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ISOLATION AND SYNTHESIS OF N-METHYL-4,7,8-TRIMETHOXY-2-QUINOLONE FROM *SPATHELIA SORBIFOLIA L*

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Abstract—The structure of a minor constituent of *Spathelia sorbifolia L* has been deduced to be N-methyl-4,7,8-trimethoxy-2-quinolone (2, R=Me) from spectral data and this has been confirmed by synthesis.

Previous work on the constituents of *Spathelia sorbifolia L.* has yielded a seco-ring A-tetranortriterpenoid (limonoid),[1] several chromones,[2] and the known 2-quinolone, N-methylflindersine.[3] The taxonomic significance of a 2-quinolone in this plant has been discussed.[3] We now report the isolation of the new 2-quinolone, N-methyl-4,7,8-trimethoxy-2-quinolone from the benzene extracts of both the roots and the stems of this plane by chromatography on alumina followed by preparative TLC.

The natural product, $C_{13}H_{15}NO_4$, m.p. 143–148°, had an IR spectrum characteristic[4,5] of a 2-quinolone. The UV spectrum had a max in the 263–298 nm region and had little change in its high wavelength spectrum in acid and no shift to short wavelength in cyclohexane as expected for a 2-quinolone.[4,6] The NMR spectrum with its two *ortho*-coupled aromatic doublets and N-Me and two O-Me singlets was very similar to that[7] of casimiroin (1)[8] and the compound was concluded to be N-methyl-4,7,8-trimethoxy-2-quinolone (2, R=Me). This has been proved by the following synthesis.

Heating together equal amounts of 2,3-dimethoxyaniline[9] and diethyl malonate resulted in a mixture of the dianilide (3), $C_{19}H_{22}N_2O_6$, m.p. 183°, and the ester (4, R=Et), $C_{13}H_{17}NO_5$, m.p. 84°. The latter compound could be obtained as the sole product and in good yield when an excess of diethyl malonate was used. Attempted cyclisation of the ester (4, R=Et) by refluxing in diphenyl ether under N_2 afforded the tricyclic product (5), m.p. 301–305°, which had an UV spectrum characteristic of this type of compound.[6,10] It had previously been observed[6,10] that prolonged heating of diethyl malonate with anilines yielded tricyclic compounds akin to 5, and that brief reflux yielded the 4-hydroxy-2-quinolone. From our result it would appear that the tricyclic compounds can be formed in the absence of diethyl malonate, presumably by reaction of the first-formed 4-hydroxy-2-quinolone (2, R=H) with the ester (4, R=Et).

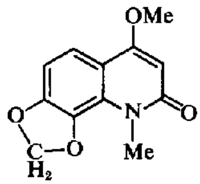
The 4-hydroxy-2-quinolone (2, R=H) could eventually be obtained by hydrolysis of the ester (4, R=Et) to the acid (4, R=H), $C_{11}H_{13}NO_5$, m.p. 115–116° followed by cyclisation of this acid to the quinolone using polyphosphoric acid. The 4-hydroxy-2-quinolone (2, R=H) $C_{11}H_{11}NO_4$, m.p. 244–246° was reacted with dimethyl sulphate and potassium hydroxide in dimethylformamide to yield 1-methyl-4,7,8-trimethoxy-2-quinolone (2, R=Me), identical in all respects with the natural product.

EXPERIMENTAL

M.ps were determined on the Kofler block and are uncorrected. IR spectra were obtained on a Perkin Elmer PE 237 instrument and UV spectra on a Unicam SP 800 spectrophotometer. NMR spectra were run on Varian T60, A60 and HA 100 instruments, low resolution mass spectra on a Hitachi RMU-6 mass spectrometer and the high resolution molecular weight was obtained on an AEI-MS9 instrument.

Isolation of N-*methyl*-4,7,8-*trimethoxy*-2-*quinolone* (2, R=Me).

The dried milled root of *Spathelia sorbifolia* (200 gm) was extracted by percolation with benzene to give a gum (5·8 g) which was chromatographed on alumina. The column was eluted with benzene, benzene-EtOAC (9:1) and benzene-EtOAC (4:1). The eluate from these latter fractions (320 mg) was separated by preparative TLC on Merck $PF_{254-366}$ silica gel using benzene: acetone (10:1) as elutent. After two runs, crude 2 (R=Me; 30 mg) was obtained which was purified by a further 20 runs of preparative TLC using the same system. The pure N-*methyl*-4,7,8-*trimethoxy*-2 *quinolone* (2, R=Me) recrystallised



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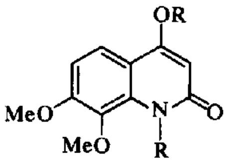

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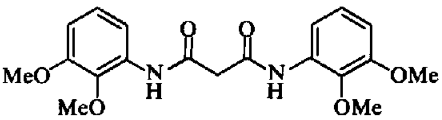

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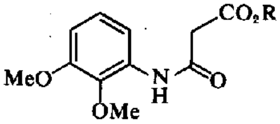

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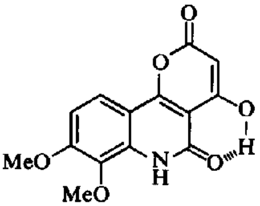

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from light petroleum (16 mg), m.p. 143–148°, (Found: C, 62·7; H, 5·9; N, 5·5; *m/e* = 249·101315; $C_{13}H_{15}NO_4$ requires: C, 62·6; H, 6·1; N, 5·6; *m/e* = 249·10011); $\nu_{max}^{CHCl_3}$ = 1635 cm^{-1} (amide); λ_{max}^{MeOH} = 228 (sh), 235, 252, 289, 313 and 323 nm (log ε = 4·57, 4·60; 4·26, 3·96, 3·85 and 3·76); λ_{max}^{H+} = 226, 235, 245 (sh), 294 and 315 nm (log ε = 4·51, 4·53, 4·42, 3·86 and 3·90); $\lambda_{max}^{cyclohexane}$ = 239, 254 (sh), 282, 288, 321 and 330 (sh) nm. (log ε = 4·67; 3·99, 3·78, 3·77, 3·63 and 3·57). The NMR spectrum showed absorption at τ 2·28 (1H, d, J = 9·5 Hz, aromatic), 3·13 (1H, d, J = 9·5 Hz, aromatic), 4·06 (1H, s, olefinic), 6·02 (3H, s) 6·08 (3H, s) and 6·20 (3H, s) (N-*Me* and two *OMe*).

Smaller amounts of 2 (R=Me) were isolated from the stems of *Spathelia sorbifolia L.*

Reaction between 2,3-*dimethoxyaniline and diethyl malonate*

(1) *Using equimolecular amounts of the reagents.* 2,3-Dimethoxyaniline (500 mg) and diethyl malonate (512 mg) were heated together under reflux for 10 hr. On cooling a solid mass was obtained which on trituration with MeOH yielded a white solid (213 mg) which crystallised from MeOH as needles, m.p. 183°, (Found: C, 60·79; H, 5·96; N, 7·60; $C_{19}H_{22}N_2O_6$ requires: C, 60·95; H, 5·92; N, 7·48%); $\nu_{max}^{CHCl_3}$ = 3390 (NH) and 1685 cm^{-1} (amide) λ_{max}^{MeOH} = 249, 284 (sh) nm (log ε 4·26 and 3·32). The compound had a parent ion at 374 in the mass spectrum and the NMR spectrum ($CDCl_3$) showed absorption at τ = 0·81 (2H,s, exchangeable D_2O, NH), 2·01 (2H, dxd, J_1 = 8, J_2 = 2Hz, aromatic), 2·97 (2H, t, J = 8 Hz, aromatic), 3·33 (2H, dxd, J_1 = 8. J_2 = 2Hz aromatic)) 6·03 (6H, s, OCH_3), 6·09 (6H, s, OCH_3), 6·40 (2H, s, $COCH_2CO$). This compound was N,N′*di*-(2,3-*dimethoxyphenyl*)*malonamide* (3)

The MeOH soln from the above trituration was taken to dryness *in vacuo* and the solid residue crystallised from diisopropylether as needles (260 mg), m.p. 84°, (Found: C, 58·41; H, 6·40; N, 5·39; $C_{13}H_{17}NO_5$ requires: C, 58·45; H, 6·37; N, 5·25%); $\nu_{max}^{CHCl_3}$ = 3300(NH) 1725 (ester) and 1680 cm^{-1} (amide); λ_{max}^{MeOH} = 247. 279 (sh) and (287 (sh) nm (log ε 4·02. 3·21 and 2·99). Continued heating above the m.p. caused resolidification and the sample melted again at 301–305°. The melted sample had an identical UV spectrum to that of compound 5 below. The compound had a parent ion at 267 in the mass spectrum and the NMR spectrum showed absorption at τ = 0·34 (1H, s, exchangeable D_2O, NH); 2·09 (1H, dxd, J_1 = 8, J_2 = 2Hz, aromatic), 3·01 (1H, t, J = 8Hz, aromatic) 3·37 (1H, dxd, J_1 = 8, J_2 = 2Hz, aromatic), 5·73 (2H, q, J = 7·5 Hz, $CO_2CH_2CH_3$) 6·08 (3H, s, OCH_3), 6·13 (3H, s, OCH_3), 6·53 (2H, s, $COCH_2CO$), 8·67 (3H, t, J = 7·5 Hz, $CO_2CH_2CH_3$). This compound was *ethyl* N-(2,4-*dimethoxyphenyl*)-*malonamate* 4, R = CH_2CH_3).

(2) *Using excess of diethyl malonate.* 2,3-Dimethoxyaniline (13 gm) and diethyl malonate (130 gm) were heated to 160° in an open flask over 30 min. The temp of the oil bath was raised to 190° for a further 1 hr, and the mixture was allowed to cool to room temp when a white solid crystallised out (7 gm). Most of the excess diethylmalonate was removed *in vacuo* and ether was added whereupon further amounts of the solid were obtained. The product was recrystallised from diisopropylether to afford an 81% yield of 4 (R = Et), identical in all respects with a sample obtained from the previous reaction.

The tricyclic compound (5)

Compound 4 (R = Et; 227 mg) was dissolved in diphenyl ether (10 ml) and heated at reflux under N_2 for 12 hr. On cooling a light brown solid separated out and this was filtered, washed thoroughly with light petroleum (b.p. 60–80°), m.p. 301–305°C, ν_{max}^{NUJOL}, 3370 (NH) and 1640 cm^{-1} (amide); λ_{max}^{MeOH} = 217. 253. 274 (sh) 300 (sh), 329, 345, 368 (sh) and 390 nm shifting to 218, 236 (sh), 252, 273 (sh), 295 (sh), 339 nm in base. The compound had a parent ion at 289 in the mass spectrum and the nmr spectrum (TFA) showed absorption at τ 2·47 (1H, d, J = 9 Hz, aromatic), 3·24 (1H, d, J = 9 Hz, aromatic), 4·56 (1H, s, –CO–CH=), 6·33 (3H, s, OCH_3) and 6·40 (3H, s, OCH_3). The compound gave a red colouration with alcoholic ferric chloride.

N-(2,3-*Dimethoxyphenyl*)*malonamic acid* (**4**, R=H)

Compound 4 (R = Et, 25·8 gm) was shaken with a 1N NaOH (500 ml) at room temp for 2 hr, after which time all of the solid had dissolved. The soln was filtered and acidified with 2N HCl to yield a white ppt which was filtered, washed well with water and dried *in vacuo*. Recrystallisation from CCl_4 yielded the acid **4** (R = H) as white plates (19·6 gm; 86%), m.p. 115–116°, (Found: C, 55·27; H, 5·67; N, 5·84; $C_{11}H_{13}NO_5$ requires: C, 55·23; H, 5·48; N, 5·86%); $\nu_{\max}^{\text{NUJOL}}$ = 3220 (NH), 2800 and 1720 cm^{-1} (carboxylic acid); $\lambda_{\max}^{\text{MeOH}}$ = 247 nm (log ϵ = 4·04). The compound had a parent ion at 239 in the mass spectrum and the NMR spectrum (TFA) had absorption at τ 2·87 (1H, dxd, J_1 = 8, J_2 = 2Hz, aromatic), 3·25 (1H, t, J = 8Hz, aromatic) 3·50 (1H, dxd, J_1 =8, J_2 = 2Hz, aromatic), 6·40 (3H, s, OCH_3), 6·43 (3H, s, OCH_3), 6·51 (2H, s, $COCH_2CO_2H$).

Increasing the temp at which the reaction was performed and the concentration of NaOH to 1·5N caused extensive hydrolysis and 2,3-dimethoxyaniline was obtained.

4-*Hydroxy*-7,8-*dimethoxy*-2-*quinolone* (2, R=H)

Compound 4 (R=H; 5 gm) was suspended in polyphosphoric acid (sp. gr = 2·2; 25 gm) and heated at 140–150° for 25 min. The dark red viscous soln was allowed to cool, water was added and the precipitated quinolone was filtered off, washed well with water and dried *in vacuo*. Recrystallisation from pyridine afforded 2(R=H, 2·1 gm; 45%) as prims, m.p. = 244–246° (Found C, 59·67; H, 5·14; N, 6·07, $C_{11}H_{11}NO_4$ requires: C, 59·72; H, 5·01; N, 6·33%); $\nu_{\max}^{\text{NUJOL}}$ = 1630 cm^{-1} (quinolone); $\lambda_{\max}^{\text{MeOH}}$ = 242, 250 (sh), 280 (sh), 288, 309 and 320 nm (log ϵ, 4·31, 4·11, 3·87, 3·94, 3·94 and 3·79) shifting to 239 (sh), 297, 311 (sh) nm (log ϵ, 4·45, 4·08 and 4·02) in base and 243, 314 nm (log ϵ, 4·61, 3·98) in acid. The compound had a parent at 221 in the mass spectrum and the NMR spectrum ($DMSOd_6$) showed absorption at τ 2·38 (1H, d, J = 9Hz, aromatic), 2·92 (1H, d, J = 9 Hz, aromatic) 3·97 (1H, s, olefinic), 6·08 (3H, s, OCH_3) and 6·20 (3H, s, OCH_3). The compound gave a purple colouration with alcoholic ferric chloride.

1-*Methyl*-4,7,8-*trimethoxy*-2-*quinolone* (**2**, R = Me)

4-Hydroxy-7,8-dimethoxy-2-quinolone (130 mg) was dissolved in DMF (8·5 ml). Powdered KOH (430 mg) was added and the soln shaken to effect dissolution. Me_2SO_4 (0·7 ml) was added and the reaction left at 50–55° for 20 hr. The soln was poured into water and extracted well with chloroform. The extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a solid which on repeated crystallisation from light petroleum (60–80°) gave needles, m.p. 145–148°, undepressed on admixture with the natural product. The compound had identical spectroscopic data to those of the natural product.

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