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THE SYNTHESIS OF JAPONINE[+]

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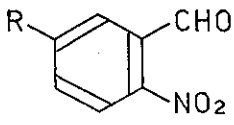
The total synthesis of japonine [I] is described. Methylation of the 3-hydroxy-4-quinolones [II] and [III] with methyl iodide in N,N-dimethylformamide afforded 3-methoxy-1-methyl-4-quinolones, whereas treatment with methyl p-toluenesulphonate or diazomethane gave 3,4-dimethoxyquinolines.

The alkaloid japonine isolated[1] from Orixa japonica Thunb. (Rutaceae) was assigned, mainly on the basis of spectroscopic data, the structure [I] of 3,6-dimethoxy-1-methyl-2-phenyl-4-quinolone, with the unusual oxygen function at C-3. We report here the first total synthesis of japonine.

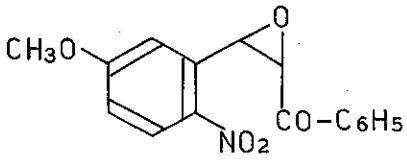
The preparation of the key intermediate [II] was undertaken following the scheme proposed[2] for the homologous 3-hydroxy-2-phenyl-4-quinolone [III]. 5-Hydroxy-2-nitrobenzaldehyde[3] [IV] was methylated with dimethyl sulphate[4] to give 5-methoxy-2-nitrobenzaldehyde [V], mp 83-84° (lit.[5], 82-83°).

This product was subjected to Darzens condensation[6]. To a solu-

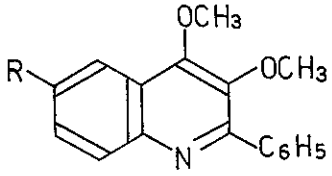
tion of [V] (1.81 g) and phenacyl bromide (1.99 g) in methanol (10 ml), a solution of sodium (0.54 g) in methanol (6 ml) was added dropwise at 12° under stirring; the collected precipitate gave the epoxide [VI] (2.5 g, 60% yield), mp 149-150° (from EtOH); uv (EtOH) λ_{max} (log ε) 246 nm (4.59), 304 (4.25); ir (nujol) 1675 (C=O), 1580 and 1325 (C-NO_2), 1227 and 890 cm^{-1} (epoxide); nmr (60 MHz, $CDCl_3$) δ 3.89 (s, OCH_3), 4.15 (d, J 2.3 Hz), 4.61 (d, J 2.3 Hz).



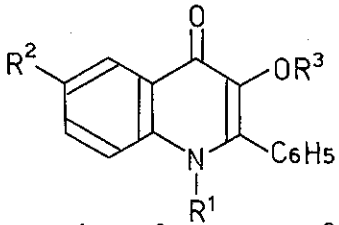
[IV] R = OH
[V] R = OCH_3



[VI]



[VIII] R = H
[XI] R = OCH_3



[I] $R^1 = R^3 = CH_3$; $R^2 = OCH_3$
[II] $R^1 = R^3 = H$; $R^2 = OCH_3$
[III] $R^1 = R^2 = R^3 = H$
[VII] $R^1 = OH$; $R^2 = OCH_3$; $R^3 = H$
[IX] $R^1 = R^3 = CH_3$; $R^2 = H$
[X] $R^1 = CH_3$; $R^2 = R^3 = H$

Acid cleavage[2] of the epoxide [VI] (2.99 g) was performed in anhydrous tetrahydrofuran (75 ml) saturated with hydrogen chloride gas and containing hydroquinone (1.4 g); the solution was left at 15° for 20 hr. The residue after evaporation of the solvent was washed with ether and then treated with aqueous methanol solution: 1,3-dihydroxy-6-methoxy-2-phenyl-4-quinolone [VII] (1.1 g, 40% yield) was obtained as yellow prisms, mp 294-296° (from EtOH); uv (EtOH) λ_{max} 265 (3.38), 321 (3.78), 367 nm (3.84); ir (nujol)3350 cm^{-1} (OH); nmr (60 MHz, DMSO-d_6) δ 3.85 (s, OCH_3), 7.32 (dd, J_o 9.0 Hz, J_m 3.0 Hz, 7-H), 7.60 (d, J_m 3.0 Hz, 5-H), 7.82 (d, J_o 9.0 Hz, 8-H), 7.50 (s, C_6H_5).

The reduction[2] of [VII] to [II] was achieved by refluxing a mixture of [VII] (2.83 g), sodium dithionite (6 g), ethanol (120 ml) and water (40 ml) for 1 hr; after filtration of the hot solution, the solvent was evaporated and the residue was washed with water to give 3-hydroxy-6-methoxy-2-phenyl-4-quinolone [II] (1.9 g, 70% yield), mp 310-312° (from EtOH), m/e 267 (M^+); uv (EtOH) λ_{max} 264 (4.30), 322 (3.72), 363 nm (3.74); ir (nujol) 3350 (OH), 3125 cm^{-1} (NH); nmr (60 MHz, DMSO-d_6) δ 3.85 (s, OCH_3), 11.50 (OH).

Methylation was tested on 3-hydroxy-2-phenyl-4-quinolone[2] at first. Treatment of [III] (100 mg) with methyl p-toluenesulphonate (1 g) in dioxane (15 ml) under reflux for 30 hr was carried out, and followed by evaporation, extraction with ether and washing with 10% sodium hydroxide solution. The resulting alkaline solution yielded unreacted [III] (30 mg) by acidification, whereas the ethereal solution gave only 3,4-dimethoxy-2-phenyl-quinoline [VIII] (60 mg), mp 62-64° (from cyclohexane); uv (EtOH) λ_{max} 249 (4.35), 288 (3.42), 318 nm (3.20); nmr (60 MHz, $CDCl_3$) δ 3.62 (s, OCH_3 at C-3), 4.20 (s, OCH_3 at C-4)[7].

N-Methylation was performed by reaction with methyl iodide and

potassium hydroxide in dimethylformamide[7]. To a solution of [III] (450 mg) in dimethylformamide (20 ml) powdered potassium hydroxide (1.5 g) was added and then methyl iodide (3 ml) was dropped at 0° under careful stirring. After stirring for 2 hr at 20°, the solution was heated at 60° for 1 hr. The solvent was evaporated and the residue taken up with water; the insoluble 3-methoxy-1-methyl-2-phenyl-4-quinolone [IX] (300 mg, 60% yield) was collected, mp 222-224° (from EtOH); uv (EtOH) λ_{max} (log ε) 251 (4.39), 338 (3.85), 346 nm (3.92); ir (nujol) 1612 and 1580 cm^{-1} (CO-NH); m/e 265 (M^+); nmr (60 MHz, $CDCl_3$) δ 3.50 (s, OCH_3), 3.62 (s, NCH_3), 7.25-7.8 (8 aromatic protons), 8.60 (m, 5-H).

On the contrary, [IX] was not obtained by treatment of [III] with diazomethane in methanol-ether solution, but unreacted [III], the quinoline [VIII] and a trace of 3-hydroxy-1-methyl-2-phenyl-4-quinolone [X] were isolated. Product [X] has mp 242-243 (decomp.); uv (EtOH) λ_{max} 252, 342, 357 nm; nmr (60 MHz, $CDCl_3$) δ 3.70 (s, NCH_3).

The treatment of [III] with diazomethane in tert.butanol solution at -10° also gave the quinoline [VIII] and unreacted [III].

On the basis of these experiments, the quinolone [II] was methylated with methyl iodide in dimethylformamide solution in the presence of potassium hydroxide. Treatment of [II] (100 mg) as described above for [III] gave a residue which was taken up with 10% sodium hydroxide solution and extracted with ethyl acetate. Evaporation of the solvent yielded a residue which was chromatographed on silica gel column. Elution with benzene yielded 20 mg of 3,4,6-trimethoxy-2-phenyl-quinoline [XI], mp 94-95° (from cyclohexane); uv (EtOH) λ_{max} (log ε) 254 (4.23), 332 nm (3.30); nmr (60 MHz, $CDCl_3$) δ 3.67 (s, OCH_3 at C-3), 3.95 (s, OCH_3 at C-6), 4.20 (s, OCH_3 at C-4). Elution with benzene-ethyl acetate (1:1)

gave 75 mg of 3,6-dimethoxy-1-methyl-2-phenyl-4-quinolone [I], mp 142-143° (from benzene or from methanol-ether), identical with japonine (lit.[1], mp 143°); uv (EtOH) λ_{max} (log ε) 252 (4.25), 342 (sh, 3.83) 357 nm (4.02); m/e 295 (M^+), 294, 280, 276, 264, 252[1]; nmr (100 MHz, $CDCl_3$) δ 3.41 (s, OCH_3 at C-3), 3.58 (s, NCH_3), 3.87 (s, OCH_3 at C-6)[1].

Methylation of [II] with methyl p-toluenesulphonate gave only the quinoline [XI] in 30% yield. Treatment of [II] with diazomethane in methanol-ether solution gave [XI] in 40% yield and a trace of japonine.

The structure proposed[1] for japonine is therefore confirmed. All the new products gave satisfactory elemental analyses.

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