

Reaction of Rifamycins with Sodium Sulfinates¹⁾Masahiro TAGUCHI,* Norio AIKAWA, Kenzaburo YOSHIDA, Mikiya KITAMURA,
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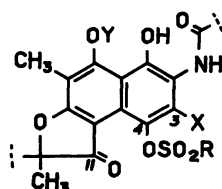
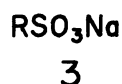
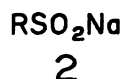
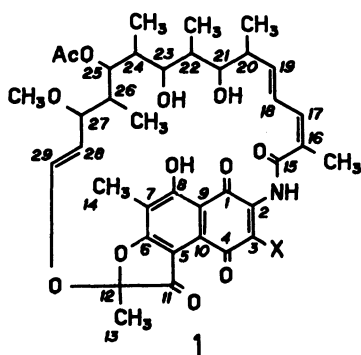
The reaction of rifamycin S and the quinonic 3-(hydrazonomethyl)rifamycin derivatives with sodium sulfinates under neutral conditions were found to afford the hydroquinone-type 4-*O*-sulfonyl derivatives of rifamycin. 3-Amino-4-deoxy-4-iminorifamycin S also gave rise to the hydroquinone-type 4-deoxy-4-sulfonylamino derivatives of rifamycin when treated with sodium sulfinates. Under acidic conditions, rifamycin S and 3-bromorifamycin S produced the hydroquinone- and quinone-type 3-sulfonyl derivatives of rifamycin, respectively, by reactions with sodium sulfinates. Some of sodium salts of 4-*O*-sulfonylrifamycin SV derivatives afforded rifamycin S and sodium sulfinates and/or sodium sulfonates when heated in AcOEt.

We have recently reported on the reaction of rifamycin S (**1A**) with sodium sulfite.²⁾ In connection with this work, we investigated the reaction of **1A** with sodium *p*-toluenesulfinate (**2a**), which is anticipated to formally resemble sodium sulfite, and found the unusual formation of sulfonic ester sodium salt **4Aa** under neutral conditions. This paper describes the reaction of **1A** with **2a** under various conditions (alkaline, neutral, or acidic), the formation of sulfonic

ester sodium salts **4**, sulfonic esters **5** and sulfonamides **9**, and the decomposition of some of **4A** in AcOEt.

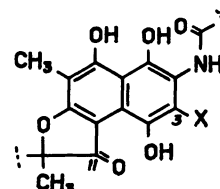
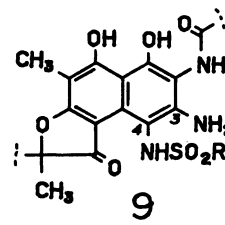
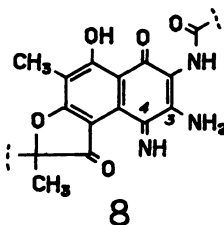
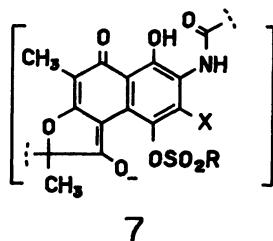
Results and Discussion

Reaction of 1A with 2a. We have reported that the reaction of **1A** with sodium sulfite under mild alkaline conditions gives the 3-substituted product, sodium rifamycin SV-3-sulfonate.²⁾ In connection with this



4: Y = Na

5: Y = H

**6**

A : X = H

B : X = Br

C : X = -CH=NN(CH₃)₂

D : X = -CH=NN

E : X = -CH=NN

F : X = -SO₂-C₆H₄-CH₃G : X = -SO₂-C₆H₄H : X = -SO₂CH₃a : R = -C₆H₄-CH₃b : R = -C₆H₄c : R = -C₆H₄-Acd : R = -C₆H₄-Cle : R = -C₆H₄-OHf : R = -C₆H₄-OCH₃g : R = -C₆H₄-NO₂h : R = -C₆H₄-N(CH₃)₂i : R = CH₃j : R = n-C₄H₉k : R = iso-C₄H₉l : R = cyclo-C₅H₉m : R = n-C₈H₁₇n : R = n-C₁₂H₂₅

observation, **1A** was allowed to react with **2a** in an aq NaHCO_3 -DMSO mixture (mild alkaline conditions). As a result, no products formed. However, in the absence of NaHCO_3 (neutral conditions) the reaction proceeded smoothly and almost quantitatively to produce a compound which fluoresced an orange color on a silica-gel TLC plate under an UV lamp (365 nm).³⁾ The reaction solution was poured into aq NaCl , and the extraction with AcOEt gave the sulfonic ester sodium salt **4Aa** in 85% yield. Sodium salt **4Aa** was converted to the corresponding acid form **5Aa** by acidification. The 4-*O*-sulfonyl structure of **5Aa** was deduced as follows. The UV spectrum (Table 2, footnote d) of **5Aa** resembling that⁴⁾ of rifamycin SV (**6A**), confirmed the 1,4-naphthalenediol derivative structure for **5Aa**; the NMR spectrum (CDCl_3) showed the signal at δ 7.42, which unfortunately overlapped with the signals of the *p*-tolyl group, but was attributed to the proton at the 3-position; the IR spectrum (KBr) showed the characteristic band of sulfonic ester at 1176 cm^{-1} (ν_{SO_2}). These spectral data suggested the 4-*O*-sulfonyl structure for **5Aa**, but the 1-*O*-sulfonyl structure is also possible. In order to distinguish these two possible structures, the 25-*O*-deacetyl derivative of **5Aa** was prepared from 25-*O*-deacetyl rifamycin S⁵⁾ and **2a**. The IR spectrum (CDCl_3) of the 25-*O*-deacetyl derivative of **5Aa** clearly showed the furanone $\nu\text{C}(11)=\text{O}$ band at 1709 cm^{-1} without disturbance of the 25-*O*-acetyl $\nu\text{C}=\text{O}$ band.⁶⁾ This observation confirms the 4-*O*-sulfonyl structure for **5Aa**, because if

5Aa takes the 1-*O*-sulfonyl structure the furanone $\nu\text{C}(11)=\text{O}$ band should appear at ca. 1650 cm^{-1} due to the intramolecular hydrogen-bonding between the furanone $\text{C}(11)=\text{O}$ group and the 4-OH group.⁷⁾ The furanone $\nu\text{C}(11)=\text{O}$ band of the 25-*O*-deacetyl derivative of sodium salt **4Aa** in CDCl_3 appeared at 1675 cm^{-1} . A decrease of $\nu\text{C}(11)=\text{O}$ in the salt form should be accounted for by the contribution of structure **7Aa**.

The formation mechanism of sulfonic ester is not clear, but the oxidation potential of **1A** seems to play an important role, because rifamycinol⁵⁾ (the 11-deoxo-11-hydroxy derivative of **1A**) did not react with **2a** under the same conditions as that described above.⁸⁾

The reaction of **1A** with **2a** in aq AcOH (acidic conditions) produced 3-(*p*-tolylsulfonyl)rifamycin SV (**6F**) as a main product (9% yield) along with many complex products in which a trace amount of **5Aa** could be detected (analytical TLC). The IR spectrum (CDCl_3) of **6F** showed the characteristic bands of sulfone at 1292 (ν_{asSO_2}) and 1137 cm^{-1} (ν_{sSO_2}), and the singlet at δ 7.82 due to the proton at the 3-position of **1A** was absent in the NMR spectrum (CDCl_3).

Formation of Sulfonic Ester Sodium Salts 4A and Their Acid Form 5A, and Decomposition of Some of 4A in AcOEt. Similarly to **2a**, various sodium sulfinates were also found to react with **1A** under neutral conditions to afford sulfonic ester sodium salts **4A**, which upon acidification produced **5A**. The results are summarized in Tables 1 and 2. All sulfonic esters, except for **5Ac** and **5Ag**, fluoresced similarly to

Table 1. Sulfonic Ester Sodium Salts **4A**

Compound ^{a)}	Yield/%	$\nu_{\text{SO}_2}/\text{cm}^{-1}$ (KBr)	Formula	Analysis ^{b)}
4Aa	85	1176	$\text{C}_{44}\text{H}_{52}\text{NNaO}_{14}\text{S} \cdot 2\text{H}_2\text{O}$	C, H, N
4Ab	76	1188	$\text{C}_{43}\text{H}_{50}\text{NNaO}_{14}\text{S} \cdot \text{H}_2\text{O}$	C, H, N
4Ac	87	1190	$\text{C}_{45}\text{H}_{52}\text{NNaO}_{15}\text{S} \cdot 2\text{H}_2\text{O}$	C, H, N
4Ad	77	1186	$\text{C}_{43}\text{H}_{49}\text{ClNNaO}_{14}\text{S}$	C, H, N
4Ae	62	1166	$\text{C}_{43}\text{H}_{50}\text{NNaO}_{15}\text{S} \cdot 3\text{H}_2\text{O}$	C, H, N
4Af	80	1169	$\text{C}_{44}\text{H}_{52}\text{NNaO}_{15}\text{S} \cdot \text{H}_2\text{O}$	C, H, N
4Ag	76	1185	$\text{C}_{43}\text{H}_{49}\text{N}_2\text{NaO}_{16}\text{S} \cdot 3/2\text{H}_2\text{O}$	C, H, N
4Aj	85	1168	$\text{C}_{41}\text{H}_{54}\text{NNaO}_{14}\text{S} \cdot 3/2\text{H}_2\text{O}$	C, H, N

a) The melting points could not be specified due to gradual decomposition during heating. b) The values were within $\pm 0.3\%$ of the calculated theoretical values.

Table 2. Sulfonic Esters **5A**

Compound ^{a)}	Procedure ^{b)}	Yield/%	$\nu_{\text{SO}_2}/\text{cm}^{-1}$ (KBr)	Formula	Analysis ^{c)}
5Aa ^{d)}	A	84	1176	$\text{C}_{44}\text{H}_{53}\text{NO}_{14}\text{S} \cdot 1/2\text{H}_2\text{O}$	C, H, N
5Ab	B	32	1192	$\text{C}_{43}\text{H}_{51}\text{NO}_{14}\text{S} \cdot 3/2\text{H}_2\text{O}$	C, H, N, S
5Ac	A	91	1193	$\text{C}_{45}\text{H}_{53}\text{NO}_{15}\text{S} \cdot 3/2\text{H}_2\text{O}$	C, H, N
5Ad	C	31	1192	$\text{C}_{43}\text{H}_{50}\text{ClNO}_{14}\text{S} \cdot \text{H}_2\text{O}$	C, H, N, S
5Ae	C	16	1166	$\text{C}_{43}\text{H}_{51}\text{NO}_{15}\text{S} \cdot \text{H}_2\text{O}$	C, H, N, S
5Af	A	75	1169	$\text{C}_{44}\text{H}_{53}\text{NO}_{15}\text{S} \cdot 3/2\text{H}_2\text{O}$	C, H, N
5Ag	A	84	1192	$\text{C}_{43}\text{H}_{50}\text{N}_2\text{O}_{16}\text{S} \cdot 3/2\text{H}_2\text{O}$	C, H, N
5Aj	A	92	1166	$\text{C}_{41}\text{H}_{55}\text{NO}_{14}\text{S} \cdot 3/2\text{H}_2\text{O}$	C, H, N

a) The melting points could not be specified due to gradual decomposition during heating. b) See Experimental.

c) The values were within $\pm 0.3\%$ of the calculated theoretical values. d) UV λ_{max} (pH 7.0 phosphate buffer) 226 (log ϵ 4.65), 296 (4.28), and 414 nm (4.24).

5Aa. The formations of **4A** proceeded very cleanly, but **4A** and **5A** were proved to decompose during work up. Accordingly, the decomposition of some of **4A** in AcOEt, which was used as an extraction solvent, was next investigated. The sodium salts **4Aa**, **4Ac**, **4Ad**, and **4Af** were heated at 70 °C in a solution of AcOEt for several hours. As a result, each salt decomposed to afford **1A** as a main product and many complex compounds along with the formation of precipitates. The precipitate from **4Ac** was found to be sodium *p*-acetylbenzenesulfonate (**2c**) by a comparison of the NMR spectra (D₂O) with that of the authentic sample. The identification was also confirmed by the reaction of **1A** with the precipitate to afford the compound identical with **4Ac** (analytical TLC). The IR spectra (KBr) of the precipitates from **4Aa** and **4Af** showed the sulfonate ν_{SO_2} bands at 1200 and 1190 cm⁻¹, respectively; these precipitates were confirmed to be sodium *p*-toluenesulfonate (**3a**) and sodium *p*-methoxybenzenesulfonate (**3f**), respectively, by comparing the NMR spectra (D₂O) with those of the authentic samples. The IR spectrum (KBr) of the precipitate from **4Ad** showed the sulfonate ν_{SO_2} band at 1200 cm⁻¹, while its NMR spectrum (D₂O) showed that it consisted of two sorts of the compounds, sodium *p*-chlorobenzenesulfonate (**2d**) and sodium *p*-chlorobenzenesulfonate (**3d**) (molar ratio, 1:ca. 2). The results are summarized in Table 3. It is of interest that the decomposition reactions of sodium salts **4Aa**, **4Ac**, **4Ad**, and **4Af** in AcOEt commonly afforded **1A**,

while the oxidation states of the precipitates were different depending upon the nature of the substituent involved in the phenylsulfonyl group. The mechanism of decomposition is not clear. Heating of **5Aa** in AcOEt at 70 °C for 4 h resulted in the decomposition of **5Aa** into many complex compounds in which **1A** could not be detected (analytical TLC).

Formation of Sulfones 6G and 6H. Sodium benzenesulfonate (**2b**) was allowed to react with **1A** in aq AcOH to afford 3-(phenylsulfonyl)rifamycin SV (**6G**) in 5% yield. On the other hand, it was observed by TLC analysis that the 1,4-naphthoquinone derivative **1G** could be produced in good yield by the reaction of 3-bromorifamycin S⁹ (**1B**) with **2b** in aq AcOH. Indeed, 3-(methylsulfonyl)rifamycin SV (**6H**) was obtained in 63% yield by the reaction of **1B** with sodium methanesulfonate (**2i**) in aq AcOH followed by reduction with L-ascorbic acid.

Formation of Sulfonic Esters 5C—E. The reactions of the 3-(hydrazonomethyl)rifamycin derivatives **1C—E** with some of **2** under neutral conditions followed by acidification, afforded the corresponding sulfonic esters **5C—E**. The sulfonic ester structures of **5C—E** were supported by the characteristic ν_{SO_2} bands of the sulfonic esters. The results are summarized in Table 4.

Formation of Sulfonamides 9. When 3-amino-4-deoxy-4-iminorifamycin S¹⁰ (**8**) were treated with some of **2** under neutral conditions, the reaction proceeded almost quantitatively to afford sulfona-

Table 3. Decomposition of Sulfonic Ester Sodium Salts **4Aa**, **4Ac**, **4Ad**, and **4Af** in AcOEt at 70 °C

Compound	Time/h	Isolation yield/% of 1A	Identification of the precipitate (Yield/%)
4Aa	5.75	46	3a (ca. 71)
4Ac	4.75	70	2c (ca. 80)
4Ad	4	49	2d and 3d (ca. 98) ^a
4Af	6.25	37	3f (ca. 67)

a) The molar ratio of **2d** to **3d** was 1:ca. 2 (determined by the NMR spectrum in D₂O on the basis of integration of the signals of aromatic protons).

Table 4. Sulfonic Esters **5C—E**

Compound ^a	Yield/%	ν_{SO_2} /cm ⁻¹ (KBr)	Formula	Analysis ^b
5Ce	52	1166	C ₄₆ H ₅₇ N ₃ O ₁₅ S·H ₂ O	C, H, N, S
5Cf	51	1169	C ₄₇ H ₅₉ N ₃ O ₁₅ S	C, H, N, S
5Ch	41	1167	C ₄₈ H ₆₂ N ₄ O ₁₄ S	C, H, N, S
5Cj	33	1167	C ₄₄ H ₆₁ N ₃ O ₁₄ S·1/2H ₂ O	C, H, N, S
5Cl	45	1164	C ₄₅ H ₆₁ N ₃ O ₁₄ S	C, H, N, S
5Cn	24	1163	C ₅₂ H ₇₇ N ₃ O ₁₄ S	C, H, N, S
5Dj	41	1164	C ₄₆ H ₆₃ N ₃ O ₁₄ S	C, H, N, S
5Dk	41	1161	C ₄₆ H ₆₃ N ₃ O ₁₄ S	C, H, N, S
5Dm	31	1165	C ₅₀ H ₇₁ N ₃ O ₁₄ S	C, H, N, S
5Dn	29	1163	C ₅₄ H ₇₉ N ₃ O ₁₄ S	C, H, N, S
5Ej	51	1164	C ₄₇ H ₆₅ N ₃ O ₁₄ S·1/2H ₂ O	C, H, N

a) The melting points could not be specified due to gradual decomposition during heating. b) The values were within ±0.3% of the calculated theoretical values.

Table 5. Sulfonamides **9**

Compound ^{a)}	Yield/%	$\nu_{\text{SO}_2}/\text{cm}^{-1}$ (CHCl ₃)	Formula	Analysis ^{b)}
9d	67	1162	C ₄₃ H ₅₂ ClN ₃ O ₁₃ S·H ₂ O	C, H, N, S
9g	66	1168	C ₄₃ H ₅₂ N ₄ O ₁₅ S	C, H, N, S
9h	70	1152	C ₄₅ H ₅₈ N ₄ O ₁₃ S·H ₂ O	C, H, N, S
9j	69	1148	C ₄₁ H ₅₇ N ₃ O ₁₃ S·1/2H ₂ O	C, H, N, S
9k	62	1148	C ₄₁ H ₅₇ N ₃ O ₁₃ S·H ₂ O	C, H, N, S
9l	74	1145	C ₄₂ H ₅₇ N ₃ O ₁₃ S·H ₂ O	C, H, N, S

a) The melting points could not be specified due to gradual decomposition during heating. b) The values were within $\pm 0.3\%$ of the calculated theoretical values.

mides **9** after acidification. The sulfonamide structures of **9** were supported by the characteristic ν_{SO_2} bands of the sulfonamides. The results are summarized in Table 5. All sulfonamides in Table 5, except for **9g**, fluoresced similarly to **5Aa**.

Conclusion

Quinone- and quinone imine-type derivatives of rifamycin were found to react with sodium sulfinates under neutral conditions, giving the sulfonic esters and the sulfonamides, respectively. To our knowledge, only limited numbers of reports are concerned with the formation of sulfonic esters and sulfonamides in the reactions of quinonic or quinoniminic compounds with sulfinic acids or their salts.¹³⁾ Novel examples of such reactions are provided as described above.

Experimental

Analytical TLC was performed on Silica gel 60 F₂₅₄ pre-coated plates (0.25 mm, Merck), using CHCl₃–CH₃OH (10:1 or 4:1) as a developing solvent. Preparative TLC was performed on Silica gel 60 F₂₅₄ pre-coated plates (2 mm, Merck). IR spectra were measured on a JASCO IRA-1, a Shimadzu IR-440 spectrometer, or a Hitachi 270-50 infrared spectrometer. UV spectra were taken with a Shimadzu UV-210 spectrometer. Measurements of NMR spectra were carried out using a JEOL PS-100, a Hitachi R-24A spectrometer, or a Hitachi R-24B spectrometer. Tetramethylsilane was used as an internal reference for a solution of CDCl₃. NMR spectra of sodium sulfinates or sodium sulfonates were recorded in a solution of D₂O without an internal reference. Elemental analyses were performed with a Yanagimoto CHN-CORDER MT-3 or at the Elemental Analysis Center of Kyoto University.

Rifamycin Derivatives 1C–E. These compounds were prepared by oxidation of compounds¹²⁾ **6C–E** in CHCl₃ with MnO₂ (70%, Wako Pure Chemical Ind., Ltd.) followed by washing with dil H₂SO₄.

Sodium Sulfinates 2a–n and Sodium Sulfonates 3a, 3d, and 3f. Compounds **2a**, **2b**, **3a**, and **3d** were purchased. Compounds **2d**,^{13a)} **2g**,^{13b)} **2i**,^{14b)} **2j**,^{14b)} and **2k–n**¹⁵⁾ were prepared by the methods reported. Compounds **2c** and **2f** were prepared as **2d** from the corresponding sulfonyl chloride.^{14a,16)} Compound **2e** was prepared as **2g** from *p*-hydroxybenzenesulfonyl chloride.¹⁷⁾ Compound **2h** was prepared¹⁸⁾ from the corresponding sulfonyl chloride.^{13c,d)}

Compound **3f** was prepared by hydrolysis of *p*-methoxybenzenesulfonyl chloride with NaHCO₃.

Preparation of Sulfonic Ester Sodium Salts in Table 1 and the 25-O-Deacetyl Derivative of 4Aa. General Procedure: A solution of an excess amount of **2** in H₂O was added to a solution of **1A** in DMSO. After being stirred for several hours, the reaction mixture was poured into aq NaCl, and extracted with AcOEt. The combined extracts were washed with aq NaCl, dried over Na₂SO₄, then evaporated in vacuo. The resulting residue was precipitated from AcOEt–hexane, AcOEt–benzene, or AcOEt–benzene–hexane to afford **4A**, tabulated in Table 1. As a typical run, the preparation of **4Aa** is described below.

A solution of **2a** (2.16 g, 12 mmol) in H₂O (10 ml) was added to a solution of **1A** (2.00 g, 2.9 mmol) in DMSO (50 ml). After being stirred at r.t. for 3 h, the reaction mixture was treated according to the general procedure to afford 2.24 g (85% yield) of **4Aa** as a dark yellow powder after precipitation from AcOEt–benzene–hexane.

The 25-O-deacetyl derivative of **4Aa** was obtained from 25-O-deacetyl rifamycin S⁹⁾ and **2a** in 82% yield. The 25-O-deacetyl derivative of **4Aa**: IR (KBr) 1175 cm^{−1} (ν_{SO_2}). IR (CDCl₃) 1675 cm^{−1} ($\nu_{\text{C(11)=O}}$). Anal. (C₄₂H₅₀NNaO₁₃S·1/2H₂O) C, H, N.

Preparation of Sulfonic Esters 5Aa, 5Ac, 5Af, 5Ag, 5Aj and the 25-O-Deacetyl Derivative of 5Aa (Procedure A). General Procedure: A sodium salt **4A** was dissolved in AcOEt, then aq NaCl acidified with H₂SO₄ (acidic aq NaCl) was added to the solution. The mixture was shaken, and the organic layer was separated, washed with aq NaCl, dried over Na₂SO₄ or MgSO₄, and evaporated in vacuo. The resulting residue was precipitated from AcOEt–hexane or AcOEt–benzene–hexane to afford the title compounds. As a typical run, the preparation of **5Aa** is described below.

A solution of 1.13 g of **4Aa** in 80 ml of AcOEt was treated according to the general procedure, and the resulting residue was precipitated from AcOEt–hexane to afford 0.91 g (85% yield) of **5Aa** as a yellow powder. **5Aa**: ¹H NMR (CDCl₃) δ =2.33 (3H, s, the methyl protons of the *p*-tolylsulfonyl group), 7.04 (2H, d, the aromatic protons of the *p*-tolylsulfonyl group), 7.34–7.52 (3H, signals due to the aromatic protons of the *p*-tolylsulfonyl group and the proton at the 3-position).

The 25-O-deacetyl derivative of **5Aa** was obtained from the 25-O-deacetyl derivative of **4Aa** in 83% yield. The 25-O-deacetyl derivative of **5Aa**: IR (KBr) 1176 cm^{−1} (ν_{SO_2}). IR (CDCl₃) 1709 cm^{−1} ($\nu_{\text{C(11)=O}}$). Anal. (C₄₂H₅₁NO₁₃S·H₂O) C, H, N.

Preparation of Sulfonic Ester 5Ab (Procedure B). A solution of **2b** (0.19 g, 1.2 mmol) in H₂O (1 ml) was added to

a solution of **1A** (0.20 g, 0.29 mmol) in DMSO (8 ml). After being stirred overnight at r.t., the reaction mixture was poured into acidic aq NaCl. The resulting precipitate was collected, washed with acidic aq NaCl, and dissolved in AcOEt. The ethyl acetate solution was washed with aq NaCl, dried over MgSO₄, then evaporated in vacuo. The resulting residue was precipitated from AcOEt–benzene–hexane to afford 0.08 g (32% yield) of **5Ab** as a dark yellow powder.

Preparation of Sulfonic Esters 5Ad and 5Ae (Procedure C). As a typical run, the preparation of **5Ad** is described below.

A solution of **2d** (0.27 g, 1.4 mmol) in H₂O (1.5 ml) was added to a solution of **1A** (0.20 g, 0.29 mmol) in DMSO (7 ml). After being stirred overnight at r.t., the reaction mixture was treated by the same procedure as that described for **5Ab**. The resulting residue was separated on preparative TLC plates (4:1 CHCl₃–CH₃OH). The yellow band was collected and extracted with CH₃OH. AcOEt was added to the methanolic extract. The ethyl acetate solution was washed successively with acidic aq NaCl and aq NaCl, dried over MgSO₄, and evaporated in vacuo. The resulting residue was precipitated from AcOEt–hexane to afford 0.08 g (31% yield) of **5Ad** as a pale-yellow powder.

Compound **5Ae** was obtained from **1A** and **2e** in 16% yield.

Preparation of 3-Sulfonylrifamycin Derivatives 6F and 6G. As a typical run, the preparation of **6F** is described below.

A solution of **2a** (2.5 g, 14 mmol) in H₂O (20 ml) was added to a solution of **1A** (0.70 g, 1.0 mmol) in AcOH (30 ml). After being stirred at r.t. for 12 h, the reaction mixture was poured into H₂O. The resulting precipitate was collected, washed with H₂O, and dissolved in AcOEt. The ethyl acetate solution was washed with aq NaCl, dried over Na₂SO₄, and evaporated in vacuo. The resulting residue was separated on preparative TLC plates (two developments with 200:20:1 CHCl₃–EtOH–AcOH). The orange band was collected and extracted with CH₃OH. The methanolic solution was diluted with AcOEt, and the organic mixture was washed successively with acidic aq NaCl and aq NaCl, dried over Na₂SO₄, and evaporated in vacuo. The resulting residue was recrystallized from acetone to afford 0.08 g (9% yield) of **6F** as orange crystals. Mp ca. 180 °C (decomp). IR (CDCl₃) 1292 ($\nu_{\text{as}}\text{SO}_2$) and 1137 cm⁻¹ ($\nu_{\text{s}}\text{SO}_2$). ¹H NMR (CDCl₃) δ =2.41 (3H, s, the methyl protons of the *p*-tolylsulfonyl group), 7.28 (2H, d, the aromatic protons of the *p*-tolylsulfonyl group), 7.88 (2H, d, the aromatic protons of the *p*-tolylsulfonyl group). Anal. (C₄₄H₅₃NO₁₄S·1/2H₂O) C, H, N.

Physical data of **6G** are as follows. Mp ca. 174 °C (decomp). IR (CDCl₃) 1295 ($\nu_{\text{as}}\text{SO}_2$) and 1140 cm⁻¹ ($\nu_{\text{s}}\text{SO}_2$). ¹H NMR (CDCl₃) δ =7.3–7.7 (3H, m, the aromatic protons of the phenylsulfonyl group), 7.9–8.1 (2H, d, the aromatic protons of the phenylsulfonyl group). Anal. (C₄₃H₅₁NO₁₄S·H₂O) C, H, N.

Preparation of 3-(Methylsulfonyl)rifamycin SV (6H). A solution of **2i** (0.47 g, 4.6 mmol) in H₂O (1 ml) was added to a solution of 3-bromorifamycin S⁹ (**1B**) (0.50 g, 0.65 mmol) in AcOH (6 ml). After being stirred at r.t. for 40 min, the reaction mixture was poured into H₂O. The resulting precipitate was collected, washed with H₂O, and dissolved in AcOEt. The ethyl acetate solution was added to a

solution of 2.5 g of L-ascorbic acid in aq CH₃OH. The mixture was shaken for several min, washed with aq NaCl, dried over MgSO₄, and evaporated in vacuo. The resulting residue was purified by preparative TLC in a similar manner to that described for **6F**, affording 0.32 g (63% yield) of **6H** as an orange powder after precipitation from AcOEt–ligroine. Mp ca. 204 °C (decomp). IR (CDCl₃) 1290 ($\nu_{\text{as}}\text{SO}_2$) and 1125 cm⁻¹ ($\nu_{\text{s}}\text{SO}_2$). ¹H NMR (CDCl₃) δ =3.50 (3H, s, the methyl protons of the methylsulfonyl group). Anal. (C₃₈H₄₉NO₁₄S) C, H, N.

Decomposition of Sulfonic Ester Sodium Salts 4Aa, 4Ac, 4Ad, and 4Af in AcOEt. As a typical run, the decomposition of **4Aa** is described below.

A 300 mg of **4Aa** was dissolved in 20 ml of AcOEt. After being stirred at 70 °C for 5.75 h, the resulting precipitate was collected by filtration and washed with AcOEt, affording 46 mg of a brownish powder. IR (KBr) 1200 cm⁻¹. The NMR spectrum in D₂O was identical with that of the authentic sample of **3a**. The filtrate and the washings were combined and evaporated in vacuo. The resulting residue was separated by a preparative TLC plate (10:1 CHCl₃–CH₃OH). The yellow band was collected and extracted with CH₃OH. The methanolic solution was diluted with AcOEt, and the organic mixture was washed successively with a mixture of a pH 4 buffer and aq NaCl and aq NaCl, dried over MgSO₄, and evaporated in vacuo. The resulting residue was crystallized from *i*-C₃H₇OH to afford 116 mg of yellow crystals. The IR spectrum in CHCl₃ was identical with that of **1A**.

Preparation of Sulfonic Esters in Table 4. These compounds were prepared from 3-(hydrazonomethyl)rifamycin derivatives **1C–E** and **2** by a similar procedure to that described for **5Ad**. As developing solvents for preparative TLC, AcOEt–CH₃OH (60:1–20:1) or CHCl₃–CH₃OH (10:1) was used. AcOEt–hexane or AcOEt–ligroine was used as a crystallizing solvent.

Preparation of Sulfonamides in Table 5. General Procedure: A solution of an excess amount of **2** in H₂O was added to a solution of 3-amino-4-deoxy-4-iminorifamycin S¹⁰ (**8**) in DMSO. After being stirred at r.t. for several min, the reaction mixture was poured into aq NaCl and extracted with CHCl₃. The chloroform extracts were combined and reextracted with H₂O. The aqueous layers were extracted again with CHCl₃ under acidic conditions which were made by addition of dil H₂SO₄. The combined extracts were washed with aq NaCl, dried over Na₂SO₄, and evaporated in vacuo. The resulting residue was precipitated from CHCl₃–hexane to afford a sulfonamide **9** in Table 5. As a typical run, the preparation of **9h** is described below.

A solution of **2h** (0.13 g, 0.59 mmol) in H₂O (0.4 ml) was added to a solution of **8** (0.14 g, 0.20 mmol) in DMSO (2.4 ml). After being stirred at r.t. for 5 min, the reaction mixture was treated according to the general procedure, affording 0.13 g (70% yield) of sulfonamide **9h** as a yellow powder.

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