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BIOMIMETIC OXIDATION OF METHYL 3,5-DIBROMO-4-HYDROXYPHENYLPYRUVATE OXIME AND RELATED PHENOLS

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Summary: Methyl 3,5-dibromo-4-hydroxyphenylpyruvate oxime and related phenols were subjected to oxidation using thallium (III) nitrate as well as to anodic oxidation to afford the corresponding spiro-isoxazols, dimeric compounds, and others.

In connection with the novel metabolites derived from brominated tyrosine (aerothionin[1] and bastadin-2[2]), we wish to describe biomimetic oxidation of methyl 3,5-dibromo-4-hydroxyphenylpyruvate oxime (**1**) and related compounds (**2** and **3**), including new and interesting results, although Forrester and his co-workers have reported the synthesis of some interesting spiro-isoxazols.[3]

When treated with thallium (III) nitrate (TTN) (2 eq) in MeOH (-35°, 20 - 25 h), **1** was mainly converted into a dimer (**4**)[4] *via* a plausible intermediate (**5**), in 37 - 44% yield, in addition to the known spiro-isoxazol (**6**)[3] (7 - 11% yield). Furthermore, this dimer (**4**) was readily reduced with excess Zn powder[5] in AcOH (room temp., 1 h) to afford a biphenyl ether (**7**)[6] in 40% yield, from which bastadin-2[2] or its geometrical isomer at the oxime C=N bond must be synthesized.[7] On the other hand, the yield of **6** was improved by means of anodic oxidation: a solution of **1** (600 mg) in MeOH (180 ml) containing $LiClO_4$ (2.4 g) was electrolyzed at +1300 mV *vs*. SCE, and quenched at *ca*. 2.1 F/mole to afford **6** in almost quantitative yield.[8]

We further carried out oxidation of 3,5-dibromo-4-hydroxyphenylpyruvic acid O-methyloxime (**2**)[9] with TTN (2 eq) in MeOH (50 - 60°, 15 h) leading to the formation of the corresponding methyl ester (**3**)[10] and a dimer (**8**) in 6 and 9% yields, respectively. Clearly, the structure of the latter is similar to that of **4**, as judged by comparing their spectral data.[11] This dimer (**8**) was also obtained from the corresponding methyl ester (**3**) in 22% yield, under the same condition as that of **2**. Finally, anodic oxidation of **2** in MeOH containing $LiClO_4$ was carried out at +1300mV *vs*. SCE under the same condition as that of **1**, and quenched at 2.3 F/mole to afford a lactone (**9**)[1 in 27% yield. Molecular formula of the compounds cited herein were determined by means of elemental analyses and/or high resolution mass spectra.

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References and Notes

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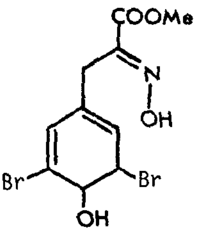

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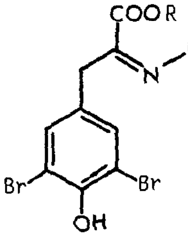

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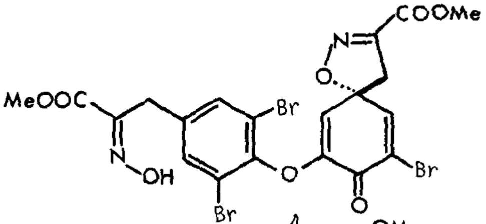
3 R = Me



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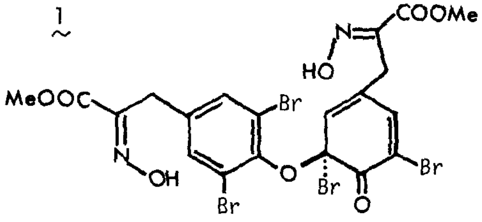

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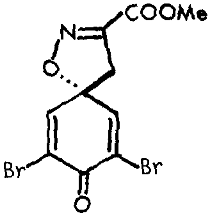

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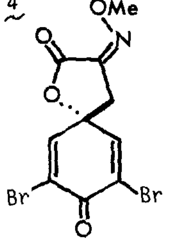

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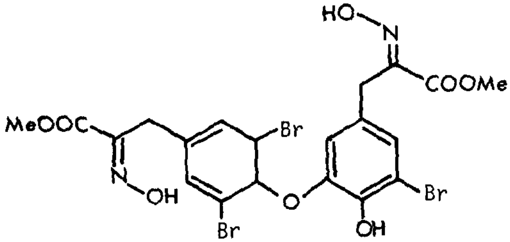

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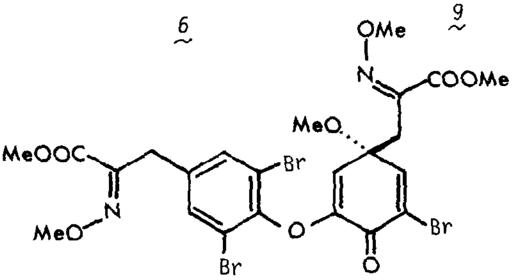

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2. R. Kazlauskas, R.O. Lidgard, P.T. Murphy, and R.J. Wells, Tetrahedron Lett., 1980, 2277.
3. A.R. Forrester, R.H. Thomson, and S.O. Woo, J. Chem. Soc. Perkin I, 1975, 2340 and 2348: Justus Liebigs Ann. Chem., 1978, 66.
4. 4: $C_{20}H_{15}N_2O_8Br_3$ [m/e 654, 652, 650, and 648(M$^+$)]; ν_{max} (Nujol) 3275, 1735br., 1695, 1655, 1605, and 1590 cm^{-1}; ^{1}H NMR (pyridine-d$_5$); δ3.30(1H, d, J= 18Hz), 3.50(1H, d, J= 18Hz), 3.72 (6H, s), 3.92(2H, s), 5.68(1H, d, J= 2.5Hz), 7.35(1H, d, J= 2.5Hz), and 7.58(2H, s); ^{13}C NMR (pyridine-d$_5$): δ30.0(t), 34.9(t), 52.9(q), 63.6(q), 77.1(s), 117.1(s), 120.1(d), 123.5(s), 133.2(d), 136.3(s), 146.1(s), 147.1(s), 148.4(s), 151.3(d), 163.1(s), 163.4(s), and 170.0(s).
5. Zinc powder was activated according to the same procedure as described in the following paper: S. Yamamura, M. Toda, and Y. Hirata, Organic Syntheses, 53, 86 (1973).
6. 7: $C_{20}H_{17}N_2O_8Br_3$ [m/e 656, 654, 652, and 650(M$^+$)]; ν_{max} (film) 3375, 3300, 3150br., 1735, 1590sh., 1570, and 1500 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ3.53(3H, s), 3.63(3H, s), 3.5-3.65(4H, superimposed on MeO signals), 6.10(1H, d, J= 2Hz), 6.92(1H, d, J= 2Hz), and 7.38(2H, s).
7. The geometry at the oxime C=N bonds remains unsettled.
8. Anodic oxidation of 1 was carried out, using a 200 ml glassy carbon beaker (GC-20) as an anod and a platinum electrode as a cathode, without separation.
9. This compound (2) was selectively obtained by treatment of 3,5-dibromo-4-hydroxyphenylpyruvic acid with methoxyamine hydrochloride in the presence of $NaHCO_3$ (room temp., 24 h). The geometry at the C=N bond is syn.
10. 3: mp 126-127° (from hexane-AcOEt); $C_{11}H_{11}NO_4Br_2$ [m/e 383, 381, and 379(M$^+$)]; ν_{max} (Nujol) 3440, 1710br., and 1610 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ3.77(2H, s), 3.83(3H, s), 4.08(3H, s), 5.78 (1H, br.s), and 7.28(2H, s).
11. 8: $C_{23}H_{23}N_2O_9Br_3$ [m/e 714, 712, 710, and 708(M$^+$)]; ν_{max} (film) 1730br., 1700, 1655, and 1615 cm^{-1}; ^{1}H NMR (CDCl$_3$)· δ3.01(2H, s), 3.14(3H, s), 3.76(3H, s), 3.84(5H, s), 3.93(3H, s), 4.09(3H, s), 5.32(1H, d, J= 2Hz), 7.06(1H, d, J= 2Hz), and 7.43(2H, s); ^{13}C NMR (CDCl$_3$): δ30.0(t), 34.9(t), 52.9(q), 63.6(q), 77.1(s), 117.1(s), 120.1(d), 123.5(s), 133.2(d), 136.3 (s), 146.1(s), 147.1(s), 148.4(s), 151.3(d), 163.1(s), 163.4(s), and 172.0(s).
12. 9: mp 207-210° (dec) (from MeOH-Et$_2$O); $C_{10}H_7NO_4Br_2$ [m/e 367, 365, and 363(M$^+$)]; ν_{max} (Nujol) 1790, 1680, 1640, and 1600 cm^{-1}; ^{1}H NMR (pyridine-d$_5$): δ3.45(2H, s), 3.90(3H, s), and 7.80(2H, s).

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