structures, in which the central part of the *ansa* chain is always in the same conformation; moreover, the same H-bond pattern was also observed in RIFCMS and TOL where the H atoms were localized.

Combining all the dihedral angles shown in Table VII, it is possible to obtain the range of variability for each angle and compare the data obtained in solution with those obtained in the solid state. The very good agreement between the two sets of data is shown in Table VIII, a possible exception being the angle H(21)–H(22) where a higher variability was found in solution.

Conclusions

The present study, in which many structures have been examined both in solution and in the solid state, leads to the conclusion that rifamycins give rise to only four kinds of isomers in spite of the apparent flexibility. These isomers are generated by the combination of two rotations, one relative to the amidic plane and the other relative to the plane containing the C(28)=C(29) double bond.

Apart from these rotations, the remaining part of the *ansa* chain between C-17 and C-27 displays only small variations. As a consequence, the spatial relationships between the four oxygens O-1, O-2, O-9, and O-10 remain the same whatever the oxidation state at O-1, the kind of C-3 substituent, or the nature of the solvent or whether the molecules are present in the solid state or in solution.

This observation is particularly important in view of the fact that the four hydroxyls (one of which, O-1, may be in the quinonic form) are responsible for the binding that leads to inhibition of bacterial DNA-dependent RNA polymerase.

Therefore, the previously proposed correlation between structure and activity derived on the basis of solid-state studies also holds in solution.

Registry No. RIFB, 13232-69-4; RIFMPSV, 13292-46-1; RIFCMS, 72393-97-6; BRTOL, 26294-93-9; TOL, 22356-23-6; RIFMPS, 13983-13-6; RIFBRS, 57375-25-4; RIFS, 13553-79-2; RIFNTS, 72788-67-1; RIFAMS, 51756-80-0; RIFMAS, 17554-98-2; RIFMOS, 19306-05-9; RIFNTSV, 72788-68-2; RIFMOSV, 16286-09-2; RIFCMSV, 81584-03-4; RIFBRSV, 59858-23-0; RIFSV, 6998-60-3.

Notes

Synthesis of 4(5)-Nitroimidazole-5(4)-carboxaldehyde by Oxidative Elimination of a Nitrate Ester[1,2]

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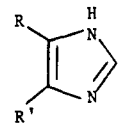
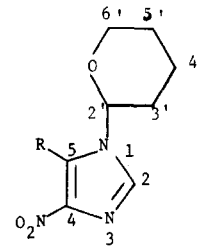
Received June 8, 1981

4(5)-Nitroimidazole-5(4)-carboxaldehyde (**1**) can serve as a precursor to a number of heterocycles of potential biological interest. It was anticipated that **1** could be prepared by controlled oxidation of 4(5)-(hydroxymethyl)-5(4)-nitroimidazole (**3**). An examination of the literature showed that **3** was unknown but had been proposed[3] as a possible intermediate in the oxidative nitration of 4(5)-(hydroxymethyl)imidazole (**2**) to the corresponding nitro carboxylic acid (**5**). We modified the reported procedure by lowering the reaction temperature and effected ring nitration of **2** without oxidation of the hydroxymethyl side chain. That nitration occurred was confirmed by the ^{1}H NMR spectrum of the crystalline reaction product which exhibited only one imidazole proton at δ 7.9. Evidence for the site of nitration as C-5(4) rather than C-2 was provided by the ^{13}C NMR spectrum of this product. The one-bond ^{13}C–^{1}H coupling constant for the unsubstituted carbon was 220 Hz. This value is in agreement with other published values for related C-2-unsubstituted imidazoles.[4,5] The observance of the methylene protons





1: R = CHO; R' = NO_2

2: R = CH_2OH; R' = H

3: R = CH_2OH; R' = NO_2

4: R = CH_2ONO_2; R' = NO_2

5: R = CO_2H; R' = NO_2

6: R = $C_\alpha H_2ONO_2$

7: R = $C_\alpha HO$

8: R = $C_\alpha H(OH)-C_\beta H_2NO_2$

9: R = $C_\alpha H(OCOCH_3)-C_\beta N$

at δ 6.0 of this crystalline product in the ^{1}H NMR spectrum indicated that oxidation had not occurred; however, the large deshielding effect experienced by these protons strongly suggested that a nitrate ester had been formed and that the product was (5(4)-nitroimidazol-4(5)-yl)-methyl nitrate (**4**). This was confirmed by elemental analysis of **4** and subsequent hydrolysis to the corresponding alcohol **3** whose ^{1}H NMR spectrum exhibited the expected upfield shift of the methylene protons to δ 5.0.

The literature on nitrate esters revealed that, in addition to base hydrolysis to the parent alcohol, an $E_{CO}2$ reaction[6,7] can occur to furnish the aldehyde. The aldehyde is gen-

(1) Presented in part at the 8th International Congress of Heterocyclic Chemistry, Graz, Austria, Aug 1981; p 61.

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0022-3263/82/1947-2661$01.25/0

Table I. Carbon-13 Chemical Shifts for Certain Imidazoles[a]

compd	chemical shift, δ										
	C2	C4	C5	C2′	C3′[b]	C4′[b]	C5′[b]	C6′	C_α	C_β	other
4[c]	135.6$_4$	124.8$_0$	144.6$_8$					64.8$_4$			
6	133.8	121.5	146.3	83.6	21.3	23.5	29.9	67.7	61.7		
7	136.2$_2$	123.6$_9$	151.0$_3$	85.8$_6$	22.3$_9$	24.9$_5$	33.6$_1$	69.2$_5$	181.3$_7$		
8	135.0	129.9	143.7	78.5	21.9	24.0	29.4	67.5	62.4	128.3	
9[c]	134.7$_2$, 134.5$_1$	120.4$_1$, 119.8$_6$	145.4$_2$	84.3$_7$, 84.0$_7$	19.7$_7$	21.7$_8$	24.0$_2$	68.0$_9$	52.3$_7$, 52.2$_7$	113.0$_3$, 112.8$_8$	168.0 ($COCH_3$), 167.5$_3$, 30.8$_5$ ($COCH_3$), 30.4$_6$

[a] Spectra were obtained on a Varian CFT-20 NMR spectrometer by using $CDCl_3$ and Me_2SO-d_6 as the solvents. A flip angle of 45° was employed. Chemical shifts are expressed in parts per million with respect to Me_4Si. [b] Tentative assignments. [c] Run in Me_2SO-d_6.

erated by base abstraction of an α-hydrogen. The reaction is facilitated by increased acidity of the proton being abstracted and by substituents which can stabilize the newly formed carbonyl bond through conjugation.[6] On the basis of these arguments, it was rationalized that a nonnucleophilic base would favor oxidative elimination over hydrolysis.

Protection of the imidazole ring at N-1 in **4** was essential prior to performing the oxidative elimination. The tetrahydropyranyl derivative **6** was obtained by treatment of **4** with dihydropyran in ethyl acetate in the presence of a catalytic amount of bis(*p*-nitrophenyl) phosphate. Although alkylation can take place at either nitrogen of **4** only one product was isolated whose structure was assigned as **6** by an X-ray crystallographic analysis.[8]

Treatment of **6** with 1 equiv of the nonnucleophilic base 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in chloroform at room temperature furnished the corresponding aldehyde (**7**) in quantitative yield. The reaction was found to take place instantaneously when followed by ^1H NMR spectroscopy which showed the disappearance of the AB quartet centered at δ 6.0 and the simultaneous appearance of an aldehyde singlet at δ 10.6.

As expected, the nitroaldehyde **7** underwent typical carbon–carbon bond formation reactions. For example, base-catalyzed addition of nitromethane[9] furnished the desired nitro adduct **8** in good yields. Similarly, treatment of the aldehyde **7** with potassium cyanide and acetic anhydride[10] in chloroform afforded the corresponding cyanohydrin acetate (**9**) as a gummy mixture of two diastereomers.

Because of difficulties encountered in the purification of **9**, an acceptable elemental analysis could not be obtained; however, NMR data strongly support the assigned structure. The ^1H NMR spectrum exhibited a singlet at δ 8.0 for the H-2 proton and two singlets at δ 7.6 and 7.7, assigned to the methine proton of the cyanohydrin group. The combined integrated areas for these singlets corresponded to one proton, indicating the presence of a mixture of diastereomers. A ^{13}C NMR analysis corroborated this conclusion when pairs of singlets were observed for a number of isomeric carbons (see Table I). In addition, the ^{13}C NMR spectrum was helpful in confirming the assignment of the cyanohydrin proton which was highly deshielded. The use of the graphical method of Freeman and Hill[11] established the correlation between the chemical shift of this proton and the carbon to which it is attached.

The title compound **1** was obtained by mild acid hydrolysis of **7** in nearly quantitative yield. However, the reverse reaction proceeded to give **7** only when a 100-fold excess of dihydropyran was used. This could be due to the increased acidity of the imidazole ring as demonstrated by an extremely broad and deshielded ^1H NMR signal (δ 12.9) for the N–H proton. Thus, the nitrate ester serves not only as a latent aldehyde function but also as a synthon that can be conveniently N protected prior to generation of the aldehyde group.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The infrared spectra were taken with a Beckman IR-8 spectrophotometer. The ^1H NMR spectra were determined on a Varian A-60 or a Varian EM-360A 60 MHz spectrometer. Chemical shifts are expressed in parts per million with respect to Me_4Si. The mass spectra were measured with a Du Pont 490 mass spectrometer. Thin-layer chromatography was run on precoated (0.25 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave ultraviolet light (254 nm) was used to detect the UV-absorbing spots. EM silica gel 60 (70–230-mesh ASTM) was employed for routine column chromatography. Evaporations were performed with a Buchi Rotovapor at 40 °C unless otherwise stated. Elemental analysis were performed by M-H-W Laboratories, Phoenix, AZ.

4(5)-Nitroimidazole-5(4)-carboxaldehyde (1). To a solution of **7** (530 mg, 2.35 mmol) in acetone (13 mL) was added 1 N HCl (13 mL), and the mixture was heated at 50 °C. After 10 min, the reaction was complete, and the solution was evaporated to afford a brown residue. The residue was dissolved in AR acetone, treated with charcoal, and filtered through Celite, and the filtrate was evaporated to dryness. The resulting solid was crystallized from acetone–chloroform to furnish **1**: 304 mg (92%); yellow crystals; mp 231–232 °C; ^1H NMR (acetone-d_6) δ 8.0 (s, 1, H-2), 10.27 (s, 1, CHO), 12.9 (br s, 1, NH).

Anal. Calcd for $C_4H_3N_3O_3$: C, 34.05; H, 2.14; N, 29.79. Found: C, 34.07; H, 2.50; N, 29.58.

4(5)-(Hydroxymethyl)-5(4)-nitroimidazole (3). Compound **4** (100 mg, 0.53 mmol) was dissolved in water (3 mL) and was boiled for 15 min. Evaporation of the water gave the product in quantitative yield. The analytical sample was obtained by crystallization from water: mp 200 °C; ^1H NMR (Me_2SO-d_6) δ 4.98 (s, 2, CH_2), 7.83 (s, 1, H-2); mass spectrum (70 eV), *m/e* (relative intensity) 143 (M^+, 55), 126 (M^+ – OH, 100), 97 (M^+ – NO_2, 43).

Anal. Calcd for $C_4H_5N_3O_3$: C, 33.57; H, 3.52; N, 29.36. Found: C, 33.66; H, 3.59; N, 29.48.

(5(4)-Nitroimidazol-4(5)-yl)methyl Nitrate (4). Small portions of 4(5)-(hydroxymethyl)imidazole hydrochloride[12] (1.0 g, 5.3 mmol) were added to cold (–10 °C) 20% oleum (2.6 mL) with stirring. After the addition was complete and the frothing subsided, nitric acid (90%, *d* ~1.5) was then added dropwise while the temperature was maintained at –10 °C. The reaction mixture was allowed to stir at 40 °C for 16 h, after which it was poured

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onto cracked ice. The title compound precipitated as a white solid. Filtration, washing with water, and air-drying gave the product: 0.93 g (66.5%); mp 145 °C. Recrystallization from ethyl acetate provided the analytical sample: mp 147–148 °C; ^{1}H NMR (Me_2SO-d_6) δ 5.98 (s, 2, CH_2), 7.95 (s, 1, H-2), 9.75 (br s, 1, NH); mass spectrum (70 eV), *m/e* (relative intensity) 188 (M^+, 23), 142 (M – NO_2, 17), 46 (NO_2^+, 94).

Anal. Calcd for $C_4H_4N_4O_5$: C, 25.55; H, 2.14; N, 29.79. Found: C, 25.74; H, 2.27; N, 29.65.

[4-Nitro-1-(tetrahydropyran-2-yl)imidazol-5-yl]methyl Nitrate (6). Dihydropyran (5.3 mL, 58.6 mmol) in ethyl acetate (60 mL) was added dropwise to a refluxing solution of **5** (10.2 g, 54.2 mmol) and bis(*p*-nitrophenyl) phosphate (75 mg) in ethyl acetate (100 mL). After complete addition, the reaction mixture was refluxed for an additional hour. A second portion of dihydropyran (3 mL) was then added, and refluxing was continued until all the starting material was consumed. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (250 g), eluting with chloroform. The product was obtained as a yellow oil (10.7 g, 72.6%) which, when cooled, crystallized: mp 79–80 °C; ^{1}H NMR ($CDCl_3$) δ 1.3–2.6 (m, 6, C-3′, C-4′, C-5′ H_2), 3.5-4.4 (m, 2, C-6′ H_2), 5.47 (m, C-2′ H), 5.93 and 6.2 (AB q, 2, CH_2–O, *J* = 13 Hz), 7.82 (s, 1, H-2).

Anal. Calcd for $C_9H_{12}N_4O_6$: C, 39.71; H, 4.44; N, 20.59. Found: C, 39.73; H, 4.49; N, 20.40.

4-Nitro-1-(tetrahydropyran-2-yl)imidazole-5-carboxaldehyde (7). To a stirred and chilled (4 °C) solution of **6** (1.38 g, 5.06 mmol) in chloroform (23 mL) was added, dropwise, a solution of 1,5-diazabicyclo[4.3.0]non-5-ene (0.66 mL, 5.31 mmol) in chloroform (8 mL). After 1 min, the reaction mixture was washed with 0.1 N HCl (3 × 20 mL) and water (2 × 10 mL), dried over magnesium sulfate, filtered, and evaporated to dryness to give a brown oil (1.95 g). Purification by column chromatography, eluting with chloroform, provided the product (1.06 g, 100%) as a yellow oil which solidified on standing: mp 49–50 °C; ^{1}H NMR ($CDCl_3$) δ 1.5–2.5 (m, 6, C-3′, C-4′, C-5′ H_2), 3.4–4.5 (m, 2, C-6′ H_2), 6.1 (m, 1, C-2′ H), 8.15 (s, 1, H-2), 10.63 (s, 1, CHO).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.93; N, 18.66. Found: C, 48.06; H, 4.78; N, 18.42.

2-Nitro-1-[(4-nitro-1-(tetrahydropyran-2-yl)imidazol-5-yl]ethanol (8). To a stirred, chilled (4 °C) solution of **7** (155 mg, 0.69 mmol) and nitromethane (0.075 mL) in 95% ethanol (5 mL) was added 10% aqueous sodium hydroxide (0.2 g). After 20 min, 2% aqueous acetic acid (2.1 mL) was added. Extraction with chloroform, drying, and evaporation gave a residue which was crystallized from ethyl acetate–hexane (2:1): mp 137 °C; 180 mg (91%); ^{1}H NMR (Me_2SO-d_6) δ 1.27–2.27 (m, 6, C-3′, C-4′, C-5′ H_2), 3.43–4.3 (m, 2, C-6′ H_2), 4.82–5.05 (m, 2, CH_2NO_2), 5.64–5.95 (m, 1, C-2′ H), 6.08–6.55 (m, 1, CHOH), 6.82 (m, 1, OH), 8.13 (s, 1, H-2).

Anal. Calcd for $C_{10}H_{14}N_4O_6$: C, 41.96; H, 4.90; N, 19.58. Found: C, 41.84; H, 4.77; N, 19.31.

2-Acetoxy-2-[4-nitro-1-(tetrahydropyran-2-yl)imidazol-5-yl]acetonitrile (9). To a stirred solution of **7** (2.85 g, 12.7 mmol) in chloroform (20 mL) were added acetic anhydride (1.62 mL, 14 mmol) and potassium cyanide (1.0 g, 20.4 mmol). After stirring at room temperature for 4 h, additional acetic anhydride (0.16 mL) and potassium cyanide (0.1 g) were added, and stirring was continued for another 4 h. Filtration of the solid followed by washing the filtrate with water (3 × 20 mL), drying, and evaporation gave a gummy residue. Purification by column chromatography on silica gel, with ethyl acetate–hexane (1:1) as an eluent, afforded the product: 3.2 g (86%); ^{1}H NMR ($CDCl_3$) δ 1.4–2.5 (m, 6, C-3′, C-4′, C-5′ H_2), 2.22, 2.25 (s, 6, CH_3), 3.55–4.42 (m, 2, C-6′ H_2), 5.72–6.17 (m, 1, C-1′ C-2′ H), 7.57, 7.70 (2 s, 1, CH, OAc), 7.97 (s, 1, H-2); IR ($CHCl_3$) 2198 cm^{-1} (CN).

Acknowledgment. Financial support for this research was provided by a grant from the National Cancer Institute, National Institutes of Health (CA-24885). We thank Mrs. Anna Mary Albert and Ms. Sylvia Stoner for technical assistance.

Registry No. 1, 81246-34-6; 3, 81246-35-7; 4, 81246-36-8; 6, 81246-37-9; 7, 81246-38-0; 8, 81246-39-1; 9, 81246-40-4; 4(5)-(hydroxymethyl)imidazole hydrochloride, 29452-13-9.

A Mild and Efficient Route to Schiff Base Derivatives of Amino Acids

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Received July 14, 1981

Our interest in the preparation of imines (Schiff bases or azomethines) is based on the use of benzophenone Schiff base derivatives of glycine alkyl esters or aminoacetonitrile as an α anion of glycine equivalent for the synthesis of higher amino acids by phase-transfer alkylations.[1] In the

$$Ph_2C{=}NCH_2CO_2R \qquad Ph_2C{=}NCH_2CN$$

past, a major limitation in this preparation of amino acids has been the tedious synthesis of the starting Schiff bases.

A commonly used method for the preparation of imines is the condensation of an aldehyde or ketone with a primary amine.[2,3] Aldimines are readily prepared by simply mixing equimolar amounts of an aldehyde and the amine with provision for the removal of water. On the other hand, when the carbonyl component is a ketone, forcing conditions (high reaction temperatures, nonstoichiometric amounts of reagents, added protic or Lewis acids, and/or long reaction times) are generally required for the preparation of ketimines. More recent studies have shown that it is often possible to prepare ketimines by a room-temperature condensation in the presence of combined catalysts–drying reagents such as $TiCl_4$,[4] molecular sieves,[5] or a catalyst prepared from molecular sieves, silica gel, and alumina.[6] Such procedures have not proven successful in our case because the amine component, e.g., glycine ethyl ester, readily self-condenses to form 2,5-dioxopiperazine (glycine anhydride) when extended reaction times are required.[7] In addition, the use of excess amine or carbonyl component is not desirable, especially if the method is to be extended to the preparation of Schiff base derivatives of higher amino acids.[8]

Results and Discussion

We now report a mild, simple, and high-yield preparation of the benzophenone Schiff base derivatives of amino acid esters (**3**). The procedure is based on transimina-

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(8) We have previously prepared the benzophenone Schiff base derivatives of glycine ethyl ester[1a] and aminoacetonitrile[1b] in 82% and 70% isolated yields, respectively, by condensation of the free amine with benzophenone in refluxing xylene or toluene with added BF_3·Et_2O. The products were purified by high-temperature vacuum distillation (to separate tars and unreacted benzophenone) followed by recrystallization.

0022-3263/82/1947-2663$01.25/0