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SYNTHESIS OF PIPERAZINOMYCIN, A NOVEL ANTIFUNGAL ANTIBIOTIC

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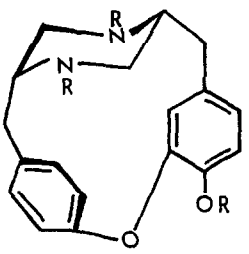
Summary: Piperazinomycin, a novel antifugal antibiotic, has been synthesized from tetrabromotyrosyltyrosine, whose oxidation with thallium trinitrate (TTN) leads to the formation of a strained 14-membered ring similar to that of piperazinomycin as a key step.

Piperazinomycin, a novel tyrosine-derived antibiotic, has been isolated as a minor metabolite of Streptoverticillium olivoreticuli subsp. neoenacticus[1] and its stereostructure has also been determined by means of an X-ray crystallographic analysis.[2] In connection with our synthetic study on tyrosine-derived metabolites,[3] we are interested in piperazinomycin which has a unique structure and shows inhibitory activity against fungi and yeasts, particularly against Trichophyton.[1] Recent publication[4] of synthetic study on piperazinomycin and herquline prompted us to describe a total synthesis of (+)-piperazinomycin (1).

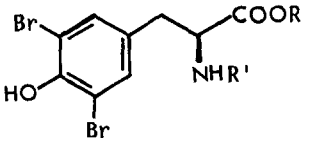
The known N-formyl-L-tyrosine methyl ester, $[\alpha]_D^{20}$ +25.8° (c 3.0, MeOH) (lit. +25.75°),[5] was subjected to bromination [Br_2 (2 equiv.) - AcONa (2 equiv.) (0 °C, 35 min and then room temp., 1 h)] to afford N-formyl-3,5-dibromotyrosine methyl ester (2),[6] in 88% yield, which was further treated with 2M HCl - MeOH (room temp., 25 min) to give 3,5-dibromotyrosine methyl ester (3)[6] as a hydrochloride, in quantitative yield. N-Formyl-3,5-dibromotyrosine (4)[6] was also obtained from 2, in quantitative yield, on hydrolysis [1) 1M aqueous NaOH (room temp., 20 min); 2) Amberlite IR-120 (H^+) (room temp., 5 min)]. These two compounds (3 and 4) so far obtained were connected to each other using DCC (1.2 equiv.) - Et_3N (1.0 equiv.) - N-hydroxysuccinimide (1.0 equiv.) in DMF (0 °C - room temp., 22 h) to afford an amide (5),[6] in 81% yield, which was hydrolyzed with 1.5M HCl - MeOH (refluxing temp., 75 min) and then treated with 0.1M AcOH in 2-butanol containing N-methylmorphorine (1.0 equiv.) (refluxing temp., 2 h)[7] to give rise to the corresponding desired diketopiperazine (6),[6] in 85% overall yield from 5.

As described in the previous paper,[3,8] we developed a new method to synthesize the biphenyl ethers by TTN oxidation of the corresponding o,o'-dibromophenols followed by zinc reduction, wherein the two ortho-positions should be occupied by two halogen atoms. As expected from its reaction mechanism, our method is quite different from other ones leading to the formation of biphenyl ethers. Particularly, it seems possible to synthesize such strained molecules as piperazinomycin[1] and bouvardin.[9]

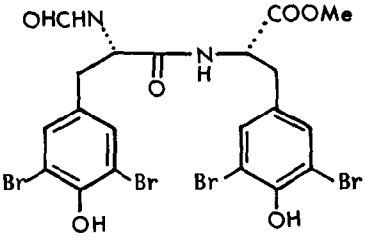
Thus, the diketopiperazine (6) in MeOH was subjected to oxidation [TTN (1.5 equiv.) (0 - 4 °C, 12 h) and then additional TTN (0.7 equiv.) (0 °C, 3 h)][10] to afford an inseparable mixture, which was directly reduced with zinc powder in AcOH - THF (room temp., 18 h) to give rise to three biphenyl ethers (7, 8, and 9)[6,11] in 19, 5, and 11% yields,



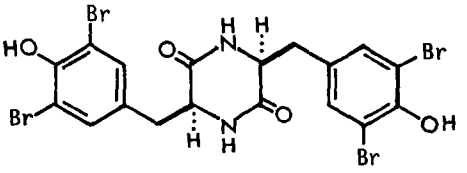
1 R = H
14 R = CH_2Ph



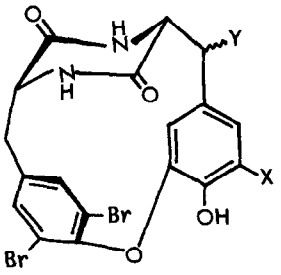
2 R = Me, R' = CHO
3 R = Me, R' = H
4 R = H, R' = CHO



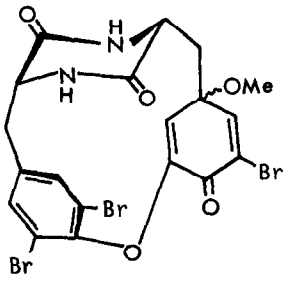
5



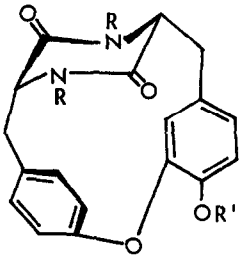
6



7 X = Br, Y = H
8 X = OMe, Y = H
9 X = Y = OMe



10



11 R = R' = H
12 R = H, R' = Ac
13 R = R' = CH_2Ph

respectively. The desired biphenyl ether (7) must be formed on zinc reduction of a plausible oxidation intermediate (10).[3,8] In the next step, this biphenyl ether (7) was subjected to catalytic hydrogenation [H_2 - 10% Pd - C - AcONa (3 equiv.) in MeOH (room temp., overnight)] to afford the corresponding phenol (11),[6,12] which was treated with Ac_2O in pyridine (room temp., 7 h) to give rise to an acetoxybiphenyl ether (12),[6] in 56% overall yield from 7. Furthermore, the compound (12) was readily converted into a tribenzyl derivative (13)[6] in 3 steps [1) $PhCH_2Br$ (5 equiv.) - NaH (3.5 equiv.) in DMF (0 °C, 21 min, under argon); 2) K_2CO_3 (1 equiv.) in MeOH (room temp., 23 min, under argon); 3) $PhCH_2Br$ (2.5 equiv.) - NaH (2 equiv.) in DMF (0 °C, 22 min, under argon); 78% overall yield].[13]

Finally, piperazinomycin (1) was successfully synthesized from 13 in 2 steps, as follows. The compound (13) so far obtained was successively treated with $NaBH_4$ (9 equiv.) - $BF_3 \cdot OEt_2$

(12 equiv.) in THF (refluxing temp., 17 h),[4,12] 2M aqueous HCl (room temp., 30 min), and then aqueous $NaHCO_3$ (pH 8) (room temp., 20 min) to afford the corresponding piperazine (14)[6] in 48% yield. This compound (14) was further subjected to catalytic hydrogenation [H_2 - 10% Pd - C in MeOH containing conc.HCl (1 drop) (room temp., overnight)] to afford a reduction product, in 75% yield, which was completely identical with natural piperazinomycin (1) in all respects of spectral data.[1] The optical rotation of the synthetic sample ($[\alpha]_D^{28}$ +24° (c 0.29, MeOH), which has been proved to be quite sensitive to pH of the solution, is roughly compatible with that of natural one ($[\alpha]_D^{23}$ +31° (c 0.74, MeOH)).[1]

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References and Notes

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5. J. C. Sheehan and D-D. Yang, J. Am. Chem. Soc., 80, 1154 (1985).
6. The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: 2: mp 163.5 - 165 °C; $[\alpha]_D^{21}$ +28.7° (c 2.9, MeOH); $C_{11}H_{11}NO_4{}^{79}Br^{81}Br$ [m/z 381.9146(M^+)]; IR (Nujol) 1750, 1670sh., and 1660 cm^{-1}; δ(pyridine-d_5) 3.70(3H, s) and 8.62(1H, s). 3: mp 119 - 120 °C; $[\alpha]_D^{21}$ +8.7° (c 2.71, MeOH); $C_{10}H_{11}NO_3{}^{79}Br^{81}Br$·HCl [m/z 353.9143($M^+$ - Cl)]; IR (Nujol) 3220 and 1750 cm^{-1}; δ(CD_3OD) 3.15(2H, d, J= 7.5Hz), 3.87(3H, s), 4.27(1H, t, J= 7.5Hz), and 7.41(2H, s). 4 as a powder: $[\alpha]_D^{21}$ +46.0° (c 3.7, MeOH); IR (Nujol) 3200br., 1755, and 1670br. cm^{-1}; δ(acetone-d_6) 7.45 (2H, s) and 8.20(1H, s). The molecular ion peak of 4 has not been detected, but its structure can be supported by the above spectral data. 5 as powder: $[\alpha]_D^{24}$ -6.2° (c 1.28, DMF); $C_{20}H_{18}N_2O_6{}^{79}Br^{81}Br$ [m/z 699.7905(M^+)]; IR (Nujol) 3300, 1725, 1650, 1635, and 1550 cm^{-1}; δ(pyridine-d_5) 3.72(3H, s), 7.45(2H, s), 7.55(2H, s), and 8.52(1H, s). 6 : mp ca. 200 °C (dec); $[\alpha]_D^{27}$ -123° (c 0.99, pyridine); $C_{18}H_{14}N_2O_4{}^{79}Br^{81}Br$ [m/z 643.7631(M^+)]; IR (Nujol) 3200, 1670, 1590, and 1550 cm^{-1}; δ(pyridine-d_5) 2.60(2H, dd, J= 9, 13.5Hz), 3.21(2H, dd, J= 4.5, 13.5Hz), 4.4 - 4.6(2H, complex), 7.60(4H, s), and 9.45(2H, br.s). 7 as a powder: $[\alpha]_D^{26}$ +124.4° (c 1.10, pyridine); $C_{18}H_{13}N_2O_4{}^{79}Br^{81}Br$ [m/z 561.8376(M^+)]; IR (Nujol) 3200, 1670, 1570, 1550, and 1500 cm^{-1}; δ(acetone-d_6) 2.6 - 3.7(4H, complex), 4.3 - 4.6(2H, complex), 4.57(1H, d, J= 2Hz), 6.90(1H, d, J= 2Hz), 7.56(1H, d, J= 2Hz), and 7.75(1H, d, J= 2Hz). 8 as a powder: $C_{19}H_{16}N_2O_5{}^{79}Br_2$ [m/z 509.9421(M^+)]; IR (nujol) 3200br., 1680br., and 1515 cm^{-1}; δ(acetone-d_6) 3.75(3H, s), 4.17(1H, d, J= 2Hz), 6.35

(1H, d, J= 2Hz), 7.50(1H, d, J= 2Hz), and 7.67(1H, d, J= 2Hz). 9 as a crystalline solid: $C_{20}H_{18}N_2O_6{}^{79}Br_2$ [m/z 539.9541(M^+)]; IR (Nujol) 3170, 1660, 1585, and 1495 cm^{-1}; δ (acetone-d_6) 2.98(1H, dd, J= 6, 15Hz), 3.38(3H, s), 3.55(1H, dd, J= 3, 15Hz), 3.80(3H, s), 4.35 - 4.75(3H, complex), 4.55(1H, d, J= 2Hz), 6.63(1H, d, J= 2Hz), 7.48(1H, d, J= 2Hz), and 7.62(1H, d, J= 2Hz). 11 as a powder: $C_{18}H_{16}N_2O_4$ [m/z 324.1118(M^+)]; IR (Nujol) 3200br., 1655, 1585, and 1515 cm^{-1}; δ (pyridine-d_5) 3.1 - 4.0(4H, complex), 4.3 - 4.85 (2H, complex), 4.90(1H, d, J= 2Hz), 6.67(1H, dd, J= 2, 7.5Hz), and 6.9 - 7.8(5H, aromatic). 12 as a powder: $[\alpha]_D^{27}$ +190° (c 0.19, pyridine); $C_{20}H_{18}N_2O_5$ [m/z 546.2138(M^+)]; IR (Nujol) 3200br., 1765, 1665, and 1585 cm^{-1}; δ (pyridine-d_5) 2.25(3H, s), 4.87(1H, d, J= 2Hz), 6.60(1H, dd, J= 2, 9Hz), and 6.7 - 7.8(5H, aromatic). 13 as a syrup: $[\alpha]_D^{26}$ -65° (c 1.29, $CHCl_3$); $C_{39}H_{34}N_2O_4$ [m/z 594.2515(M^+)]; IR (film) 1650, 1645, 1600, 1580, and 1510 cm^{-1}; δ ($CDCl_3$) 2.6 - 4.4(8H, complex), 4.12(1H, d, J= 2Hz), 5.18(2H, s), 5.28 (1H, d, J= 18Hz), 5.80(1H, d, J= 18Hz), 6.52(1H, dd, J= 2, 9Hz), and 6.6 - 7.6(20H, aromatic). 14 as an oil: $[\alpha]_D^{28}$ -22° (c 0.69, $CHCl_3$); $C_{39}H_{38}N_2O_2$ [m/z 566.2936(M^+)]; IR (film) 1590, 1575, and 1510 cm^{-1}; δ ($CDCl_3$) 2.0 - 3.4(12H, complex), 3.80(1H, d, J= 13.5Hz), 5.20(2H, s), 6.02(1H, d, J= 2Hz), 6.40(1H, dd, J= 2, 9Hz), and 6.55 - 7.7 (20H, aromatic).

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10. The reaction condition for this TTN oxidation is not always optimum.
11. The formation process of these cyclization products will be described elsewhere in detail.
12. Although direct reduction of 11 as well as of 12 with excess amounts of $NaBH_4$ - $BF_3 \cdot OEt_2$ in THF has been attempted, piperazinomycin has not yet been obtained.
13. Direct benzylation of 11 has been also carried out to give the corresponding tribenzyl derivative (13). However, its yield is not so high as expected.

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