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THE SYNTHESIS OF dl-FURANOMYCIN

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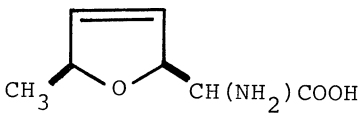
The synthesis of dl-furanomycin, an antibiotic α-amino acid with a 2,5-dihydrofuran moiety, is described.

Furanomycin (1), an isoleucine antagonist, was isolated from a culture filtrate of Streptomyces L-803 and formulated as α-amino(cis-2,5-dihydro-5-methyl)furan-2-acetic acid by Katagiri and coworkers.[1] We describe herewith the synthesis of dl-furanomycin as a result of continuing studies on dihydrofurans.[2]

The Birch reduction of 5-methyl-2-furoic acid under limited conditions[2a] produced a partially crystalline mixture of diastereoisomeric 5-methyl-2,5-dihydrofuroic acids (2), from which a trans-isomer,[3] mp 52.5-54°C, with $J_{2,5}$[2a] of 4 Hz, was isolated in 23% yield. The remaining acid mixture, bp 99-101°C (4 mmHg), obtained in 53% yield, contained a cis-isomer with $J_{2,5}$[2a] of 6 Hz (estimated by triple resonance) as a major component (75-80%) and was used for subsequent transformation[4] without further purification.

The acids were converted into acid chlorides (3), bp 48-50°C (8 mmHg), m/e 83, and ν_{max} 1810 cm^{-1}, in 65% yield. These were transformed successively with diazomethane[5] to diazoketones, ν_{max} 2122 and 1637 cm^{-1}, with acetic acid at 50-60°C[5] to keto-acetates, ν_{max} 1760 (sh), 1742, 1258, and 1230 cm^{-1}, and then with hydroxylamine to oxime acetates (4), bp 138-140°C (bath temp) (14 mmHg), m/e 199 and 83, and ν_{max} 3320, 1746, and 1696 cm^{-1}, in 47% yield. The oxime acetates (4), after being derived to the dihydropyranyl ethers (5), m/e 85 and 83, and ν_{max} 1747, 1115, and 1078 cm^{-1}, with dihydropyran (2 equiv) and acid (PTS), was submitted to saponification with potassium carbonate (1 equiv) in aqueous methanol to give a mixture of alcohols (6), bp 136-137°C (bath temp) (14 mmHg), m/e 241, 85, and 83, and ν_{max} 3443, 1118, and 1079 cm^{-1}, in 65% yield.



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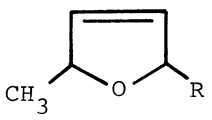
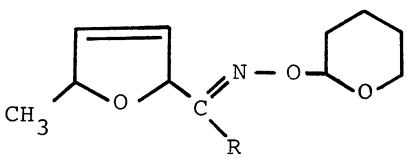


2 R=COOH
3 R=COCl
4 R=C(=NOH)CH_2OCOCH_3
8 R=C(=NOH)$COOCH_3$
9 R=CH(NH_2)$COOCH_3$



5 R=CH_2OCOCH_3
6 R=CH_2OH
7 R=$COOCH_3$

A modification of the Collins oxidation[6] of alcohols 6 afforded aldehydes, ν_{max} 1705, 1115, and 1075 cm^{-1}, and δ ($CHCl_3$) 10.24 (ca., 1H, s), which were further oxidized with silver oxide to the corresponding acids, ν_{max} 3200 and 1735 cm^{-1}, and δ ($CHCl_3$) 8.70 (1H, s), and then treated with diazomethane to give methyl esters (7), bp 166-167°C (bath temp) (14 mmHg), m/e 85 and 83, and ν_{max} 1747, 1118, and 1068 cm^{-1}, in 77% yield. Treatment of esters 7 with acid (PTS) in boiling methanol produced oximino esters (8) in 85% yield, which were purified by column chromatography over silicic acid to separate a mixture (8-c) of the cis,syn- and cis,anti-isomers, bp 155-157°C (bath temp) (14 mmHg), and m/e 185, 183, 126, and 83, and ν_{max} 3320 and 1745 cm^{-1}, in 53% yield. Reduction of oximino esters 8-c with aluminum amalgam in aqueous ethanol followed by preparative TLC over silica gel led to isolation of one (9), ν_{max} ($CHCl_3$), 3380, 1738, 1590, 1263, and 1220 cm^{-1}, and δ 1.26 (3H, J = 6 Hz), 2.01 (2H, br, NH_2), 3.54 (1H, br), 3.80 (3H, s), 5.02 (1H, br qui J = 6 Hz, H at C_5), 5.21 (1H, br, H at C_2), 5.76 and 6.00 (each 1H, br ABq J = 6 Hz, 2H at C_4 and C_5), and $J_{2,5}$ = 6 Hz (estimated by double resonance), of diastereoisomeric amino esters, in 18% yield, which was identical with an authentic specimen derived from d-furanomycin[1] (1) in IR ($CHCl_3$) and NMR spectra ($CDCl_3$), and TLC. Compound 9 was converted into the hydrochloride, white needles, mp 204-208°C (dec), which on hydrolysis with base (1M aq NaOH) and subsequent purification by paper chromatographies[1] (PC) gave dl-furanomycin (dl-1), white needles, mp 208-211°C, ν_{max} (Nujol) 3060, 2060, 1630, 1600, 1530, 1405, and 1095 cm^{-1}, in 69% yield, which was identical with the natural sample in NMR spectrum (D_2O), PC and TLC.[7]

REFERENCES and FOOTNOTES

1) K. Katagiri, K. Tori, Y. Kimura, T. Toshida, T. Nagasaki, and H. Minato, J. Med. Chem., 10, 1149 (1967).

2) a) T. Masamune, M. Ono, and H. Matsue, Bull. Chem. Soc. Japan, 48, 491 (1975). b) T. Masamune, S. Numata, H. Matsue, T. Sato, A. Matsuyuki, and H. Murase, Bull. Chem. Soc. Japan, in press.

3) All numbered, new compounds gave elementary analyses in good accord with the assigned structures. The IR spectra were measured in liquid state, unless otherwise stated.

4) All attempts to prepare 1 by usual amino acid synthetic methods, e.g., via the corresponding aldehydes, failed owing to instability of the aldehydes; cf., D. O. Holland and J. H. C. Nayler, J. Chem. Soc., 1952, 3403; K. Matsumoto, M. Suzuki, M. Miyoshi, J. Org. Chem., 38, 2094 (1973).

5) Cf., H. K. Mangold, J. Org. Chem., 24, 405 (1959).

6) R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).

7) We are indebted to Doctors K. Katagiri, T. Yoshida, H. Minato and coworkers, Shionogi Research Laboratory, Osaka, for providing us with samples and spectral charts of natural furanomycin and its derivatives.

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