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AN EFFECTIVE SYNTHESIS OF A BROMINE-CONTAINING ANTIBACTERIAL COMPOUND FROM MARINE SPONGES

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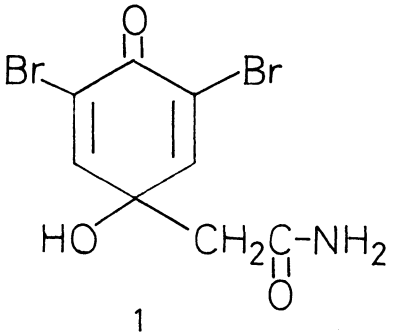
An antibacterial compound 1, 4-acetamido-2,6-dibromo-4-hydroxy-2,5-cyclohexadien-1-one, was effectively synthesized by an oxidation of phenolic amide 3 with thallium triperchlorate in aqueous media.

Recently a series of bromine-containing antibiotics and other closely related compounds have been isolated from marine sponges.1-3) Sharma and Burkholder1) have described the synthesis of an antibacterial compound, 4-acetamido-2,6-dibromo-4-hydroxy-2,5-cyclohexadien-1-one 1, isolated from *Verongia cauliformis*, by means of the reaction of phenolic amide 3 with concentrated nitric acid according to the procedure reported by Müller et al.,4) although details are not mentioned. Now we report a simple and effective synthesis of the compound 1 by the direct oxidation of the phenolic amide 3 with thallium triperchlorate in aqueous media. This method which we recently developed5) permitted efficiently the synthesis of the 4-hydroxycyclohexadienones.



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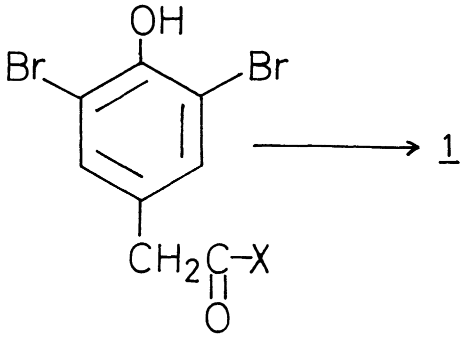


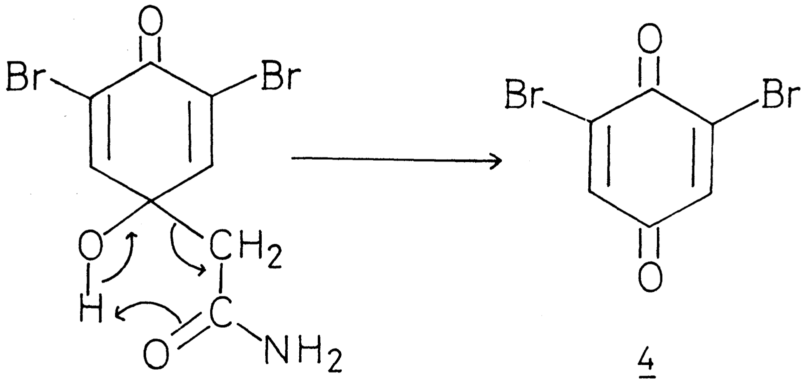
2 X=OH
3 X=NH2

Reaction of the dibromide 2, which was prepared from p-hydroxyphenylacetic acid by the usual bromination2), with diphenyl phosphite6) in pyridine followed by an addition of 28 % aqueous ammonia at room temperature afforded the phenolic amide 3 in 70 % yield; m.p. 190-191°, ν_{max}(KBr) 3420, 1630 and 1595 cm^{-1}, δ_{ppm}(pyridine-d_5) 3.70(2H,s) and 7.72(2H,s), m/e 311, 309 and 307 (1:2:1). Oxidation of the phenolic amide 3 with a solution7) (10 equiv.) of thallium triperchlorate in 60 % perchloric acid at 0° for 8 hours afforded exclusively the 4-hydroxycyclohexadienone 1 in 82 %

yield. All the following physical properties were in good agreement with those reported1); m.p. 192-194°, λ_{max}(MeOH) 259 nm(ε 8200), ν_{max}(nujol) 3420, 1700, 1675, 1660 and 1595 cm^{-1}, δ_{ppm}(acetone-d_6) 2.79(2H,s,$-CH_2CO-$), 2.85(2H,s,$-NH_2$), 5.93(1H,s, -OH) and 7.60(2H,s,olefinic H), m/e 327,325 323 (1:2:1), 308, 280, 246 and 244.

The compound 1 was presumably formed by a nucleophilic attack of a water molecule regiospecifically to the para-position of the phenol 3, whose hydroxyl oxygen atom was co-ordinated with thallium ion in aqueous media. The biosynthesis of the compound 1 is envisioned to involve a step of the oxidative hydroxylation of a phenolic intermediate derived from tyrosine.1) Our result suggests a possibility of the similar participation of a transition metal ion in the biological oxidative hydroxylation.

Similar reaction in tetrahydrofuran or dimethoxyethane also afforded the compound 1 (50-55 % yield) with a concomitant formation of a bromoquinone 4 [m.p. 125°, ν_{max}($CHCl_3$) 1685, 1645 and 1570 cm^{-1}, δ_{ppm}($CDCl_3$) 7.23(2H,s), m/e 268, 266 and 264 (1:2:1) in 10-15 % yield. The formation of the bromoquinone 4 can be explained by the loss of an acetamide molecule from the compound 1 as indicated.



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7) The thallium triperchlorate solution was prepared by dissolving 6.0 g of Tl_2O_3 in 100 ml of 60 % $HClO_4$ with heating at 130° for 2 hours,followed by filtration.5)

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