Synthesis of optically active deacetyl anisomycin

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Optically active (−)-deacetyl anisomycin and the enantiomer (+)-deacetyl anisomycin were synthesized starting with (+)-2R 3R tartaric acid. The asymmetric centers of the tartaric acid correspond to the C-2 and C-3 asymmetric centers of anisomycin. *N*-Benzyl tartarimide (**3**) was attacked by the Grignard reagent of anisyl chloride followed by lithium aluminium hydride reduction to give two diols (**7**) and (**8**) separated by thin-layer chromatography. The diol (**8**) was debenzylated giving the natural (−)-deacetyl anisomycin. The diol (**7**) was converted into the epoxide (**10**) by selective acetylation of the C-4 hydroxy group followed by treatments with phosphorus pentachloride and sodium ethoxide. Opening of the epoxide ring of **10** in boiling acetic acid followed by basic hydrolysis gave (+)-*N*-benzyl deacetyl anisomycin (**11**) which was debenzylated to give (+)-deacetyl anisomycin.

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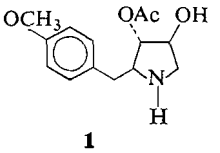
Introduction

The structure of anisomycin was reported recently as **1** (1) and was revised to **2** (2, 3) by X-ray investigation. The absolute configuration was not reported in the X-ray result and was deduced in this laboratory (4) as 2R 3S 4S as shown in **2**. We would like to report a simple synthetic approach leading to the natural (−)-deacetyl anisomycin and the enantiomer (+)-deacetyl anisomycin not in the form of a (DL)-mixture. This synthesis also verifies our assignment of the absolute stereochemistry to anisomycin.

Results and Discussion

(+)-Tartaric acid was refluxed with benzyl amine in xylene solution to give *N*-benzyl tartarimide (**3**) (5). The Grignard reagent of anisyl chloride was then stirred with the tartarimide (**3**) in dry tetrahydrofuran in 40 °C oil bath for 1 h. After decomposition of the excess Grignard



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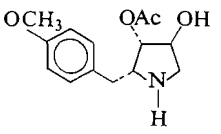

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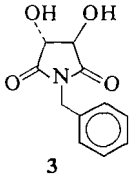

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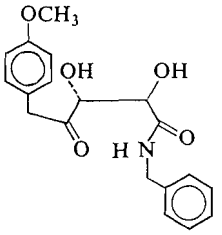

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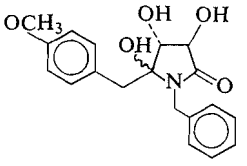

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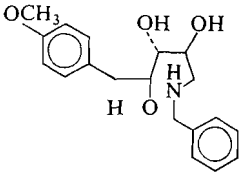

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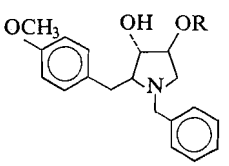
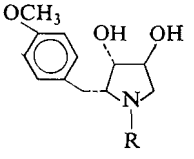


7 R = H
9 R = Ac

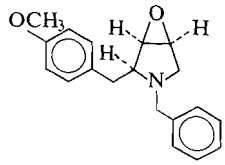


8 R = —CH_2Ph
13 R = H

reagent, the keto-amide (**4**) was isolated in 55% yield. Contrary to the usual results of the reaction of Grignard reagents with *N*-substituted maleimides (6), not even a trace of the triol (**5**) could be detected. However, if lithium aluminium hydride was added to the above reaction mixture before the excess Grignard reagent was destroyed, three compounds **6**, **7**, and **8** were isolated in 2, 12, and 3% yield respectively.

Acetylation of the diol (**7**) with acetic anhydride gave the hydroxy acetate (**9**). The assignment of the acetoxy group at C-4 was based on the smooth conversion of the acetate (**9**) to the epoxide (**10**)[1] and the conformational argument of the diol (**7**).[2] Thus, the acetate (**9**) was treated with phosphorus pentachloride in dry chloroform at room temperature followed by hydrolysis in alkaline alcoholic solution for ½ h to give the epoxide (**10**). Refluxing **10** in glacial acetic acid gave a mixture of hydroxy acetates which was hydrolyzed by aqueous sodium hydroxide solution to two glycols (**7** and **11**) in equal amounts. Total yield of the two diols from **10** was 56%. The diol (**11**) had a superimposable infrared (i.r.) spectrum but opposite specific rotation to that of *N*-benzyl deacetyl anisomycin derived from benzylation of (−)-deacetyl anisomycin in chloroform solution with benzyl bromide.

Debenzylation of the diol (**11**) in dilute ethanolic hydrochloric acid solution with 5% Pd/C under hydrogenation conditions gave deacetyl anisomycin hydrochloride quantitatively. Liberation of the free base by aqueous sodium hydroxide gave (+)-deacetyl anisomycin (**12**). The i.r. spectra of the (+)-deacetyl anisomycin and its hydrochloride were identical to those of the natural (−)-deacetyl anisomycin and its hydrochloride.



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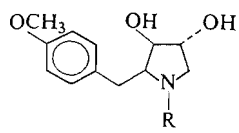

11 R = —CH_2—Ph
12 R = H

The diol (**8**) has i.r., nuclear magnetic resonance (n.m.r.), and mass spectra identical to those of **11** and those of the natural *N*-benzyl deacetyl anisomycin. Debenzylation of **8** as above gave quantitatively deacetyl anisomycin hydrochloride which by treatment with aqueous base gave (−)-deacetyl anisomycin. Both the synthetic deacetyl anisomycins and their hydrochlorides were identical in every respect to the natural products.

Experimental

All infrared (i.r.) spectra were measured on a Perkin–Elmer model 137 spectrophotometer. Melting points were measured on a Fisher–Johns apparatus and are uncorrected. Nuclear magnetic resonance (n.m.r.) spectra were measured on a Varian A 56/60 A model using TMS as internal standard. Mass spectra were measured on a Hitachi Perkin–Elmer RMU-6D mass spectrometer. All new crystalline synthetic compounds gave satisfactory analyses which were performed by Dr. C. Daessle of Montreal.

Preparation of Tartarimide (3)

Giustiniani prepared the tartarimide (**3**) by heating (+)-tartaric acid and benzylamine together (5). The yield was too low to be useful. A slightly modified method described in the following gave very good yield of the tartarimide (**3**).

2R 3R (+)-Tartaric acid (19 g) was added to *p*-xylene (500 ml) in a 2 l 3-necked flask fitted with a water separator and condenser. To the vigorously stirred and refluxing xylene solution was added benzylamine (16.5 g) in a period of ½ h and reflux was continued for 3 h. The solution was cooled in an ice bath and the crystalline product was filtered. After being washed twice with cold benzene, the crystalline product was recrystallized from water to give the tartarimide (**3**) (17 g), m.p. 196–198°, $[\alpha]_D^{25}$ + 126° (MeOH).

Reaction of Anisyl Magnesium Chloride with the Tartarimide (3)

To a 300 ml 3-necked flask containing magnesium (10 g) was added anisyl chloride (0.5 g), dissolved in

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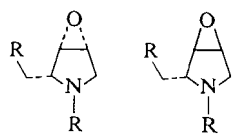
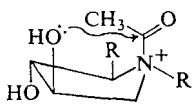
[1]The assignment of the epoxide ring *cis* to the anisyl ring is established by comparing the i.r. of (**10**) with the i.r. spectra of many synthetic and natural derivatives. Epoxides of the type (*i*) have strong and sharp absorption at 865 cm^{-1}. Epoxides of the type (*ii*) have strong and sharp absorption at 848 cm^{-1}.



(*i*) (*ii*)

[2]For the most stable conformation of the diol (**7**), the lone pair of electrons of the basic nitrogen atom should be *cis* to the C-4 hydroxy group. Thus a base catalyzed acetylation should acetylate the C-4 hydroxy group only as shown in (*iii*).

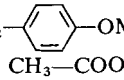


(*iii*)

anhydrous tetrahydrofuran (30 ml). After stirring for about 10 min, anhydrous tetrahydrofuran (150 ml) containing anisyl chloride (20 g) was added dropwise to the flask and the mixture was stirred vigorously for an additional 30 min. *N*-Benzyl tartarimide (**3**) (4.8 g) in anhydrous tetrahydrofuran (50 ml) was added to the Grignard reagent and the solution was stirred at room temperature overnight. Water (20 ml) was added to decompose the excess Grignard reagent. The excess magnesium was filtered and the clear solution was separated from the aqueous pasty residue which was further exhaustively extracted with ether. The combined organic extracts, dried over anhydrous magnesium sulfate, were evaporated to dryness to give a light-yellow solid residue. Recrystallization of the solid residue from nitromethane gave the white crystalline keto-amide (**4**) (5.3 g), m.p. 164–166 °C.

Infrared: ν_{max} (CH_2Cl_2) 3550, 3300, 3200, 1720, 1640, 1625, and 1590 cm^{-1}.

Mass spectra: M^+/e; 343, 325, 236, 218, 194, and 181.

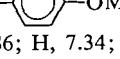
Nuclear magnetic resonance: $\tau(CDCl_3)$ (diacetate of **4**); 2.84 (s, 5 H's, aromatic), 3.15 (A_2B_2, 4H's, aromatic), 4.40 (AB quartet, 2 H's, J_{AB} = 3 c.p.s., C*H*—OCOMe), 5.57–5.71 (2 quartets, 2 H's, J_{AB} = 10 c.p.s., —NH—*CH*$_2$—Ph), 6.29 (s, 2 H's, —CO—CH_2—  —OMe), 6.35 (s, 3 H's, —OCH_3), 8.05 (s, 3 H's, CH_3—COO—), and 8.11 (s, 3 H's, CH_3COO—).

Anal. Calcd. for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.15; N, 4.08. Found: C, 66.76; H, 6.35; N, 4.09.

The first half of the above experiment was repeated and the excess magnesium was filtered from the tetrahydrofuran solution. It was then added dropwise to a refluxing tetrahydrofuran solution (300 ml) containing lithium aluminium hydride (3 g) and refluxing was continued for 6 h. After distilling off most of the solvent, ethyl acetate (500 ml) was added very slowly to the residue followed by 6 *N* hydrochloric acid (50 ml). After vigorous shaking, the ethyl acetate was separated. The aqueous fraction was made strongly basic and extracted with chloroform. Evaporation of the chloroform solution gave only a trace of residue. The ethyl acetate solution was concentrated and extracted by hydrochloric acid solution (5%). The acidic solution was made basic and the resulting precipitate was extracted into chloroform. Evaporation of the chloroform solution gave a gummy residue (2.1 g) from which the diol (**7**) (1.1 g) was obtained by crystallizing the residue from benzene and heptane, m.p. 113–114 °C, $[\alpha]_D^{25}$ +78° ($CHCl_3$).

Infrared: ν_{max} (CH_2Cl_2) 3560, 2900, 2780, 1600, and 1040 cm^{-1}.

Mass spectra: M^+/e;[3] 192, 121, and 91.

Nuclear magnetic resonance: $\tau(CDCl_3)$ 2.94 (s, 5 H's aromatic), 3.04 −3.40 (A_2B_2, 4 H's aromatic), 6.30 (s, 3 H's, —OCH_3), 6.00 and 6.72 (AB quartet, 2 H's, J_{AB} = 13 c.p.s. —N—CH_2—Ph), 6.25 (unresolved 2 H's, C_3—H and C_4—H), 7.10 (s, 2 H's, —OH), and 7.2–7.5 (unresolved 5 H's, C_2—H, C_5—H_2 and —*CH*$_2$—  —OMe).

Anal. Calcd. for $C_{19}H_{23}O_3N$: C, 72.86; H, 7.34; N, 4.47. Found: C, 72.84; H, 7.36; N, 4.50.

The mother liquor was purified by thin-layer chromatography (t.l.c.) over silica to give the triol (**6**), m.p. 120–123 °C.

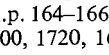
Infrared: ν_{max}(CH_2Cl_2) 3400, 1620, 1500, and 1075 cm^{-1}.

Mass spectra: M^+/e; 331, 313, 210, 121, and 91.

This triol was correlated with the lithium aluminium hydride reduction product of the keto-amide (**4**). The diol (**8**) (120 mg) was also isolated by t.l.c. from the mother liquor, m.p. 80–82 °C, $[\alpha]_D^{25}$ −51.0°.

Infrared: ν_{max}(CH_2Cl_2) 3570, 3450, 2900, 1600, and 1500 cm^{-1}.

Mass spectra: M^+/e;[3] 192, 121, and 91.

Nuclear magnetic resonance: $\tau(CDCl_3)$ 3.03 (s, 5 H's aromatic), 3.32 (A_2B_2, 4 H's aromatic), 6.16 and 6.81 (AB quartet, 2 H's, J_{AB} = 12 c.p.s. —N—*CH*$_2$—Ph), 6.42 (s, 3 H's, —OCH_3), 6.28 and 6.52 (unresolved 2 H's, C_3—H and C_4—H), 6.97 (s, 2 H's, —OH), 6.92–7.04 (unresolved 2 H's, C_5—H_2), 7.26 (broad s, 2 H's, —*CH*$_2$—  — OMe), and 7.96 (broad quartet, 1 H, C_2—H).

Conversion of the Diol (7) into the Epoxide (9)

The diol (7) (940 mg) was stirred in acetic anhydride (10 ml) for 20 min. Evaporation of the acetic anhydride to complete dryness gave a hydroxy acetate which was then dissolved in dry chloroform. To the chloroform solution was added phosphorus pentachloride (640 mg) in small portions; the mixture was stirred for 10 min and the chloroform solution was evaporated to dryness giving an orange foamy residue. To the residue was added ethanol (3 ml) followed by 20% KOH in ethanol (5 ml). After stirring for ½ h the solution was diluted with water (20 ml) and exhaustively extracted with chloroform. The chloroform solution was evaporated to dryness and the residue was separated by t.l.c. on silica to yield the epoxide (**10**) (240 mg), m.p. 113–115 °C, $[\alpha]_D^{25}$ ($CHCl_3$) +94°.

Infrared: ν_{max}(CH_2Cl_2) 1620, 1075, and 865 cm^{-1}.

Mass spectra: M^+/e; 295, 277, 174, and 91.

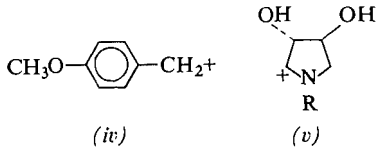
Nuclear magnetic resonance: $\tau(CDCl_3)$ 2.95 (s, 5 H's aromatic), 3.04 and 3.40 (A_2B_2, 4H's aromatic), 6.12 and 6.63 (AB, 2 H's, J_{AB} = 13 c.p.s. —N—CH_2— ), 6.37 (s, 3 H's, —OCH_3), and 7.73 (broad doublet 1 H, C_2—H).

Anal. Calcd. for $C_{19}H_{21}O_2N$: C, 77.30; H, 7.11; N, 4.74. Found: C, 77.22; H, 7.10; N, 4.88.

Preparation of (+)-N-Benzyl Deacetyl Anisomycin

The epoxide (**10**) (240 mg) was refluxed in glacial acetic acid for 1½ h. After evaporating the glacial acetic acid to dryness, sodium hydroxide solution (1 *N*, 20 ml) was added to the residue and the solution was refluxed for 2 h. Extraction of the cold basic solution with chloroform and evaporation of the chloroform solution to

[3]All compounds with a basic nitrogen atom in the pyrrolidine ring showed no parent peak in the mass spectrum. Only fragments (*iv*) and (*v*) were observable.



(*iv*) (*v*)

dryness gave a white foamy residue which was separated by t.l.c. on silica into two major diols (**7**) (66 mg) and (**11**) (78 mg), m.p. 79–81 °C, $[\alpha]_D^{25}$ ($CHCl_3$) +51.4°. Infrared, n.m.r., and mass spectra were identical to those of (**8**).

Debenzylation of N-Benzyl Deacetyl Anisomycin

(−)-*N*-Benzyl deacetyl anisomycin (60 mg) dissolved in ethanol (10 ml) containing 2 drops of concentrated hydrochloric acid and Pd/charcoal (5%) (20 mg) was hydrogenated for 3 h under atmospheric pressure. The catalyst was filtered off and the ethanolic solution evaporated to dryness to give the (+)-deacetyl anisomycin hydrochloride (45 mg); this was then recrystallized from methanol and ether, m.p. 224–226 °C, $[\alpha]_D^{25}$ +7°. Liberation of the free base by sodium hydroxide solution gave (−)-deacetyl anisomycin identical in every respect with the natural product. Debenzylation of (+)-*N*-benzyl deacetyl anisomycin as before gave (−)-*N*-deacetyl anisomycin hydrochloride, m.p. 219–221 °C, $[\alpha]_D^{25}$ −7°. Treatment of the hydrochloride with sodium hydroxide solution gave the free base (+)-deacetyl anisomycin, m.p. 168–170 °C, $[\alpha]_D^{25}$ ($CHCl_3$) +20°. Infrared, n.m.r., and mass spectra were identical to the natural (−)-deacetyl anisomycin except opposite sign of specific rotation.

Acknowledgments

The authors would like to express their appreciation to the National Research Council of Canada and Charles Pfizer and Co., Inc., for financial support and for the supply of anisomycin.

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