Synthesis of 2,3-Dimethoxy-7-methyl-7,12-dihydro-6H-[1]-benzofuro-[2,3-c]-[1]-benzazepin-6,12-dione.

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Abstract: Treatment of 5,6-dimethoxy-2-(methylphenylcarbamoyl)-benzofuran-3-carboxylic acid with PPA yielded 2,3-dimethoxy-7-methyl-7,12-dihydro-6H-[1]-benzofuro-[2,3-c]-[1]-benzazepin-6,12-dione. The analogous 2-[(5,6-dimethoxybenzofuran-2-carbonyl)methylamino]benzoic acid was resistant to cyclization, whereas 2-[(6-methoxybenzofuran-2-carbonyl)-amino]benzoic acid underwent cyclization to the corresponding 3,1-benzoxazin-4-one.

Keywords: PPA, cyclization, benzoxazinone, benzofuro-[2,3-c]-[1]-benzazepin-6,12-dione.

Introduction

Rotenonoids, of general structure 1a, are 6-oxo analogues of the rotenoids, which are naturally occurring insecticidal compounds with a range of other biological activity (antimicrobial, antiviral, piscicidal etc.)[1-3]. Rearrangement of β-rotenonoids 2a to rotenonoids 1a under basic conditions is well known [4, 5].
Azarotenonoids (e.g. compounds 1b, 1c) – nitrogen analogues of rotenonoids – on the other hand, are not widely known. The 5-azarotenonoid 1b has been prepared by photo-oxidative cyclization of N-phenyl-4\((H)\)-oxo-1-benzopyran-2-carboxamides [6]. To date, there are no references to 7-azarotenonoids (1c), or to nitrogen analogues of β-rotenonoids (e.g. 2b). We explored synthesis of compounds of type 2b with a view to investigating their biological properties and carrying out structure/activity relation studies. The de-oxo system 2d is known [7], and synthesis of the desired 2b from this compound by oxidation seems a logical and straightforward path. Oxidation of 3-benzylbenzofurans to 3-aroylbenzofurans, and of [1]-benzofuran-[2,3-c]-[6H,12H-1]-benzoxepin-6-ones (2c) to β-rotenonoids, have been reported as being anything but trivial [8, 5a]. Other approaches, therefore, needed to be employed.

Results and Discussion

The pathway shown in Scheme 1 was first explored. Rotenoids are often oxygenated at positions 2 and 3 [9]. Use of 3-bromo-7-methoxycoumarin (3) would result in only the monomethoxy rotenonoids, however this material was available in quantity and was seen as a useful prototype for our studies.

Scheme 1. Synthetic plan

We anticipated that Ullmann-type condensation [10,11] of 3 with anthranilic acid would afford compound 4, which should undergo intramolecular cyclization to the desired azarotenonoid 5. Reaction of 3 with anthranilic acid in the presence of copper, however, produced acid 6 (42%) after 4 hours, and upon treatment of 6 with polyphosphoric acid (PPA), 3,1-benzoxazin-4-one 7a was obtained (70%, Scheme 2).

Scheme 2

Reagents: i) antranilic acid, Cu, CuBr, K\(_2\)CO\(_3\), DMF, 140°C; ii) PPA
Reagents: i) PCl5; ii) anthranilic acid

Strong IR absorptions at 1635 and 1773 cm\(^{-1}\), corresponding to the C=N and ester functionality, were observed. Compounds of this type are known to undergo base hydrolysis to produce the corresponding N-acyl anthranilic acids, which are then readily reconverted to benzoxazinones on treatment with NaOAc/\text{Ac}_2\text{O} [12]. Our reaction product exhibited this reactivity, forming compound 6 on treatment with KOH. Subsequent treatment of compound 6 with NaOAc/\text{Ac}_2\text{O}, caused reformation of benzoxazinone 7a.

We also obtained benzoxazinone 7a in 40% yield by treatment of acid 8a with PCl5 and then reacting the resultant acid chloride with anthranilic acid (Scheme 3). It is clear that under Ullmann reaction conditions, 3-bromo-7-methoxycoumarin (3) underwent rearrangement to 6-methoxybenzofuran-2-carboxylic acid (8a). The rearrangement of such coumarins is known to occur in alkaline media [13, 14]. We verified our observation by subjecting compound 3 to treatment with potassium carbonate in DMF at 140°C for 4 hours – conditions as obtained for the attempted Ullmann reaction but without copper and anthranilic acid. Quantitative conversion to compound 8a, identical in all respects with an authentic sample [15], was achieved.

Compounds of type 6, then, would cyclize to yield 3,1-benzoxazin-4-ones more readily than they would to give the desired benzazepines. (Compound 8b on treatment with PCl5 followed by anthranilic acid gave 7b.) We considered that absence of the amide proton would disallow benzoxazinone formation, and could augur well for occurrence of the desired cyclization. With this in mind, compound 10a was prepared as shown in Scheme 4. Treatment of 10a with PPA, however, yielded none of the required 11a and as predicted, none of the corresponding benzoxazinone was formed. Even after heating 10a in PPA at 80-100°C for 24 hours, only starting material was recovered. Compound 10a was also unreactive to Friedel-Crafts conditions. Treatment with PCl5 followed by SnCl4 for 23 hours at 95°C afforded only starting material. Our work with the analogous 2-carbophenoxy-5,6-dimethoxybenzofuran-2'-carboxylic acid (10b, X = O) also shows that it is inert to Friedel-Crafts reaction conditions (using SnCl4 as Lewis acid) [16].
Synthesis of compound 11a was eventually achieved by the pathway shown in Scheme 5. Attempts at direct oxidation of 13 to 16a using KMnO₄ were unsuccessful. Oxidation of 14 using trimethylamine-N-oxide (TMANO), however, produced aldehyde 15 (50%), which on further oxidation yielded 16a (90%) [17-19]. Heating 16a in PPA at 90°C for 24 hours effected intramolecular cyclization to 11a in 25% yield.

Reagents: i) N-methylaniline, DCC, DMAP, CH₂Cl₂, rt; ii) NBS, CCl₄, hv; iii) TMANO, DMSO, rt; iv) NBS, CCl₄, hv, then H₂O; v) PPA
The fact that we achieved hydrolysis of amide 13 in refluxing NaOH (40% aqueous) prompted us to investigate the possibility of similar reaction with our compound 11a in hope of possible rearrangement to the azarotenonoid. Compound 11a, however, proved resistant to treatment with NaOH.

Conclusions

We have synthesized 2,3-dimethoxy-7-methyl-7, 12-dihydro-6H-[1]-benzofuro-[2,3-c]-[1]-benzazepin-6,12-dione (11a) via acid-catalysed cyclization of 16a. This pathway is not useful for formation of β-rotenonoids, since under the reaction conditions the ester linkage of compounds such as 10b and 16b are quite labile.

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Experimental

General

All melting points are uncorrected. IR spectra (KBr disks) were obtained on a Perkin Elmer 735B model or a Perkin Elmer 1600 FT-IR spectrometer. NMR spectra were recorded were determined in CDCl₃ solutions on a Bruker 200 MHz spectrometer. The resonances are reported in δ units downfield from TMS; J values are given in Hz. For ease of reporting ¹H-NMR data, the protons on the benzofuran side of the molecule have been labelled as H and those on the phenyl ring as H'. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, UK.

2-[(6-Methoxybenzofuran-2-carbonyl)-amino]benzoic acid (6)

To a 25 mL round bottomed flask fitted with a reflux condenser and a calcium chloride guard tube, were added 7-methoxy 3-bromocoumarin (3) (0.50 g, 1.97 mmol) and N, N-dimethylformamide (10 mL). Anthranilic acid (0.27 g, 1.97 mmol), potassium carbonate (0.875 g, 6.30 mmol), copper powder (5.0 mg) and copper (I) bromide (8 mg) were added with stirring to this solution and the mixture was heated at 140°C for 4 hours. The mixture was then allowed to cool, diluted with water (40 mL), and treated with decolorizing carbon (0.12 g). After filtration the filtrate was acidified with hydrochloric acid (3N) and the resulting precipitate was collected and washed with water (25 mL). Recrystallization from ethanol gave 6 (0.26 g, 42%); mp 209-212°C; IR cm⁻¹: 1624, 1675, 3350 (br); ¹H-NMR δH: 3.92 (3H, s, -OCH₃), 5.95 (1H, br, -N-H), 6.85 (1H, dd, J = 2, 8, H-5), 7.15 (2H, m, H-7, 4'), 7.50 (3H, m, H-3, 4, 5'), 8.15 (1H, dd, J = 1, 8, H-6'), 8.80 (1H, dd, J = 1, 8, H-3'), 12.5 (1H, s,
COOH); $^{13}$C-NMR $\delta$C: 55.6, 95.8, 111.1, 113.4, 116.0, 120.1, 120.7, 122.7, 122.7, 131.5, 134.1, 141.1, 148.2, 156.2, 157.1, 159.9, 170.3; MS m/e (relative intensity) 311.03 (M$^+$, 82), 293.02 (14), 192.03 (22), 175.04 (100), 119.06 (46). HRMS calcd. for C$_{17}$H$_{13}$NO$_5$: 311.0794. Found: 311.0794.

2-(6'-Methoxybenzofuran)-3,1-benzoxazin-4-one (7a)

a) Compound 6 (2.0 g, 6.43 mmol) was added to well-stirred PPA (20 mL) which had been preheated to 90°C. This mixture was stirred at 110°C for 2 h, then poured onto ice (200 g), neutralized with 6N ammonia, and the resultant precipitate filtered and washed with saturated sodium bicarbonate. The solid was air-dried and purified by chromatography (neutral alumina, 4:1 hexane-CH$_2$Cl$_2$) to give 7a (1.3 g, 70%), mp 210-212°C (MeOH); IR cm$^{-1}$: 1773, 1635, 1599; $^1$H-NMR $\delta$H: 3.90 (3H, s, -O-CH$_3$), 6.95-7.00 (1H, dd, $J$ = 2, 8, 5'-H), 7.15 (1H, d, $J$ = 2, H-7'), 7.50-7.65 (3H, m, H-6, H-8, H-3'), 7.65-7.95 (2H, m, H-7, H-4'), 8.20-8.26 (1H, dd, $J$ = 1, 8, H-5); $^{13}$C-NMR $\delta$C: 55.5, 95.6, 113.5, 113.9, 116.7, 120.4, 122.8, 127.0, 128.3, 128.6, 136.7, 144.3, 146.4, 157.5, 160.5. Anal. Calcd. for C$_{17}$H$_{11}$NO$_4$: C, 69.61; H, 3.78; N, 4.78; Found: C, 69.46. H, 3.74; N, 4.76%.

b) PCl$_5$ (0.63 g, 3.04 mmol) was added, with stirring, to a mixture of 6-methoxybenzofuran-2-carboxylic acid (8a, 0.38 g, 1.99 mmol) [13] in benzene (5mL). This was heated at reflux for 2 h, after which time it was cooled to room temperature and then in an ice-bath. Anthranilic acid (0.28 g, 2.01 mmol) was dissolved in pyridine (1 mL) and this solution was added dropwise to the reaction mixture with cooling and stirring. Upon completion of addition the ice-bath was removed and the reaction mixture was stirred at room temperature for 3 h. Benzene was then evaporated in vacuo and water added to the resultant crude brown precipitate. This was then collected by filtration and air dried. Recrystallisation from methanol yielded 7a as pale yellow crystals (0.235 g, 40%).

**Alkaline hydrolysis of compound 7a.**

Compound 7a (51.6 mg, 0.18 mmol) was added to ethanol (2 mL) with stirring. To this mixture potassium hydroxide (50 mg, 0.89 mmol) was added and the mixture heated at reflux for 2 h. The reaction mixture was then concentrated in vacuo and the crude product dissolved in the minimum amount of water and acidified with conc. HCl. The product was collected by filtration, washed with cold water and dried at the pump, to yield 6 as a white powder (51.4 mg, 94%), mp 209-212°C.

**Conversion of 6 to 7a using sodium acetate and acetic anhydride.**

A mixture of 6 (38.7 mg, 0.12 mmol), acetic anhydride (0.65 mL) and sodium acetate (204 mg) was heated to 140°C with stirring for 1 h. The reaction mixture was then cooled in an ice-bath and immediately solidified to give a pale yellow precipitate. Water (5 mL) was added to this precipitate and the solution extracted with dichloromethane. The organic extract was then concentrated in vacuo...
and the crude product recrystallised from methanol to yield 7a as a pale yellow powder (20.3 mg, 56%), mp 210-213°C.

2-(5',6'-Dimethoxybenzofuran)-3,1-benzoxazin-4-one (7b).

PCl$_5$ (0.76 g, 3.63 mmol) was added, with stirring, to a mixture of 5,6-dimethoxybenzofuran-2-carboxylic acid (8b, 0.50 g, 2.26 mmol) [20] in benzene (8 mL). This was heated at reflux for 2 h, then cooled to room temperature and then in an ice-bath. A solution of anthranilic acid (0.33 g, 2.41 mmol) in pyridine (1 mL) was added dropwise to the reaction mixture with cooling and stirring. Upon completion of addition the ice-bath was removed and the reaction mixture was stirred at room temperature for 3 h. Benzene was then evaporated in vacuo and water added to the resultant crude precipitate which was collected by filtration and air dried. The crude was purified by chromatography (SiO$_2$, dichloromethane) to yield 7b as yellow crystals (0.28 g, 39%), mp 231-232°C (MeOH); IR cm$^{-1}$ 1751, 1632, 1598; $^1$H-NMR $\delta$H 3.90 (3H, s, O-CH$_3$), 4.00 (3H, s, -O-CH$_3$), 7.00 (1H, s, H-3'), 7.12 (1H, s, H-7'), 7.40-7.55 (1H, m, H-7), 7.60 (1H, s, H-4'), 7.70-7.90 (2H, m, H-6, H-8), 8.20-8.30 (1H, dd, $J = 2$, 8, H-5); $^{13}$C-NMR $\delta$C 56.2, 56.3, 95.2, 95.2, 102.4, 113.8, 119.4, 127.2, 128.2, 128.7, 128.7, 136.7, 144.4, 146.7, 147.7, 151.1, 151.9, 158.6. Anal. Calcd. for C$_{18}$H$_{13}$NO$_5$: C, 66.86; H, 4.06; N, 4.33 %; Found: C, 66.60; H, 4.03; N, 4.31.

2-[(5,6-Dimethoxybenzofuran-2-carbonyl)-amino]benzoic acid methyl ester (9).

5,6-Dimethoxybenzofuran-2-carboxylic acid [20] (0.513 g, 2.437 mmol) was added, with stirring to a solution of methyl anthranilate (0.303 g, 2.00 mmol) in dichloromethane (10 mL). To this mixture was added 4-(N,N-dimethylamino)pyridine (DMAP) (0.036 g, 0.294 mmol) and 1,3-dicyclohexylcarbodiimide (DCC) (0.506 g, 2.45 mmol) and the whole left to stir at room temperature for 24 h. The reaction mixture was then filtered under vacuum and the filtrate concentrated in vacuo. The crude product was recrystallised from CH$_2$Cl$_2$/MeOH to yield compound 9 as feathery brown crystals (0.530 g, 77%), mp 210-211°C; IR cm$^{-1}$: 1695, 1670, 1568; $^1$H-NMR $\delta$H: 3.90 (3H, s, -O-CH$_3$), 4.00 (3H, s, -O-CH$_3$), 4.10 (3H, s, -CO$_2$-CH$_3$), 7.10-7.20 (3H, m, H-4, H-7, H-4'), 7.50-7.65 (2H, m, H-6, H-8), 8.10 (1H, d, $J = 8$, H-6'), 8.90 (1H, d, $J = 8$, H-3'); $^{13}$C-NMR $\delta$C: 52.4, 56.2, 56.2, 95.3, 102.5, 111.8, 115.2, 119.5, 120.5, 122.7, 130.9, 134.6, 141.1, 147.3, 148.1, 150.3, 150.5, 157.2, 168.6. Anal. Calcd. for C$_{19}$H$_{17}$NO$_6$: C, 64.22; H, 4.82; N, 4.34%. Found: C, 63.91; H, 4.87; N, 4.11%.

2-[(5,6-Dimethoxybenzofuran-2-carbonyl)-methylamino]benzoic acid (10a).

Sodium hydride (0.093 g, 3.87 mmol) was stirred with pre-dried THF (6 mL) in an atmosphere of nitrogen. Compound 9 (0.20 g, 0.58 mmol) was added and the mixture was stirred at room temperature for 30 minutes. Iodomethane (0.11 mL, 1.72 mmol) was added and the reaction mixture was then heated at reflux for 6 h. After this time, ethanol was added to the reaction mixture, solvent
was removed in vacuo and water (20 mL) added to the resultant precipitate. The solution formed was then extracted exhaustively with CH$_2$Cl$_2$, the extract concentrated in vacuo, and the crude product recrystallised from hexane to yield 10a as light brown shiny crystals (0.102 g, 70%), mp 194-196°C; IR cm$^{-1}$: 1727, 1678, 1621; $^1$H-NMR $\delta$H: 3.45 (3H, s, -NH-CH$_3$), 3.85 (3H, s, -O-CH$_3$), 3.90 (3H, s, -O-CH$_3$), 6.05 (1H, s, H-7), 6.80-6.90 (2H, m, H-4, H-4'), 7.29-7.38 (1H, dd, $J$ = 1, 8, H-5'), 7.50-7.70 (2H, m, H-3, H-6'), 8.09-8.18 (1H, dd, $J$ = 1, 8, H-3'); $^{13}$C-NMR $\delta$C: 39.2, 55.7, 55.7, 94.5, 102.1, 111.6, 118.4, 128.0, 129.1, 129.4, 131.7, 132.8, 143.3, 146.5, 147.0, 149.2, 149.5, 159.1, 166.4; MS m/e (relative intensity) 355 (M$^+$, 46), 310 (12), 205 (100), 149 (40). HRMS calcd. for C$_{19}$H$_{17}$NO$_6$: 355.1056. Found: 355.1071.

5,6-Dimethoxy-3-methylbenzofuran-2-carboxylic acid methyl phenyl amide (13).

To a mixture of N-methylaniline (0.462 g, 4.31 mmol) in CH$_2$Cl$_2$ (25 mL), 3-methyl-5,6-dimethoxybenzofuran-2-carboxylic acid [21] (1.01 g, 4.27 mmol) was added with stirring. DMAP (0.090 g, 0.44 mmol) was then added, followed by DCC (0.934 g, 4.53 mmol). The reaction mixture was left to stir at room temperature for 23 h. After this time the mixture was filtered and the filtrate was washed successively with water (2 x 10 mL), 5% acetic acid (2 x 10 mL) and again with water (2 x 10 mL). The organic solution was then dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude product was recrystallised from hexane to yield 13 as brown diamond shaped crystals (0.852 g, 62%), mp 102-103°C; IR cm$^{-1}$: 1653, 1620, 1597; $^1$H-NMR $\delta$H: 2.40 (3H, s, Ar-CH$_3$), 3.50 (3H, s, -N-CH$_3$), 3.80 (3H, s, -O-CH$_3$), 5.00 (2H, s, -CH$_2$-Br), 6.50 (1H, s, H-7), 7.05 (1H, s, H-4), 7.15-7.36 (5H, m, -N-Ar); $^{13}$C-NMR $\delta$C: 9.2, 39.2, 56.2, 56.2, 94.7, 100.8, 120.7, 122.6, 126.0, 126.3, 128.9, 143.3, 144.5, 146.7, 148.4, 149.8, 161.6. Anal. Calcd. for C$_{19}$H$_{19}$NO$_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.81; H, 6.04; N, 4.58%.

3-Bromomethyl-5,6-dimethoxybenzofuran-2-carboxylic acid methyl phenyl amide (14).

To a mixture of the amide 13 (1.66 g, 5.10 mmol) in CCl$_4$ (100 mL), N-bromosuccinimide (NBS) (1.11 g, 6.24 mmol) was added with stirring. The reaction was then enclosed in a dark box and irradiated with a 100 W light bulb which allowed gentle reflux. After 24 h the mixture was filtered, the filtrate was washed successively with water (2 x 10 mL) and then with 5% acetic acid (2 x 10 mL) and water (2 x 10 mL). The resulting crude product was triturated with hot hexane to yield 14 as a tan powder (1.50 g, 73%), mp 113-115°C; IR cm$^{-1}$: 1702, 1602, 1595; $^1$H-NMR $\delta$H: 3.50 (3H, s, -N-CH$_3$), 3.80 (3H, s, -O-CH$_3$), 3.90 (3H, s, -O-CH$_3$), 5.00 (2H, s, -CH$_2$-Br), 6.50 (1H, s, H-7), 7.05 (1H, s, H-4), 7.15-7.36 (5H, m, -N-Ar); $^{13}$C-NMR $\delta$C: 22.2, 39.3, 56.3, 56.3, 94.6, 100.8, 118.5, 123.24, 126.0, 126.1, 126.8, 128.9, 129.1, 143.9, 144.0, 147.1, 148.5, 150.3, 160.4. Anal. Calcd. for C$_{19}$H$_{18}$BrNO$_4$: C, 56.45; H, 4.49; N, 4.36. Found: C, 56.19; H, 4.57; N, 3.86%.
5,6-Dimethoxy-3-formylbenzofuran-2-carboxylic acid methyl phenyl amide (15).

To 14 (1.41 g, 3.50 mmol) was added a solution of TMANO (0.40 g, 5.31 mmol) in DMSO (15 mL) and the mixture was stirred at room temperature for 1h, then poured into 5% saline solution (200 mL) with swirling. The resultant yellow precipitate was collected by filtration. Recrystallisation from hexane/ethyl acetate yielded 15 as pale yellow crystals (0.60 g, 50%), mp 124-125°C; IR cm⁻¹: 1673, 1639, 1594; ¹H-NMR δH: 3.50 (3H, s, -N-CH₃), 3.80 (3H, s, -O-CH₃), 3.90 (3H, s, -O-CH₃), 6.60 (1H, s, H-7), 7.10-7.45 (5H, m, -N-Ar), 7.60 (1H, s, H-4), 10.65 (1H, s, -CHO); ¹³C-NMR δC: 38.0, 55.8, 55.8, 93.8, 102.5, 115.1, 123.2, 125.7, 127.0, 128.9, 142.8, 148.0, 148.2, 150.0, 153.3, 158.8, 187.6. Anal. Calcd. for C₁₉H₁₇NO₅: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.03; H, 5.06; N, 4.28%.

5,6-Dimethoxy-2-(methyl phenylcarbamoyl)-benzofuran-3-carboxylic acid (16a).

Compound 15 (0.39 g, 1.15 mmol) was dissolved in CCl₄ (47 mL) and NBS (0.26 g, 1.46 mmol) was added with stirring. The reaction was enclosed in a dark box and irradiated with a 100 W light bulb for 24 h. The reaction mixture was then filtered and the filtrate concentrated in vacuo. To this brown residue, water (20 mL) was added and the mixture was left to stand overnight. The water was decanted and the resultant brown solid was dissolved in ethyl acetate. The solution was dried (Na₂SO₄) and concentrated in vacuo. The crude product was recrystallised from ethanol to yield 16a as a tan powder (0.37 g, 90%); mp 170-172°C; IR cm⁻¹: 1705, 1638, 1619, 1549; ¹H-NMR δH: 3.55 (3H, s, -N-CH₃), 3.80 (3H, s, -O-CH₃), 3.95 (3H, s, -O-CH₃) 7.20-7.55 (6H, m, -N-Ar, H-7), 7.70 (1H, s, H-4); ¹³C-NMR δC: 39.2, 56.1, 56.1, 93.4, 103.1, 117.9, 125.9, 127.8, 129.1, 142.7, 148.0, 148.3, 150.7, 161.0, 162.6; MS m/e (relative intensity) 355 (M⁺, 14), 337 (24), 311 (100), 249 (67). HRMS calcd. for C₁₉H₁₇NO₆: 355.1056. Found: 355.1054.

2,3-Dimethoxy-7-methyl-7,12-dihydro-6H-[1]-benzofuro-[2,3-c]-[1]-benzazepin-6,12-dione (11a).

To PPA (2 mL) which had been pre-heated to 90°C, compound 16a (0.100 g, 0.28 mmol) was added with stirring over 15 min. The reaction mixture was then heated at 90°C for 24 h, poured into water/crushed ice (100 mL) and was extracted exhaustively with ethyl acetate. The organic extract was dried (Na₂SO₄) and concentrated in vacuo and the crude product was chromatographed (SiO₂, 2:1 dichloromethane-ethyl acetate) to yield 11a as bright yellow needles (0.024 g, 25%); mp 227-229°C; IR cm⁻¹: 1637, 1617, 1563; ¹H-NMR δH: 3.70 (3H, s, -N-CH₃), 3.95 (3H, s, -O-CH₃), 4.00 (3H, s, -O-CH₃), 7.19 (1H, s, H-4), 7.35-7.50 (2H, m, H-1, H-10), 7.60-7.70 (2H, m, H-9, H-8), 8.15 (1H, dd, J = 1, 8, H-11); ¹³C-NMR δC: 39.0, 56.3, 56.3, 94.8, 103.0, 116.3, 122.0, 125.2, 125.7, 130.2, 132.8, 132.9, 140.0, 147.5, 148.7, 150.7, 151.7, 157.7, 184.6. Anal. Calcd. for C₁₉H₁₅NO₅: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.15; H, 4.51; N, 4.35%.
References

1. Crombie, L.; Josephs, J. L.; Larkin, J.; Weston, J. B. *J. Chem. Soc., Chem. Commun.*, 1990, 14, 972.
2. Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M. *J. Chem. Soc., Perkin Trans. 1*, 1992, 3015.
3. Ashack, R. J.; McCarty, L. P.; Malek, R. S.; Goodman, F. R.; Peet, N. *J. Med. Chem.*, 1980, 23, 1022.
4. Takei, M. O. *Chem. Ber.*, 1932, 65, 1041.
5. a) Marriott, K-S. C.; Anderson, M.; Jackson, Y. A. *Heterocycles*, 2001, 55, 91; b) Sakakibara, J.; Nagai, S.; Akiyama, T.; Ueda, T.; Oda, N.; Kidouchi, K. *Heterocycles*, 1988, 27, 423.
6. Srimannarayana G.; Akshaya Kumar, K. *Ind. J. Chem.*, Sect. B., 1981, 20B, 604.
7. Chatterjea, J. N. *J. Indian Chem. Soc.*, 1957, 34, 347.
8. Whalley, W. B.; Lloyd, G. J. *Chem. Soc.*, 1956, 3213.
9. Carlson, D. G.; Weisleder, D.; Tallent, W. H. *Tetrahedron*, 1973, 29, 2731.
10. Goshayev, M.; Otroshchenko, O. S.; Sadykov, A. S. *Russ. Chem. Rev.*, 1972, 12, 1046.
11. Fanta, P. E. *Chem. Rev.*, 1964, 64, 613.
12. a) Zentmeyer D. T.; Wagner, E. C. *J. Org. Chem.*, 1949, 14, 967; b) Errede, L. A. *J. Org. Chem.*, 1976, 41, 1763.
13. Fuson, R. C.; Kneisley, J. W.; Kaiser, E. W. *Organic Syntheses, Coll. Vol. III*, 1955, 209.
14. Jackson, Y. A.; Williams, M. F. *Heterocycles*, 1997, 45, 787.
15. Ramachandran, P.; Tefteller, A.; Paulson, G.; Cheng, T.; Lin, C.; Horton, W. *J. Org. Chem.*, 1963, 28, 398.
16. Jackson, Y. A.; Marriott, K-S. C. unpublished results.
17. Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.*, 1986, 59, 3287.
18. Franzen, V.; Otto, S. *Chem. Ber.*, 1961, 94, 1360.
19. Cheung, Y. *Tetrahedron Lett.*, 1979, 40, 3809.
20. Singh, G.; Nair, G. V.: Aggarwal, K. P. *J. Sci. Ind. Res.*, 1956, 15B, 190.
21. Patel, M. G.; Sethna, S. J. *Indian Chem. Soc.*, 1960, 37, 227.

Sample Availability: Samples of compounds 7, 9, 12 and 14 are available from the authors.

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