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Reaction of 3-Formylrifamycin S with Secondary Amines[1)]

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3-Formylrifamycin S (**9**) was found to react with secondary aliphatic amines to give 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives **4**, in which the 2′-position was substituted with an alkyl group. When 7-, 8-, and 9-membered alicyclic amines were used, 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives **5**, in which the 1′- and 2′-position were linked with a methylene chain, were obtained. The configuration of the 2′-position in **4** and **5** is discussed. The mechanism of formation of **4** and **5** is also discussed.

Keywords——rifamycin; secondary amine; pseudo base; configuration; UV

We have already reported the formation of 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives **1** from rifamycin S (**2**) or 3-formylrifamycin SV (**3**).[2)] This paper describes the formation of 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives **4** and **5**; in the former, the 2′-position is substituted with an alkyl group, and in the latter the 1′- and 2′-position are linked with a methylene chain. Moreover, the configuration of the 2′-position in **4** and **5** is discussed.

Maggi *et al.* reported that in the synthesis of 3-formylrifamycin SV (**3**) by the disproportionation of a manganese salt of 3-(diethylamino)methylrifamycin S (**6**), the 2,3-dihydropyrimido[4,5-*b*]rifamycin derivative **4a** was obtained as a deep-blue by-product.[3,4)] They considered an iminium salt **7** as a probable intermediate in the formation of **3** from the manganese salt of **6**.[3a)] However, no information is available on the mechanism of formation of the deep-blue by-product **4a** or on the configuration of the 2′-position in **4a**.

We considered that the iminium salt **7** might also be the intermediate of **4a** formation *via* **8**. Thus, the 2,3-dihydropyrimido[4,5-*b*]rifamycin derivative **4a** should be generated from the reaction of 3-formylrifamycin S (**9**) with diethylamine *via* the iminium salt **7** (X=OH).

After oxidation of **3** with MnO_2 in AcOEt followed by the removal of an excess amount of MnO_2 by filtration, diethylamine was added to the filtrate.[5)] The reaction proceeded rapidly to give **4a** in 15% yield. In a similar manner, the 25-*O*-desacetyl derivative of **4a** was obtained from the 25-*O*-desacetyl derivative of **3** and diethylamine in 17% yield. The ultraviolet (UV) spectrum (pH 7.0 phosphate buffer) and the nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) of the 25-*O*-desacetyl derivative of **4a** were in good agreement with the data reported by Maggi *et al.*[3b,c)] Compound **4b** was obtained in 62% yield from **3** and dibutylamine. In the formation of **4**, only one of the two epimers based on the asymmetric center of the 2′-position was obtained. The configuration of the 2′-position in **4** will be discussed later.

When cyclic amines (hexamethyleneimine, heptamethyleneimine, and octamethyleneimine) were used instead of acyclic amines, the two epimers of 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives **5** based on the asymmetric center of the 2′-position were obtained. The dihydropyrimido structure of **5** is supported by the close resemblance of the UV spectra to those of **4**. When pyrrolidine was allowed to react, the formation of a deep-blue compound was detected on analytical thin-layer chromatography (TLC), but this product was too unstable to be isolated. In the case of the 6-membered cyclic amines (piperidine, morpholine,

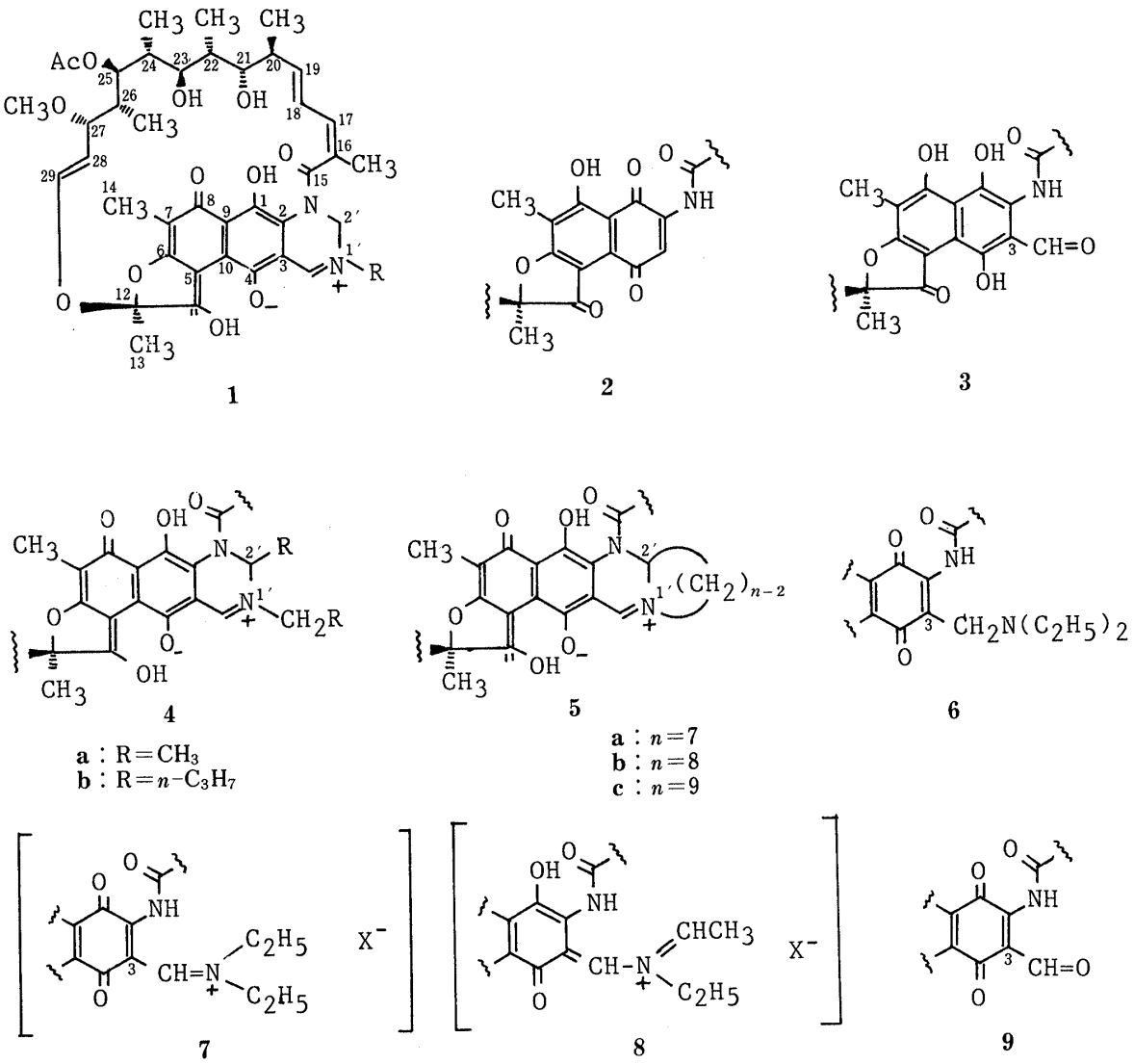
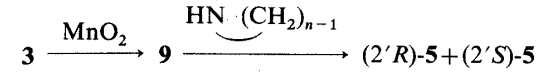


Chart 1

TABLE I. The Formation of 2,3-Dihydropyrimido[4,5-*b*]rifamycin Derivatives **5**



Cyclic amine	Yield (%)	
	(2′*R*)-**5**	(2′*S*)-**5**
n=7	17	6
n=8	42	4
n=9	3	42
n=5	Too unstable to be isolated	
n=6	No reaction	
Morpholine	No reaction	
N-Methylpiperazine	No reaction	

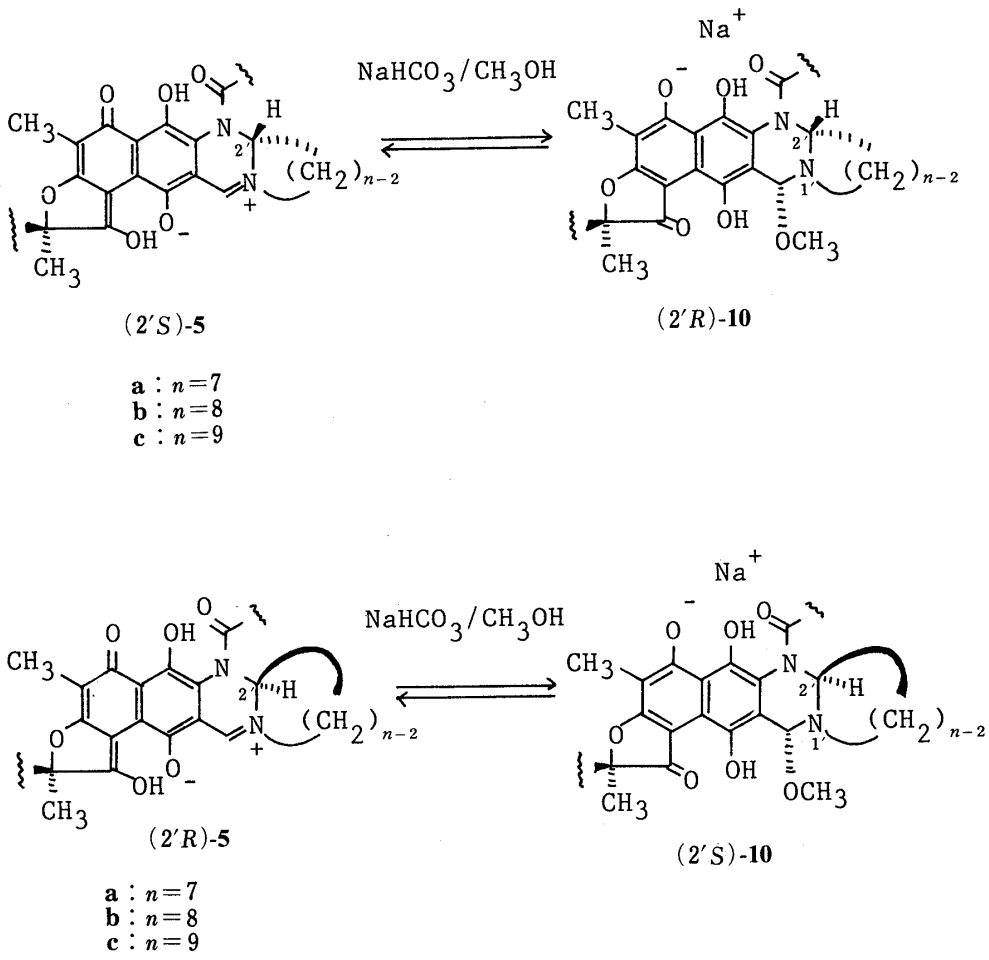


Chart 2

TABLE II. The Degree (%) of Association of the Methoxy Group with the Iminium Carbon of **5** in CH_3OH Saturated with $NaHCO_3$ at Room Temperature[a)]

5a		**5b**		**5c**	
(2'*S*)	(2'*R*)	(2'*S*)	(2'*R*)	(2'*S*)	(2'*R*)
11	46	5	53	23	59

a) The values were calculated by comparison of the absorbance, $E^{1\%}_{1cm}$, at 620 nm in CH_3OH with that in CH_3OH saturated with $NaHCO_3$. The absorbance of the pseudo-salts **10** at 620 nm was assumed to be zero (see Fig. 2 in ref. 2*b*). About 0.2 mg of **5** was dissolved in 5 ml of solvent.

and *N*-methylpiperazine), the reaction did not proceed. The results are summarized in Table I.

We have already reported that 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives **1** are in equilibrium with the pseudo bases in CH_3OH saturated with $NaHCO_3$.[2b)] The same phenomenon was also observed in **5**. That is, the maximum absorbance at about 610 nm in the UV spectra of **5** in CH_3OH decreased in CH_3OH saturated with $NaHCO_3$, and a new absorption appeared at about 450 nm. This implies that (2'*S*)-**5** and (2'*R*)-**5** are in equilibrium with the pseudo bases (2'*R*)-**10** and (2'*S*)-**10** respectively. The results are summarized in Table II.

The configuration of the 2′-position in **5** was deduced by comparison of the degrees of the association of the methoxy group to the iminium carbon of **5** in CH_3OH saturated with $NaHCO_3$ in the two epimers as follows. The equilibrium reaction between **5** and **10** should be influenced mainly by the thermodynamic stability of the dihydropyrimidine ring and the tetrahydropyrimidine ring.

Firstly, thermodynamic stabilities of the dihydropyrimidine ring in **5** for the two epimers, (2′*S*)-**5** and (2′*R*)-**5**, can be estimated as follows. To avoid the eclipsed arrangement of the methylene chain at the 2′-position with respect to the acyl group of the amide group, in the (2′*S*)-epimer the methylene chain should take the axial-like position and the amide bond should be at the β-oriented position, whereas in the (2′*R*)-epimer the methylene chain should also take the axial-like position, but the amide bond should be at the α-oriented position. This leads to the hypothesis that the thermodynamic stabilities of the dihydropyrimidine ring in **5** are almost equal in the two epimers, (2′*S*)-**5** and (2′*R*)-**5**, because the 1 : 2 steric repulsions in the dihydropyrimidine ring are almost equal for the two epimers.

Secondly, the thermodynamic stabilities of the tetrahydropyrimidine ring in **10** for the two epimers, (2′*R*)-**10** and (2′*S*)-**10**, can be estimated as follows. The association of the methoxy group to the iminium carbon of **5** is presumed to take place only from the α-side due to the steric hindrance of the ansa-chain.[6] Further, the stereoelectronic requirements for the equilibrium reaction between **5** and **10** should restrict the confirmation of the tetrahydropyrimidine ring in **10** to that in which the associated methoxy group and the lone-pair on the 1′-nitrogen atom take the anti-conformation with respect to each other and take the axial-like positions. Moreover, to avoid the eclipsed arrangement of the methylene-chain at the 2′-position with respect to the acyl group of the amide group, the tetrahydropyrimidine ring in (2′*R*)-**10** should take the half-chair-like conformation, which restricts the methylene chain at the 2′-position to the axial-like position and the amide bond to the β-oriented position; the tetrahydropyrimidine ring in (2′*S*)-**10** should take the half-boat-like conformation, which restricts the methylene chain at the 2′-position to the axial-like position and the amide bond to the α-oriented position. This leads to the hypothesis that the thermodynamic stability of the tetrahydropyrimidine ring is less in (2′*R*)-**10** than in (2′*S*)-**10**, because the 1 : 2 steric repulsions in the tetrahydropyrimidine ring are almost equal in the two epimers, while in (2′*R*)-**10** 1 : 3 steric repulsion between the associated methoxy group and the axial-like methylene chain at the 2′-position is present.

The above considerations regarding the thermodynamic stabilities of the dihydropyrimidine ring in **5** and the tetrahydropyrimidine ring in **10** for the two epimers permit the assignment of the configuration of the 2′-position in **5**. That is, the association of the methoxy group in **5** is favored in the (2′*R*)-epimer rather than in the (2′*S*)-epimer.

In the case of **4**, the configuration of the 2′-position could not be determined from the degree of association of the methoxy group, because only one of the two epimers could be obtained as mentioned above. However, the configuration of the 2′-position in **4** is suggested by a comparison of the NMR spectra ($CDCl_3$) of **4** with those of **5**. The signals due to the methyl group at the 26-position in (2′*S*)-**5** were at lower field than the signal of tetramethylsilane (TMS) (δ about 0.75), whereas those in (2′*R*)-**5** were at higher field (δ about -0.15). In addition, the chemical shifts of the proton at the 2′-position in (2′*S*)-**5** were in the vicinity of δ 6.4, whereas those in (2′*R*)-**5** were in the vicinity of δ 5.3. The signals due to the methyl group at the 26-position in **4a** and **4b** were at lower field than the signal of TMS (δ about 0.75). The chemical shifts of the proton at the 2′-position in **4** were in the vicinity of δ 6.4 (δ 6.50 in **4a** and δ 6.46 in **4b**). These observations in the NMR spectra of **4** suggest that the configuration of the 2′-position of **4a** and **4b** is *S*. The difference in the NMR spectra of the two epimers of **5** may be based on the difference in the conformation of the dihydropyrimidine ring as discussed above.

The degree of association of the methoxy group to the iminium carbon of **4** in CH_3OH saturated with $NaHCO_3$ was 27% in **4a** and 14% in **4b**. The comparison of **4a** with **1** (R = ethyl, 96%)[2b] as regards the degree of association of the methoxy group implies that the substituent at the 2′-position is an important factor which affects the equilibrium between 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives and the pseudo bases in CH_3OH saturated with $NaHCO_3$. This supports the above discussion concerning the configuration of the 2′-position in **5** based on the presence of the 1 : 3 steric repulsion between the associated methoxy group and the axial-like methylene chain at the 2′-position in (2′*R*)-**10**.

The mechanism of formation of 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives **4** and **5** is considered to be as shown in Chart 3.

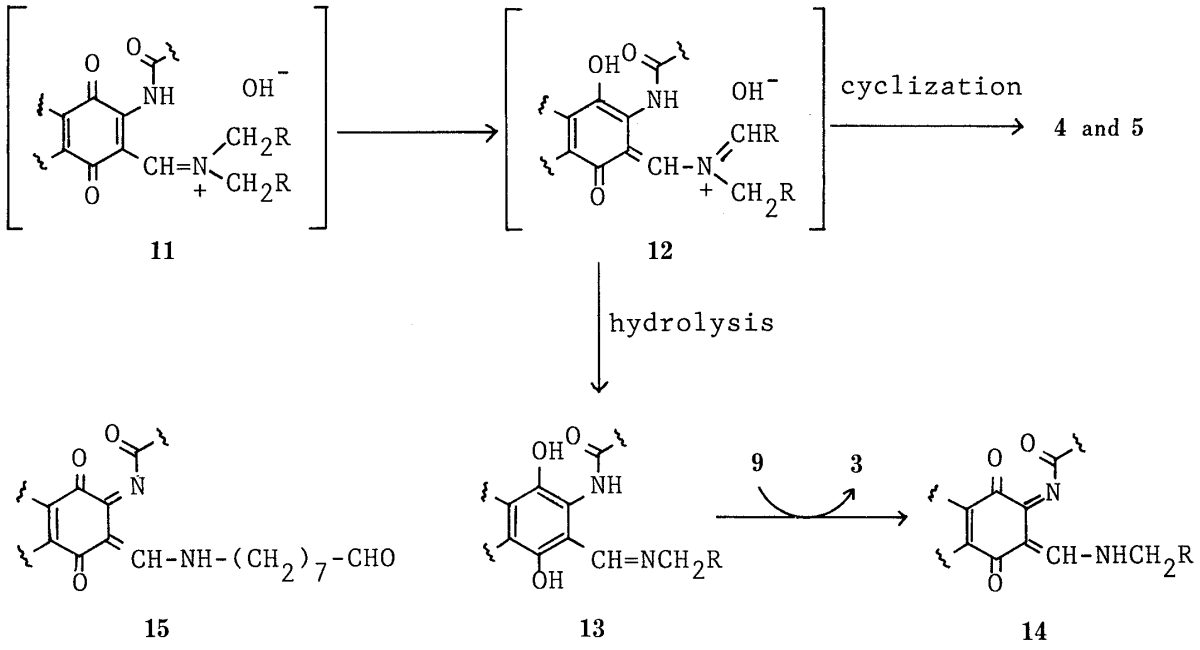


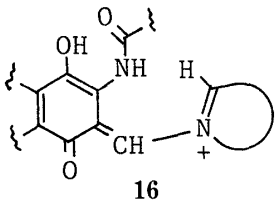
Chart 3

In the reaction mixture for the formation of **4a** and **4b**, the 3-iminomethylrifamycin derivatives **14** (R = methyl and propyl, respectively) and 3-formylrifamycin SV (**3**) were detected by analytical TLC.[7] Further, in the formation of **5c**, 3-(ω-oxooctylimino)-methylrifamycin S (**15**) was isolated in 5.5% yield. The infrared (IR) spectrum (KBr) of **15** showed a band at 2720 cm^{-1} (Fermi resonance) which is characteristic of the formyl group.[8] Moreover, a triplet ($J < 1$ Hz) due to the formyl group was observed at δ 9.74 in the NMR spectrum ($CDCl_3$). The detection of **14** and the isolation of **15** strongly support the presence of the intermediate **12**. The addition of the nitrogen atom of the amide group to the iminium carbon in the intermediate **12** presumably leads to the formation of the 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives **4** and **5**. The hydrolysis of the iminium bond in the intermediate **12** leads to 3-iminomethylrifamycin SV derivatives **13**, then to **14** by oxidation with 3-formylrifamycin S (**9**), which changes to 3-formylrifamycin SV (**3**).

The involvement of the intermediate **12** accounts well for the ratio of the isolation yields of the two epimers in **5**. In compounds **5a** and **5b**, the yield of the (2′*R*)-epimer was greater than that of the (2′*S*)-epimer. In contrast, in **5c** the yield of the (2′*S*)-epimer was greater than that of the (2′*R*)-epimer (Table I). Generally, the formation of the internal *cis*-double bond predominates over the formation of the internal *trans*-double bond in 7- and 8-membered rings. In 9-membered rings, the formation of the internal *trans*-double bond is predominant.[9]

This implies that in the formation of **5a** and **5b**, the preferred configuration of the cyclic iminium bond in the intermediate **12** is the *cis*-configuration **16**, whereas in **5c** it is the *trans*-configuration **17**. For the ring closure reaction, only two conformations (**18** and **19** for **16**, **20**, and **21** for **17**) are suitable. In **18** and **20**, the nitrogen atom of the amide group attacks the iminium carbon from the upper side. In **19** and **21** the nitrogen atom of the amide group attacks the iminium carbon from the rear side. Of the two conformations, **19** and **21** should be limited to some degree by the steric repulsion between the ansa-chain and the cyclic methylene chain of the iminium group. Thus, the ring closure proceeds mostly *via* the conformations **18** and **20**. This implies that the formation of the (2′*R*)-epimer is preferred in **5a** and **5b**, whereas that of the (2′*S*)-epimer is preferred in **5c**.

In the formation of **4**, the ring closure should proceed only *via* the conformation **22**,



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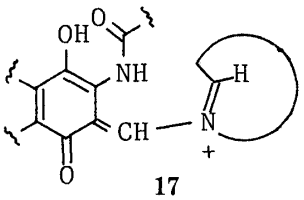

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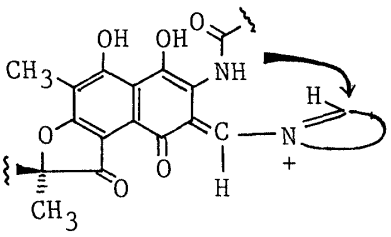

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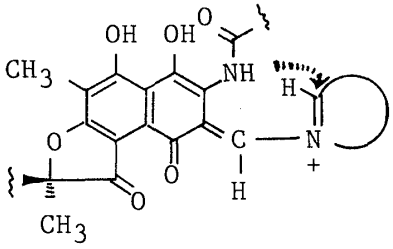

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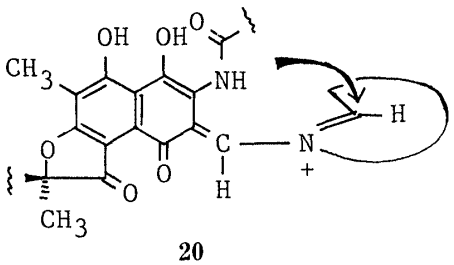

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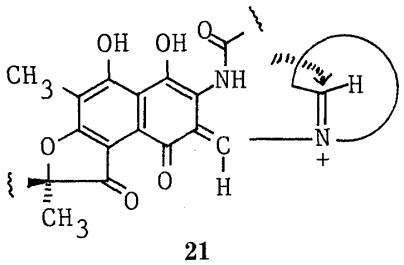

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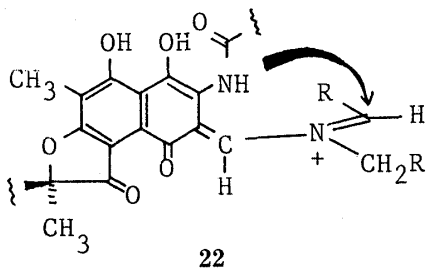

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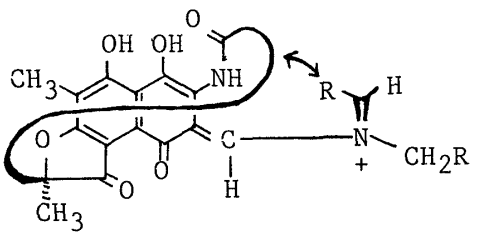

23

Chart 4

because only the (2′*S*)-epimer could be obtained. The conformation **23** is presumably highly unfavorable because of the steric repulsion between the ansa-chain and the group R substituted on the iminium carbon.

The reaction of 3-formylrifamycin S (**9**) with the 6-membered cyclic amines did not proceed, as mentioned above. The lower reactivity of the 6-membered cyclic amines on **9** can be interpreted by assuming that the iminium intermediate **11** is not formed, because the formation of an *exo* double bond in 6-membered ring systems is not favored.[10]

Experimental

Analytical TLC was performed on Silica gel 60 F_{254} pre-coated plates (layer thickness 0.25 mm, E. Merck), using $CHCl_3$–CH_3OH (10 : 1 or 4 : 1) as a developing solvent. Isolation of products was performed by preparative TLC (Silica gel 60 F_{254} pre-coated plates with layer thickness 0.5 mm or Silica gel 60 pre-coated plates with layer thickness 2 mm, E. Merck), using $CHCl_3$–CH_3OH (20 : 1—5 : 1) as a developing solvent, or by column chromatography (Silica gel 60 with 70—230 mesh particle size, E. Merck, or Wakogel C-200, Wako Pure Chemical Ind., Ltd.), using $CHCl_3$–CH_3OH (100 : 1—40 : 1) as an eluent. Analytical samples were obtained by precipitation from $CHCl_3$–hexane or $CHCl_3$–ligroin.

All melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. NMR spectra were recorded on a JEOL PS-100 spectrometer with TMS as an internal reference. IR spectra were obtained with a Shimadzu IR-440 spectrometer. UV spectra were obtained with a Shimadzu UV-210A spectrometer. CH_3OH solution saturated with $NaHCO_3$ was prepared as previously reported.[2b] Elemental analyses were performed at the Elemental Analysis Center of Kyoto University.

2,3-Dihydropyrimido[4,5-*b*]rifamycin Derivatives 4 and 5——As a typical run, the preparation of **5c** is described below.

A 10.0 g portion of manganese dioxide (70%, Wako Pure Chemical Ind., Ltd.) was added to a solution of 2.3 g of 3-formylrifamycin SV (**3**) in 20 ml of $CHCl_3$. The mixture was stirred at room temperature for 45 min, then insoluble materials were filtered off, and 1.0 g of octamethyleneimine was added to the filtrate. After being stirred at room temperature for 15 min, the reaction solution was washed with 10% AcOH to remove the excess amine, then washed with brine, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford 2.8 g of residue. Upon preparative TLC (Silica gel 60, 5 : 1 $CHCl_3$–CH_3OH), the residue afforded 70 mg (yield, 3%) of (2′*R*)-**5c** and 1.1 g (yield, 42%) of (2′*S*)-**5c** as a deep-blue solid, and 149 mg (yield, 5.5%) of compound **15** as an orange solid. (2′*R*)-**5c**: mp 194—200 °C (dec.). UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 227 (4.51), 252 (4.36, shoulder), 278 (4.29, shoulder), 326 (4.13, shoulder), 364 (4.19), 614 (3.94). IR ν_{max}^{KBr} cm^{-1}: 3460, 1720, 1676, 1642, 1600. NMR ($CDCl_3$) δ: −0.14 (3H, d, J=6.4 Hz, 26-CH_3), 5.36 (m, 2′-H, overlapped by another signal), 8.91 (1H, s, iminium proton), 14.25 (br s, 1-OH or 11-OH), 17.13 (br s, 1-OH or 11-OH). *Anal.* Calcd for $C_{46}H_{60}N_2O_{12}$: C, 66.33; H, 7.26; N, 3.36. Found: C, 66.22; H, 7.50; N, 3.07. (2′*S*)-**5c**: mp 200—204 °C (dec.). UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 226 (4.55), 281 (4.29), 312 (4.16, shoulder), 366 (4.24), 620 (4.01). IR ν_{max}^{KBr} cm^{-1}: 3440, 1720, 1650, 1597. NMR ($CDCl_3$) δ: about 0.72 (26-CH_3, overlapped by other signals), 6.36 (1H, m, 2′-H), 8.90 (1H, s, iminium proton), 15.13 (s, 1-OH or 11-OH), 16.32 (s, 1-OH or 11-OH). *Anal.* Calcd for $C_{46}H_{60}N_2O_{12}\cdot 2H_2O$: C, 63.58; H, 7.42; N, 3.22. Found: C, 63.79; H, 7.20; N, 3.07. **15**: mp 130—140 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 2720 and 1726 (formyl group). NMR ($CDCl_3$) δ: 9.74 (1H, t, J<1 Hz, formyl group). *Anal.* Calcd for $C_{46}H_{60}N_2O_{13}\cdot 1/2H_2O$: C, 64.39; H, 7.17; N, 3.27. Found: C, 64.44; H, 7.21; N, 3.08.

Reaction conditions for the formation of 2,3-dihydropyrimido[4,5-*b*]rifamycin derivatives **4** and **5** are summarized in Table III.

Table III. Reaction Conditions for the Formation of 2,3-Dihydropyrimido-[4,5-*b*]rifamycin Derivatives **4** and **5** from **3**

Amine (mol ratio to **3**)	Solvent	Time (min)	Yield (%)
Diethylamine (5.9)	AcOEt	25	**4a**: 15
Diethylamine (2.0)[a]	$CHCl_3$	30	**4a** (25-*O*-desacetyl): 17
Dibutylamine (6.5)	AcOEt	40	**4b**: 62
Hexamethyleneimine (2.2)	$CHCl_3$	40	(2′*R*)-**5a**: 17; (2′*S*)-**5a**: 6
Heptamethyleneimine (1.0)	$CHCl_3$	40	(2′*R*)-**5b**: 42; (2′*S*)-**5b**: 4
Octamethyleneimine (2.5)	$CHCl_3$	15	(2′*R*)-**5c**: 3; (2′*S*)-**5c**: 42

a) The 25-*O*-desacetyl derivative of **3** was used.

Physical constants are as follows. **4a**: mp 175—179 °C (dec.). UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 226 (4.52), 275 (4.32), 310 (4.17, shoulder), 358 (4.18), 595 (3.94). IR ν_{max}^{KBr} cm^{-1}: 3440, 1725, 1650, 1610. NMR ($CDCl_3$) δ: about 0.74 (26-CH_3, overlapped by other signals), 6.50 (1H, q, J=6.4 Hz, 2′-H), 8.79 (1H, s, iminium proton), 15.06 (s, 1-OH or 11-OH), 16.32 (s, 1-OH or 11-OH). *Anal.* Calcd for $C_{42}H_{54}N_2O_{12}\cdot 3/2H_2O$: C, 62.59; H, 7.13; N, 3.48. Found: C, 62.41; H, 6.96; N, 3.37.

The 25-*O*-Desacetyl Derivative of **4a**: mp 178—185 °C (dec.). UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 227 (4.51), 275 (4.33), 313 (4.16, shoulder), 360 (4.20), 592 (3.98). UV $\lambda_{max}^{pH\ 7.0\ phosphate\ buffer}$ nm (log ε): 228 (4.52), 271 (4.31), 310 (4.18, shoulder), 355 (4.17), 565 (3.99). (lit.,[3c] UV $\lambda_{max}^{pH\ 7.38}$ nm (ε): 227 (41000), 273 (21870), 306 (17270), 355 (17510), 565 (12830)). IR ν_{max}^{KBr} cm^{-1}: 3430, 1648, 1612. NMR ($CDCl_3$) δ: 0.72 (3H, d, J=7.2 Hz, 26-CH_3), 6.62 (1H, q, J=6.4 Hz, 2′-H), 9.00 (1H, s, iminium proton), 14.96 (s, 1-OH or 11-OH), 16.32 (s, 1-OH or 11-OH). *Anal.* Calcd for $C_{40}H_{52}N_2O_{11}\cdot H_2O$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.79; H, 6.97; N, 3.31. **4b**: mp 155—160 °C (dec.). UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 225 (4.56), 275 (4.32), 310 (4.17, shoulder), 360 (4.23), 598 (3.99). IR ν_{max}^{KBr} cm^{-1}: 3440, 1724, 1656, 1605. NMR ($CDCl_3$) δ: about 0.74 (26-CH_3, overlapped by other signals), 6.46 (1H, t, J=6.4 Hz, 2′-H), 8.76 (1H, s, iminium proton), 15.02 (s, 1-OH or 11-OH), 16.19 (s, 1-OH or 11-OH). *Anal.* Calcd for $C_{46}H_{62}N_2O_{12}\cdot 1/2H_2O$: C, 65.46; H, 7.52; N, 3.32. Found: C, 65.25; H, 7.59; N, 3.23. (2′*R*)-**5a**: mp 201—205 °C (dec.). UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 225 (4.52), 252 (4.40, shoulder), 278 (4.33, shoulder), 326 (4.14, shoulder), 362 (4.24), 603 (4.02). IR ν_{max}^{KBr} cm^{-1}: 3450, 1720, 1680, 1607. NMR ($CDCl_3$) δ: −0.15 (3H, d, J=6.4 Hz, 26-CH_3), 5.32 (m, 2′-H, overlapped by another signal), 8.80 (1H, s, iminium proton), 14.30 (br s, 1-OH or 11-OH), 17.00 (br s, 1-OH or 11-OH). *Anal.* Calcd for $C_{44}H_{56}N_2O_{12}\cdot H_2O$: C, 64.22; H, 7.10; N, 3.40. Found: C, 64.12; H, 7.09; N, 3.27. (2′*S*)-**5a**: mp 200—207 °C (dec.). UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 226 (4.54), 278 (4.28), 312 (4.14, shoulder), 363 (4.22), 606 (4.00). IR ν_{max}^{KBr} cm^{-1}: 3440, 1717, 1695, 1649, 1606. NMR ($CDCl_3$–DMSO-d_6) δ: 0.58 (3H, d, J=7.2 Hz, 26-CH_3), about 6.18 (2′-H, overlapped by another signal), 9.24 (1H, s, iminium proton), 14.64 (s, 1-OH or 11-OH), 16.12 (br s, 1-OH or 11-OH). (2′*R*)-**5b**: mp 198—202 °C (dec.). UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 227 (4.53), 250 (4.40, shoulder), 280 (4.32, shoulder), 326 (4.15, shoulder), 363 (4.23), 610 (4.00). IR ν_{max}^{KBr} cm^{-1}: 3460, 1720, 1677, 1645, 1602. NMR ($CDCl_3$) δ: −0.18 (3H, d, J=6.4 Hz, 26-CH_3), 5.52 (1H, m, 2′-H), 8.90 (1H, s, iminium proton), 14.33 (s, 1-OH or 11-OH), 17.24 (br s, 1-OH or 11-OH). *Anal.* Calcd for $C_{45}H_{58}N_2O_{12}\cdot 1/2H_2O$: C, 65.28; H, 7.18; N, 3.38. Found: C, 65.22; H, 7.11; N, 3.19. (2′*S*)-**5b**: mp 205—213 °C (dec.). UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 226 (4.57), 280 (4.31), 310 (4.19, shoulder), 365 (4.26), 615 (4.03). IR ν_{max}^{KBr} cm^{-1}: 3420, 1720, 1698, 1650, 1605. NMR ($CDCl_3$–CD_3OD) δ: 0.47 (3H, d, J=7.2 Hz, 26-CH_3), about 6.24 (2′-H, overlapped by other signals), 9.34 (1H, s, iminium proton). *Anal.* Calcd for $C_{45}H_{58}N_2O_{12}\cdot 3H_2O$: C, 61.91; H, 7.39; N, 3.21. Found: C, 62.04; H, 7.08; N, 3.07.

References and Notes

1) This work was reported at the 101st Annual Meeting of the Pharmaceutical Society of Japan, Kumamoto, April 1981.
2) *a*) G. Tsukamoto, N. Aikawa, and M. Taguchi, *Chem. Lett.*, **1979**, 1313; *b*) G. Tsukamoto, M. Taguchi, and N. Aikawa, *Chem. Pharm. Bull.*, **28**, 2309 (1980).
3) *a*) N. Maggi, G. G. Gallo, and P. Sensi, *Framaco, Ed. Sci.*, **22**, 316 (1967); *b*) N. Maggi, G. G. Gallo, and A. Vigevani, *Tetrahedron Lett.*, **1968**, 1763; *c*) Gruppo Lepetit S. p. A., Brit. Patent 1226050 (1971) [*Chem. Abstr.*, **75**, 20428*x* (1971)]; *d*) N. Maggi, Brit. Patent 1276482 (1972) [*Chem. Abstr.*, **77** 114449*y* (1972)].
4) The structure of a deep-blue by-product suggested by Maggi *et al.*[3b] should be partly revised to **4a**.[2a]
5) The quinonoid form of **3**, namely 3-formylrifamycin S (**9**), was not stable. This was the reason why **9** and its 25-*O*-desacetyl derivative were allowed to react without isolation.
6) The presence of steric hindrance due to the ansa-chain has already been suggested.[2b]
7) Compound **14** are the quinonoid forms of **13**. Thus, **14** can be described as 3-iminomethylrifamycin S derivatives. The formation and structure of **14** were reported by Maggi *et al.*[3b] Authentic samples of **14** could also be obtained by MnO_2 oxidation of **13** in $CHCl_3$; compounds **13** were obtained by the reaction of an excess amount of primary amines with **3** in $CHCl_3$ followed by washing with dilute aqueous H_2SO_4 solution.
8) The band due to the carbonyl stretching of the formyl group overlapped the band due to the 25-acetoxy group (1726 cm^{-1}).
9) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., 1962 ["Tansokagobutsu No Rittaikagaku," translated by O. Shimamura, T. Migita, K. Tokumaru, and M. Yoshida, Tokyo Kagaku Dozin, Ltd., Tokyo, 1965, p. 295].
10) H. C. Brown, J. H. Brewster, and H. Shechster, *J. Am. Chem. Soc.*, **76**, 467 (1954).