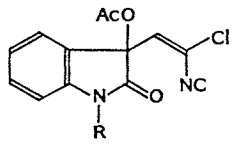
TOTAL SYNTHESIS OF INDISOCIN AND *N*-METHYLINDISOCIN

Sir:

Recently, we isolated a new isonitrile antibiotic indisocin[1] (**1**) (Fig. 1) from the culture filtrate of actinomycete strain MG323-hF2 and accomplished the synthetic method for the unique 1-chlorovinylisocyanide moiety[2]. In this paper, we report the total synthesis of (±)-(*E*,*Z*)-indisocin and (±)-(*E*,*Z*)-*N*-methylindisocin and the configuration of olefinic group in indisocin.

The synthesis of indisocin (**1**) and *N*-methylindisocin (**2**) were accomplished as follows (Scheme 1). Isatin was treated with Grignard reagent, vinylmagnesium bromide (2 eq) in THF to afford 3-hydroxy-3-vinyloxindole (**3**) in 63% yield [mp 138.5~140.0°C; ^{1}H NMR (acetone-d_6) δ 5.10 (1H, s), 5.20 (1H, dd, J=1.5 and 10.5 Hz), 5.30 (1H, dd, J=1.5 and 17.5 Hz), 6.04 (1H, dd, J=10.5 and 17.5 Hz), 6.85~7.40 (4H, m), 9.30 (1H, br); IR ν_{max}^{KBr} cm^{-1} 3310, 3175, 1715, 1625, 1475, 1390]. Compound **3** was acetylated with acetic anhydride and pyridine in the presence of 4-dimethylaminopyridine (DMAP) in dichloromethane (CH_2Cl_2) to give diacetyl derivative (**4a**) in 77% yield [mp 109.0~110.0°C; ^{1}H NMR ($CDCl_3$) δ 2.10 (3H, s), 2.66 (3H, s), 5.17 (1H, d, J=17.0 Hz), 5.42 (1H, d, J=10.5 Hz), 6.05 (1H, dd, J=10.5 and 17.0 Hz), 7.20~7.55 (3H, m), 8.30 (1H, br d, J=7.5 Hz); IR ν_{max}^{KBr} cm^{-1} 1765, 1740, 1720, 1610, 1465, 1370]. The *N*-acetyl group in **4a** was selectively removed with sodium bicarbonate in methanol to afford **4b** in 75% yield [mp 143.0~144.0°C; ^{1}H NMR ($CDCl_3$) δ 2.09 (3H, s), 5.28 (1H, d, J=17.0 Hz), 5.35 (1H, d, J=10.5 Hz), 6.03 (1H, dd, J=10.5 and 17.0 Hz), 6.80~7.40 (4H, m), 9.03 (1H, br s); UV λ_{max}^{MeOH} nm (ε) 288 (2,200), 255 (7,700), 217 (16,300); IR ν_{max}^{KBr} cm^{-1} 3425, 3100, 1755, 1740, 1705, 1625, 1475, 1240]. Methylation of **4b** with sodium hydride and methyl iodide in THF at 0°C gave the *N*-methyl derivative (**4c**) in 73% yield [^{1}H NMR

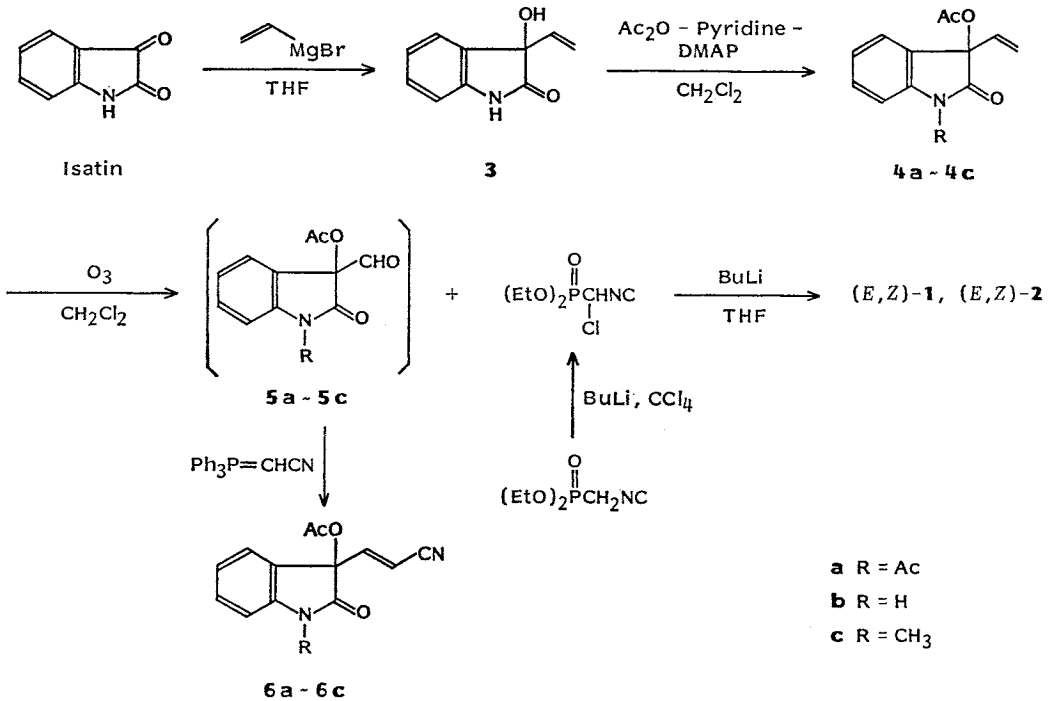
Fig. 1.



Indisocin (**1**) R = H

N-Methylindisocin (**2**) R = CH_3

Scheme 1.



($CDCl_3$) δ 2.07 (3H, s), 3.23 (3H, s), 5.26 (1H, d, J=17.0 Hz), 5.34 (1H, d, J=10.5 Hz), 6.03 (1H, dd, J=10.5 and 17.0 Hz), 6.8~7.5 (4H, m)]. In ozonolysis (O_3 in CH_2Cl_2 at −78°C then $(CH_3)_2S$) of **4a**~**4c**, the resulting aldehyde **5a**~**5c** would not be obtained as a pure form. However, the formation of the aldehyde was recognized as the intermediate as follows. After ozonolysis of **4a** to give the intermediary **5a**, the reaction mixture was concentrated under reduced pressure and dissolved in benzene. Cyanomethylenetriphenylphosphorane was added to this solution and the mixture was stirred for 3 hours at room temp to give **6a** in 62% yield [^{1}H NMR ($CDCl_3$) δ 2.13 (3H, s), 2.66 (3H, s), 5.64 (1H, d, J=16.5 Hz), 6.63 (1H, d, J=16.5 Hz), 7.20~7.60 (3H, m), 8.32 (1H, br d, J=9.0 Hz)]. Compounds **6b** and **6c** were also prepared from **4b** and **4c** respectively by the same way as described above in 65% and 58% yield [**6b**: MP 79.5~82.0°C; ^{1}H NMR ($CDCl_3$) δ 2.13 (3H, s), 5.69 (1H, d, J=16.5 Hz), 6.62 (1H, d, J=16.5 Hz), 6.85~7.50 (4H, m), 8.07 (1H, br); IR ν_{max}^{KBr} cm^{-1} 2230, 1750, 1715, 1620, 1470, 1240, **6c**: ^{1}H NMR ($CDCl_3$) δ 2.11 (3H, s), 3.25 (3H, s), 5.71 (1H, d, J=16.5 Hz), 6.58 (1H, d, J=16.5 Hz), 6.8~7.55 (4H, m)]. Now, (±)-(*E*,*Z*)-indisocin and (±)-(*E*,*Z*)-*N*-methylindisocin were similarly synthesized. The THF solution of the crude aldehyde (**5b** or **5c**) which was prepared by ozonolysis of **4b** or **4c**, was added to the THF solution of diethyl chloroisocyanomethylphosphonate[2] which was prepared from diethyl isocyanomethylphosphonate[3] and carbon tetrachloride in the presence of butyllithium at −78°C. After 20 minutes, the reaction mixture was quenched with acetic acid and poured into CH_2Cl_2. The CH_2Cl_2 solution was washed with 0.1 M phosphate buffer (pH 7.0) and chromatographed on a silica gel column to give (±)-(*E*,*Z*)-**1** or (±)-(*E*,*Z*)-**2**. (*E*:*Z*≒1:1) [(±)-(*E*,*Z*)-**1**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.11 and 2.14 (3H, each s), 6.03 and 6.47 (1H, each s), 6.88 and 6.91 (1H, each d, J=8.0 Hz), 7.08 and 7.10 (1H, each t, J=8.0 Hz), 7.25~7.40 (2H, each m), 7.83 and 7.86 (1H, each br s), (±)-(*E*,*Z*)-**2**: Electron impact mass spectra (EI-MS) *m*/*z* 292 and 290 $(M)^+$; ^{1}H NMR ($CDCl_3$) δ 2.08 and 2.12 (3H, each s), 3.26 and 3.27 (3H, each s), 6.08 and 6.49 (1H, each s), 6.85 and 6.89 (1H, each d, J=9.0 Hz), 7.0~7.6 (3H, each m)]. *E*-Configuration of natural indisocin was determined by comparison of the chemical shift of the vinylic proton in natural indisocin (δ 6.03) and those of synthetic isomer (δ 6.03 and 6.47)[2,4].

Thus, labile antibiotics, indisocin and *N*-methylindisocin have been effectively synthesized by our procedure using diethyl haloisocyanomethylphosphonate, which is promising for application to the synthesis of antibiotic substances containing 1-halogenated vinylisocyanides.

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