.

The most significant evidence which permitted elucidation of the structure of anydrosibiromycinone was obtained from studying the products of alkaline hydrolysis of the dimethyl ether **5**. Hydrolysis of **5** with 0.1 N sodium hydroxide gave 3, 5-dimethoxy-4-methylanthranilic acid (**9**), $C_{10}H_{13}NO_4$, m.p. 178°C, λ_{max}^{MeOH} 250 and 350 nm; and the formylpyrrole derivative (**10**), C_8H_9NO, m.p. 115~116°C, λ_{max}^{MeOH} 242, 250 (shoulder) and 325 nm.

The structure of the acid **9** was determined as 3,5-dimethoxy-4-methylanthranilic acid. Deamination of **9** with hypophosphorous acid gave 3,5-dimethoxy-*p*-toluic acid (m.p. 216~217°C), which was subsequently methylated with diazomethane to the methyl ester (m.p. 105°C). Both derivatives were identified by comparison of their IR, PMR and mass-spectra with an authentic samples obtained by synthesis from *p*-toluic acid[5].

The structure of the formylpyrrole **10** was established from the analysis of its physicochemical properties and PMR spectral data. Compound **10** consumes two moles of hydrogen on hydrogenation over palladium on charcoal and with 2,4-dinitrophenylhydrazine **10** affords

Fig. 2. PMR spectra of (A) dimethyl ether of anhydrosibiromycinone; (B) anthranilic acid derivative **9**, and (C) formyl-pyrrole derivative **10** ($CDCl_3$, 100 Mc).



a brown crystalline hydrazone. The PMR spectrum of **10** is presented in Fig. 2 C. Observed signals are as follows: a 3-proton doublet at δ 1.83 ppm corresponning to the terminal CH_3 in the propenyl group ($J_{CH_3,\ H_b}$=6.5 Hz); a 2-proton multiplet centered at δ 6.1 ppm attributable to two olefinic protons H_b and H_c (*trans*) ($J_{H_b,\ H_c}\sim$17 Hz; $J_{H_b,\ CH_3}$=6.5 Hz); two 1-proton signals with the chemical shift values of δ 6.96 and 7.06 ppm corresponding to the α, β'-protons of a pyrrole-ring (H_d and H_e; $J_{d,e}\sim$1.3 Hz); a 1-proton signal at δ 9.44 ppm representing the signal H_f in the aldehyde group; a broad 1-proton signal at δ 10.35 ppm corresponding to H_z in the NH-group of the pyrrole ring. Interpretation of PMR spectrum of **10** is completely in accordance with the literary data concerning the PMR spectroscopy of the similar substituted pyrrole derivatives[6,7]. The infrared spectrum of **10** also checks well with the proposed structure of α-formyl-β'-propenylpyrrole: $\nu_{max}^{CCl_4}$ 3450 cm^{-1} (NH-pyrrole, unassociated); 3280 cm^{-1} (broad band diminished on dilution, hydrogen-bonded NH); 1665 cm^{-1} (C=O formyl); 1565, 1490, 1390$\sim$1360 cm^{-1} (skeletal oscillation of pyrrole ring)[8,9].

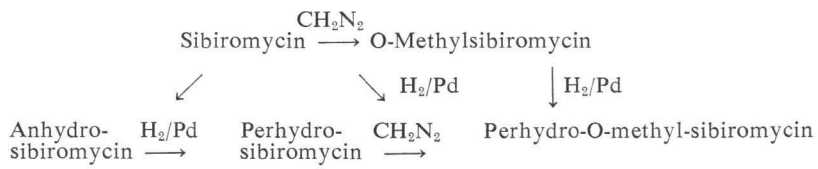
Inspection of the PMR spectra of the dimethyl ether **5** and the products of alkaline hydrolysis, **9** and **10** (Fig. 2 A,B,C), together with analysis of the chemical properties allowed us to propose the structure 7,9-dihydroxy-8-methyl-2-(1-propenyl)-5H-pyrrolo (2, 1-c) (1, 4) benzodiazepin-5-one (**3**) for anhydrosibiromycinone (Fig. 2A).

As stated above the glycoside of anhydrosibiromycinone (anhydrosibiromycin) had the aminosugar moiety in its molecule. It could be seen from the molecular formulae that the molecule of anhydrosibiromycin consisted only of the fragments anhydrosibiromycinone and sibirosamine.

$$\underset{\text{Anhydro-sibiromycin}}{C_{24}H_{29}N_3O_6} + CH_3OH \longrightarrow \underset{\text{Anhydro-sibiromycinone}}{C_{16}H_{14}N_2O_3} + \underset{\text{Methyl-sibirosaminide}}{C_9H_{19}NO_4}$$

In the molecule of anhydrosibiromycinone there are only two possible places to locate of the aminosugar moiety, the C-7 and C-9 phenolic OH-groups. The following series of reactions permitted us to determine the location of the glycosidic bond. When anhydrosibiromycin was treated with diazomethane no reaction occurred; however, the parent sibiromycin gave on methylation with diazomethane the biologically inactive mono-methyl ether. On catalytical reduction over palladium-charcoal sibiromycin as well as anhydrosibiromycin consumed 4 equivalents of hydrogen and both substances yielded the same product—perhydrosibiromycin, $C_{24}H_{37}N_3O_6$, λ_{max} (in methanol) 229, 260 (shoulder) and 350 nm (ε 30,000; 8,800 and 3,500). Methylation of perhydrosibiromycin with diazomethane yielded the mono-methyl ether (about 6% of OCH_3). The same product was formed on hydrogenation of the methyl ether of sibiromycin (shown by IR, UV and TLC). The transformations described can be illustrated in Scheme 1.

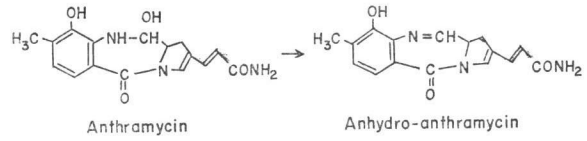
Scheme 1.



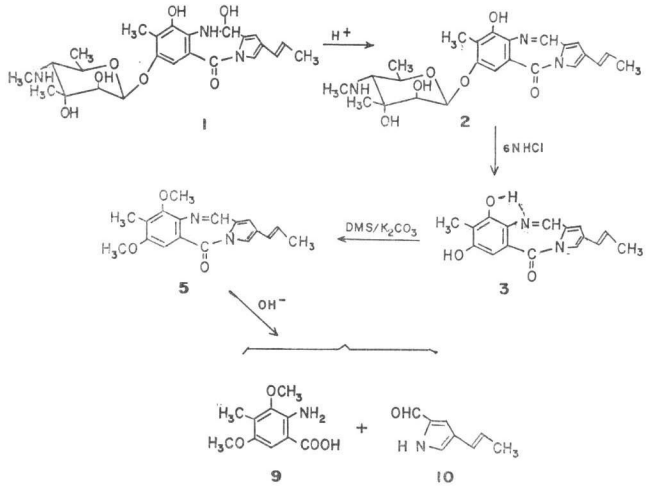
The fact that the same perhydro-O-methyl-sibiromycin is formed from sibiromycin as well as from anhydrosibiromycin showed that in both substances the same phenolic OH-group is free. Inasmuch as anhydrosibiromycin was not methylated with diazomethane it indicated that the unglycosidated phenolic hydroxy in that molecule took part in the formation of a stable hydrogen bond (ν_{max}^{KBr} 3500~3250 cm^{-1}, broad band). The phenolic OH-group located at C-9 (see formula **3**) could possess this property. This evidence permitted to assign the structure **2** to anhydrosibiromycin. It can be seen from the proposed structure that anhydrosibiromycinone **3** is similar to anhydroanthramycin, the product of dehydratation of the antibiotic anthramycin (Fig. 3)[10].

Comparison of the physicochemical properties of sibiromycin and anthramycin (the character of the ultraviolet spectra, extremely high dextrorotation in dimethylformamide solution, mutarotation in methanolic solution, the character of the ultraviolet spectra of perhydroderivatives) indicated the similarity in the structures of both antibiotics. Inspection of the PMR spectra of sibiromycin and anhydrosibiromycin showed that in the spectrum of **2** a characteristic signal appeared at δ 8.35 ppm due to the grouping —N=CH— in the diazepine-ring of the anhydrosibiromycin molecule.

Fig. 3.



Scheme 2.



From the chemical and spectral properties described above the chemical structure of sibiromycin is assigned as 7-O-[4′-methylamino-4′,6′-dideoxy-3′-C-methyl-β-D-altropyranosyl]-9, 11-dihydroxy-10,11-dihydro-8-methyl-2-(1-propenyl)-5H-pyrrolo-(2,1-c) (1,4)-benzodiazepin-5-one (**1**). The β-glycosidic attachment of the sibirosamine was evident from the laevorotation of both anhydrosibiromycin and methyl sibirosaminide (β-anomer), whereas anhydrosibiromycinone, an aglycone of anhydrosibiromycin, was optically inactive.

The basic steps of our investigation are summarized in Scheme 2 and presented in the accompanying Experimental Section.

Experimental Section

Sibiromycin (1)

The methods of isolation of sibiromycin and its properties were described previously[2,3].

O-Methyl-sibiromycin

To a solution of **1**, 3 g in 150 ml methanol, was added dropwise a solution of diazomethane (0.6 g) in 45 ml ether. The mixture was left overnight at room temperature. Removal of solvent *in vacuo* yielded an oil which was purified by column chromatography on silica gel (eluant: ethylacetate-acetone, 7:3) to give 2.5 g of pure O-methyl-sibiromycin as an amorphous yellowish powder, $[\alpha]_D$+121° (*c* 0.5, DMF); λ_{max}^{MeOH} 230 and 310 nm (ε 25,950 and 21,800).

Anal. Calcd. for $C_{25}H_{33}N_3O_7$: C 61.60; H 6.78; N 8.62; OCH_3 6.36.
Found: C 61.45: H 6.89; N 8.92; OCH_3 6.0.

Perhydrosibiromycin

A solution of 500 mg of **1** in 30 ml of carbonyl-free ethanol was hydrogenated in the

presence of 10 % palladium charcoal (300 mg) at room temperature and pressure. Absorption of H_2 ceased within 3 hours and 4 mol equivalents were consumed. Removal of the catalyst by filtration and evaporation of the solvent *in vacuo* gave 0.5 g of colorless resin. Recrystallization from methanol yielded 0.3 g perhydrosibiromycin as white needles, $C_{24}H_{37}N_3O_6$; m.p. 228~230°; λ_{max}^{MeOH} 229, 260 (shoulder) and 350 nm (ε 30,000; 8,800 and 3,500).

Anal. Found: C 62.03; H 7.81; N 8.91.

O-Methyl-perhydrosibiromycin

a. From O-methyl-sibiromycin. A solution of 300 mg of O-methyl-**1** was hydrogenated in 20 ml of ethanol over 200 mg of 10 % palladium-charcoal. The H_2-uptake corresponded to 4 mol equivalents per mol O-methyl-**1**. The catalyst was filtered off and solvent removed *in vacuo* to give an oily residue. The product was dissolved in ethyl acetate and chromatographed on silica gel (eluant: ethylacetate - acetone, 2:1). The pure O-methyl-perhydrosibiromycin was obtained as an amorphous colorless powder; λ_{max}^{MeOH} 235 and 350 nm (ε 13,900 and 2,390).

Anal. Found: C 63.12; H 8.28; N 8.47; OCH_3 6.12.

b. From perhydrosibiromycin. A solution of 200 mg of perhydrosibiromycin in 25 ml of methanol was treated with excess of diazomethane (4 % solution in ether) during 24 hours at room temperature. Removal of the solvent *in vacuo* and subsequent chromatography on silica gel afforded the homogenous O-methyl-perhydrosibiromycin obtained as an amorphous powder, λ_{max}^{MeOH} 235 and 350 nm (ε 14,000 and 2,400).

Both substances (obtained in **a** and **b**) have the same IR spectra ($\nu_{max}^{CHCl_3}$ 3400, 3060, 2980, 2950, 1625, 1450, 1380~1360, 1260, 1150, 1110, 1085 cm^{-1}) and are identical on comparison by TLC on silica gel G and on prefabricated plates "Silufol" (made in Czechoslovakia) in different solvents.

Anhydrosibiromycin (**2**)

To a solution of 10 g of **1** in 100 ml of 1-butanol 10 ml of conc. hydrochloric acid was added and the mixture was left overnight at 0~2°C. The precipitate which formed was filtered off, washed with *n*-hexane and dried over potassium hydroxide *in vacuo*. The substance was dissolved in 50 ml of methanol and a 1 N solution of ammonium hydroxide in methanol was added dropwise to pH 7.0~7.5. The yellow precipitate of anhydrosibiromycin was filtered off, washed with ether and dried. Recrystallization from 1-butanol affords 4.0~4.5 g of anhydrosibiromycin as yellow needles, m.p. 203°C (decomp.), $[\alpha]_D$ −170° (*c* 0.4, DMF), λ_{max}^{MeOH} 277, 407 and 435 nm (ε 40,000; 12,300 and 12,400).

Anal. Calcd. for $C_{24}H_{29}N_3O_6$: C 62.75; H 6.65; N 9.32.
Found: C 63.28; H 6.42; N 9.23; Mol. wt. 455 (Mass spectr.)

O-Methyl-perhydrosibiromycin from **2**

Hydrogenation of 500 mg of **2** in ethanol over 10 % palladium-charcoal (300 mg) gave about 450 mg of crystalline perhydro-**2**, m.p. 229~230°C; λ_{max}^{MeOH} 229, 260 (shoulder) and 350 nm (ε 30,200; 9,000 and 3,650). The mixture of perhydro-**2** with perhydro-**1** have m.p. 228~229°C.

Methylation of 300 mg of perhydro-**2** in methanol with excess of diazomethane gave O-methyl-perhydrosibiromycin, obtained after column chromatography on silica gel as an amorphous white powder, λ_{max}^{MeOH} 235 and 350 nm (ε 14,000 and 2,400).

Anal. Calcd. for $C_{25}H_{39}O_3O_6$: C 62.89; H 8.18; N 8.81; OCH_3 6.5.
Found: C 63.01; H 8.13; N 8.67; OCH_3 6.22.

IR spectrum and TLC of the product are identical with that of O-methyl-perhydrosibiromycin from sibiromycin.

Anhydrosibiromycinone (**3**)

A suspension of 4 g of **2** in 100 ml of 6 N hydrochloric acid was stirred and heated for 1

hour on a steam bath. The solid of **2** dissolved, then a yellow crystalline product formed. The solid was filtered, washed with mixed water - pyridine (1:1) and then with water. After drying *in vacuo* the product was recrystallized from 1-butanol to give 2 g of **3** as yellow needles, m.p. 270°C (decomp.), λ_{max}^{MeOH} 290,375,410 and 435 nm (ε 49,000; 9,900; 10,200 and 8,800).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C 68.07; H 5.00; N 9.90.
Found: C 68.25; H 5.22; N 9.75; Mol. wt. 282 (Mass spectr.)

O,O-Diacetyl-anhydrosibiromycinone (**4**)

A suspension of 500 mg of **3** in 50 ml of mixture of acetic anhydride - pyridine (1:1) was stirred at room temperature during one hour. In 20 minutes the solid dissolved and then a yellow crystalline substance formed. Filtration and recrystallization from benzene gave 500 mg of diacetate **4** as bright yellow needles, m.p. 225~226°C, $\nu_{max}^{CHCl_3}$ 1775, 1680, 1625, 1565 cm^{-1}.

Anal. Calcd. for $C_{20}H_{18}N_2O_5$: C 65.57; H 4.92; N 7.65; $COCH_3$ 23.5.
Found: C 65.19; H 4.97; N 7.98; $COCH_3$ 23.1; Mol. wt. 366 (Mass-spectr.)

O, O-Dimethylanhydrosibiromycinone (**5**)

To a boiling solution of 200 mg of **3** in 50 ml of acetone were added 500 mg of potassium carbonate and 300 mg of dimethyl sulfate in 5 portions during 48 hours. The hot reaction mixture was filtered and the solid cake was discharged. The bright yellow crystalline product which formed after cooling of the filtrate was separated and recrystallized from acetone to yield 200 mg of O,O-dimethyl-**3** (**5**), m.p. 192~193°C, δ 3.89 and 3.96 ppm. In the IR-spectrum there is no absorption at 3600~3100 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C 69.66; H 5.84; N 9.02; OCH_3 20.0.
Found: C 69.54; H 5.77; N 8.99; OCH_3 19.6; Mol. wt. 310 (Mass spectr.)

Octahydro-anhydrosibiromycinone (**6**)

A suspension of 500 mg of **3** in 25 ml of aldehyde-free acetic acid was stirred for 3 hours in the presence of 10 % palladium charcoal (250 mg) at room temperature and pressure. The H_2-uptake corresponded 4 mol equivalents per mol of **3**. The catalyst was filtered off and the solvent evaporated *in vacuo*. The residue was kept over potassium hydroxide till constant weight then dissolved in 10 ml of methanol and precipitated with ether. The yield of practically homogenous **6** was 450 mg, λ_{max}^{MeOH} 229,260 (shoulder) and 350 nm (ε 34,000; 10,000 and 4,000).

Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C 66.20; H 7.59; N 9.66.
Found: C 65.68; H 7.24; N 9.38; Mol. wt. 290 (Mass spectr.)

Triacetate of octahydro-**3** (**7**)

A solution of 200 mg of **6** in 10 ml of mixture of acetic anhydride - pyridine (1:1) was kept at room temperature for 48 hours. The solvent was removed *in vacuo* and residue was chromatographed on silica gel (eluant: *n*-hexane - ethylacetate, 1:1). The pure **7** was recrystallized from the mixture ether - *n*-hexane (1:5). Yield 150 mg, white needles, m.p. 131~133°C, $\nu_{max}^{CHCl_3}$ 1775, 1680~1660, 1580, 1210 cm^{-1}.

Anal. Calcd. for $C_{22}H_{28}N_2O_6$: C 63.46; H 6.73; N 6.73; $COCH_3$ 31.0.
Found: C 63.35; H 6.83; N 6.39; $COCH_3$ 30.8; Mol. wt. 416 (Mass spectr.)

N-Acetyl-O,O-dimethyl-**6** (**8**)

To a suspension of 100 mg of **6** in 10 ml of methanol the excess of 4 % solution of diazomethane in ether was added and the mixture was left for 20 hours at room temperature. The solvent was removed *in vacuo*, the residual oil was acetylated in 5 ml of mixture acetic anhydride - pyridine (1:1) during 20 hours at room temperature. The solvent was evaporated

under reduced pressure, the residue was chromatographed on silica gel (eluant: *n*-hexane-ethylacetate, 2:1). Recrystallization from the mixture ether - hexane affords 80 mg of white needles m.p. 161~163°C.

Anal. Calcd. for $C_{20}H_{28}N_2O_4$: C 66.66; H 7.78; N 7.78; OCH_3 17.2; $COCH_3$ 11.9.
Found: C 66.12; H 7.33; N 7.86; OCH_3 16.6; $COCH_3$ 10.9; Mol. wt. 360 (Mass spectr.)

Alkaline hydrolysis of O,O-dimethylanhydrosibiromycinone

A suspension of 500 mg of dimethylanhydrosibiromycinone (**5**) in a mixture of 20 ml of 0.15 N sodium hydroxide and 10 ml of methanol was heated for 20 minutes on a steam bath. The resulting colorless solution was cooled, methanol was removed *in vacuo* and the solid formed was filtered and dried over phosphorus pentoxide to give about 100 mg of crude formyl-pyrrole **10**. Recrystallization from *n*-hexane yielded colorless fine needles, m.p. 115~116°, λ_{max}^{MeOH} 242, 250 (shoulder) and 325 nm (ε 19,000; 15,000 and 9,800).

Anal. Calcd. for C_8H_9NO: C 71.09; H 6.75; N 10.35.
Found: C 71.08; H 6.55; N 10.50; Mol. wt. 135 (Mass spectr.)

The filtrate after separation of the formyl-pyrrole was acidified with 2 N hydrochloric acid to pH 5.0. The resulting white crystalline product was filtered and dried over phosphorus pentoxide. Recrystallization from *n*-hexane yielded 100 mg of 3,5-dimethoxy-4-methylanthranilic acid, m.p. 178°C, λ_{max}^{MeOH} 250 and 350 nm (ε 7,400 and 5,000); $\lambda_{max}^{0.1NHCl}$ 250 and 298 nm; $\lambda_{max}^{0.1NNaOH}$ 245 and 335 nm; ν_{max}^{KBr} 3490, 3390, 3100~2600, 1680, 1590, 1560 cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}NO_4$: C 56.86; H 6.20; N 6.62.
Found: C 56.74; H 6.14: N 6.51; Mol. wt. 211 (Mass spectr.)

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