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AN EFFICIENT TOTAL SYNTHESIS OF MALEIMYCIN

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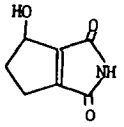
Abstract—Maleimycin (1), a minor metabolite of *Streptomyces showdoensis* possesses antibiotic and antitumor activity but is not available in sufficient quantity from natural sources for complete biological testing. Described is an efficient four step total synthesis of racemic maleimycin from readily available cyclopenten-1,2-dicarboxylic acid, which now makes this metabolite available in quantity.

Maleimycin, a minor metabolite of *Streptomyces showdoensis*, was recently isolated and assigned structure 1 by



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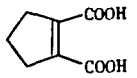
Suhadolnik *et al.*[2] Maleimycin was shown to have antibiotic and antitumor properties, but sufficient material is not available from natural sources for complete evaluation of biological activity. We describe a total synthesis of racemic maleimycin which now makes this compound available in gram quantity.

Cyclopentene-1,2-dicarboxylic acid (2), which can be prepared on a large scale in three steps from pimelic acid,[3] was converted to maleamic acid 3 (98% yield) by treatment with acetic anhydride followed by ammonium



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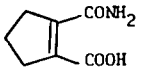

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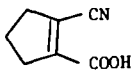

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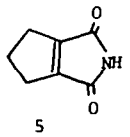
hydroxide. Attempted cyclization of 3 with acetic anhydride gave the known nitrile-acid 4[4] in 70% yield. It was found that the desired cyclization could be effected in 77% yield by treatment of 3 with refluxing trifluoroacetic anhydride, producing bicyclic imide 5.[5] As expected,[6] imide 5 shows a strong band at 1720 cm^{-1} and a weak band



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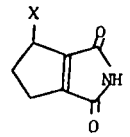

6 : X = Br
7 : X = $OCOCH_3$
8 : X = $OCOCF_3$

at 1770 cm^{-1} in the IR spectrum. This compound was cleanly brominated by N-bromosuccinimide, affording the crystalline allylic bromide 6 in 83% yield.

Treatment of bromide 6 with silver acetate in glacial acetic acid resulted in formation in 70% yield of maleimycin acetate (7). An alternative route to 7 (66% yield) involved treating bromide 6 with anhydrous potassium acetate in acetonitrile containing a catalytic amount of 18-crown-6 ether. Considerable effort was expended in an attempt to hydrolyze 7 to maleimycin. The best condition which be found (concentrated aqueous HCl in acetone/25°) resulted in only a 20% yield of racemic maleimycin (1) along with recovery of 50% of the starting maleimycin acetate. Reaction conditions more vigorous than these gave products resulting from hydrolysis of the imide ring.

These difficulties were overcome by utilizing an alternative procedure. Bromide 6, on treatment with silver trifluoroacetate, gave trifluoroacetate 8, which, without isolation or characterization, was hydrolyzed using a pH 4 buffer solution to give racemic maleimycin, m.p. 110–112° (58% from bromide 6). Synthetic maleimycin was identical to natural material except for optical rotation.[7]

EXPERIMENTAL

Δ^1-Cyclopentene-1,2-dicarboxylic acid monoamide (3). A suspension of 2 (1.00 g) in Ac_2O (10 ml) was stirred at room temp. for 16 hr. The resulting soln was evaporated to dryness *in vacuo* to give a brown oil: IR (max) ($CHCl_3$) 1815 and 1770 cm^{-1}. This oil was cooled in an ice bath and 10 ml of conc. ammonium hydroxide was added slowly. The resulting clear soln was acidified and the white solid that separated was washed with water and dried to give 0.98 g (98%) of 3. An analytical sample was recrystallized from EtOH giving white needles, m.p. 245°: IR (max) (Nujol) 3250, 1675 and 1610 cm^{-1}. (Found: 54.39; H, 5.98. Calc. for $C_7H_9NO_3$: C, 54.19; H, 5.85%).

2-Cyanocyclopenten-1-carboxylic acid (4). A suspension of 3 (466 mg; 3 mmol) in Ac_2O (5 ml) was heated on a steam bath for 3 hr and the resulting soln was evaporated to dryness *in vacuo*. The semi-solid, brown mass was chromatographed on 30 g of silica gel eluting with MeOH–$CHCl_3$ (2:98) giving 4 (290 mg; 70%) which crystallized from chloroform–hexane as needles, m.p. 95–97°. An analytical sample, m.p. 108–110°, was obtained by crystallization from chloroform–hexane (lit.[4] m.p. 109–110°): IR (max) ($CHCl_3$) 2200 (vw) and 1690 cm^{-1}; NMR ($CDCl_3$) δ 10.96 (1H, s), 1.82–3.18, (6H, m); *m/e* Calc. for $C_7H_7NO_2$: 137.04768. Found: 137.04697. (Found: C, 60.91; H, 5.10. Calc. for $C_7H_7NO_2$: C, 61.31; H, 5.14%).

3-Azabicyclo[3.3.0]oct-$\Delta^{1,5}$-ene-2,4-dione (5). A soln of 3 (930 mg; 6 mmol) in trifluoroacetic anhydride (5 ml) was heated at reflux for 16 hr, and the mixture was evaporated to dryness *in vacuo*. The residue was crystallized from chloroform–hexane to give 640 mg (77%) of shining needles, m.p. 171–173°. An analytical

sample, m.p. 177–179°, was obtained by sublimation (bath temp. 80–90°; 0.05 torr): IR (max) ($CHCl_3$) 3415, 1770 and 1720 and 1435 cm^{-1}; NMR ($CDCl_3$) δ 7.12–7.97 (1H, m), 2.27–3.27 (6H, m); UV (max) (C_2H_5OH) 223 nm (ϵ 10,700), 233 (10,900); mass spectrum: *m/e* 137 (11), 136 (100), 119 (8), 94 (71), 66 (99); *m/e* Calc. for $C_7H_7NO_2$: 137.04768. Found: 137.04735. (Found: C, 61.10; H, 5.30. Calc. for $C_7H_7NO_2$: C, 61.31; H, 5.14%).

3-Aza-6-bromobicyclo[3.3.0]*oct-*$\Delta^{1,5}$*-ene-2,4-dione* (**6**). A suspension containing **5** (411 mg; 3.0 mmol) and N-bromosuccinimide (540 mg; 3.03 mmol) in 20 ml of chloroform was heated at reflux for 15 min while being irradiated by a 275 W sun lamp. The pale yellow soln was washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to give a pale yellow solid. This material was crystallized from methylene chloride–hexane to give **6** (540 mg; 83%), m.p. 135-136°. An analytical sample was prepared by sublimation (bath temp. 110°; 0.05 Torr): IR (max) ($CHCl_3$) 3420, 1770, 1730 and 1340 cm^{-1}; NMR ($CDCl_3$) δ 8.7 (1H, m), 5.27 (1H, m), 2.17–3.62 (4H, m). (Found: C, 38.59; H, 2.71. Calc. for $C_7H_4NBrO_2$: C, 38.88, H, 2.77%).

3-Aza-6-acetoxybicyclo[3.3.0]*oct-*$\Delta^{1,5}$*-ene-2,4-dione* (*Racemic maleimycin acetate*) (**7**)

(a) A stirred soln of **6** (430 mg; 2 mmol) in glacial AcOH (10 ml) containing AcOAg (500 mg; 3 mmol) was heated under reflux for 2 hr. AgBr was filtered off, washed with AcOH (5 ml) and the combined filtrate was evaporated to dryness *in vacuo*. The dark residual oil was chromatographed on 50 g of silica gel eluting with acetone–benzene (5:95) to give 269 mg (70%) of a colorless oil: IR (max) ($CHCl_3$) 3395, 1770, 1730, 1375 and 1350 cm^{-1}; NMR ($CDCl_3$) δ 8.8 (1H, m), 6.05 (1H, m), 2.68 (4H, m), 2.1 (3H, s).

(b) A suspension of 18-crown-6 ether (13 mg; 0.05 mmol) and fused AcOK (148 mg; 1.5 mmol) in 5 ml of dry acetonitrile was stirred at room temp. for 30 min and freshly prepared **6** (162 mg; 0.75 mmol) was added. The resulting suspension was stirred for 20 hr. Water (10 ml) was added and the soln extracted twice with 10 ml portions of EtOAc. The combined EtOAc extract was washed with water, dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The oily residue was chromatographed on 10 g of silica gel eluting with hexane–EtOAc (3:1) to give 97 mg (66%) of a colorless oil identical by TLC, IR and NMR with the acetate obtained in part (a).

(*RS*) - 2 - *Aza* - 6 - *hydroxybicyclo*[3.3.0]*oct* - $\Delta^{1,5}$ - *ene* - 2,4 - *dione* (*Racemic maleimycin*) (**1**)

(a) Compound **7** (1.0 gm) was dissolved in acetone (20 ml) containing 1 ml of conc. HCl and the soln was allowed to stand for 2 hr at 25°. Water (20 ml) was added and the soln was extracted twice with 25 ml portions of EtOAc. The combined EtOAc extract was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The semi-solid residue was chromatographed on 15 g of silica gel eluting with hexane–EtOAc (1:1) affording 0.5 g of recovered maleimycin acetate in the early fractions. Later fractions gave 210 mg (53% based on maleimycin acetate consumed, 26% based on amt of maleimycin acetate used) of racemic **1**, which was recrystallized from benzene-hexane, m.p. 110–112°. This material had IR, UV, TLC, NMR and mass spectrum identical with natural material.[7] (Found: C, 54.54; H, 4.56; N, 9.08. Calc. for $C_7H_7NO_3$: C, 54.90; H, 4.60; N, 9.20%).

(b) Freshly prepared **6** (1.08 g; 5 mmol) was dissolved in trifluoroacetic acid (10 ml) containing silver trifluoroacetate (1.32 g; 6 mmol) and the mixture was stirred and heated at reflux for 2 hr. The soln was cooled and inorganic salts were removed by filtration and washed twice with 20 ml portions of methylene chloride. The combined filtrate was evaporated to dryness *in vacuo* leaving a brown residue. A soln of this product in 10 ml of hexane–EtOAc (3:1) was rapidly filtered through 10 g of silica gel and the column was eluted with an additional 100 ml of this same solvent mixture. Evaporation of the total eluant *in vacuo* gave 0.9 g of a pale yellow oil. A soln of this oil in 10 ml acetone was diluted with 10 ml of a standard pH 4.0 phosphate buffer soln and the resulting soln was allowed to stand at room temp. for 2 hr. Water (20 ml) was added and the mixture was extracted twice with 25 ml portions of EtOAc. The combined EtOAc extract was dried ($MgSO_4$) and evaporated *in vacuo* to give a crystalline residue. This material was chromatographed on 10 g of silica gel eluting with hexane–EtOAc (1:1) to give 0.45 g (58% yield based on bromide **6**) of racemic **1**, m.p. 110–112°, which was identical with synthetic maleimycin prepared in part (a).[7]

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[7]We are grateful to Prof. R. J. Suhadolnik, Temple University, for a sample of natural maleimycin.