HETEROCYCLES FROM 2-AMINOPYRIDINE AND DERIVATIVES OF 3-METHYLBENZOFURAN-2-CARBOXYLIC ACID

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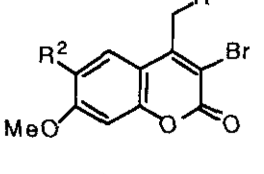
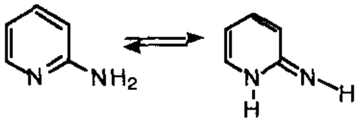
Abstract - 3-Bromomethyl-2-carboethoxy-5,6-dimethoxybenzofuran (**3b**) reacted with 2-aminopyridine to give not only the expected 2-carboethoxy-5,6-dimethoxy-3-benzofuranmethyl-2'-aminopyridinium bromide (**4b**), but also *N*-(2-carboethoxy-5,6-dimethoxy-3-benzofuranmethyl)-*N*-2-pyridylamine (**5**). Synthesis of 3-methoxy-6,7,12-trihydro-6-oxo-[1]benzofurano-[2,3-*c*]-1*H*-pyrido[1,2-*a*][1,3]diazepinium bromide (**12**) is also described.

It has been reported that whereas 3-bromo-4-bromomethyl-7-methoxycoumarin (**1a**)[1] reacted reluctantly with phenoxides, it was rapidly converted into pyridinium salts by simply substituted pyridines.[2] When 2-aminopyridine (**2**) was used, where there was the possibility of attack by either the ring nitrogen or the amino group, the only product obtained by Box and Humes,[2] was that due to attack in the former manner. They report that some of the pyridinium salts in this series show interesting pharmacological activity. The salts (**1**) (R^1 = pyridinium bromide, R^2 = H, and R^1 = quinolinium bromide, R^2 = H) show anticoagulant properties and also precipitate an excitement in rats before causing their death.[2]



1a R^1 = Br, R^2 = H
1b R^1 = H, R^2 = OMe



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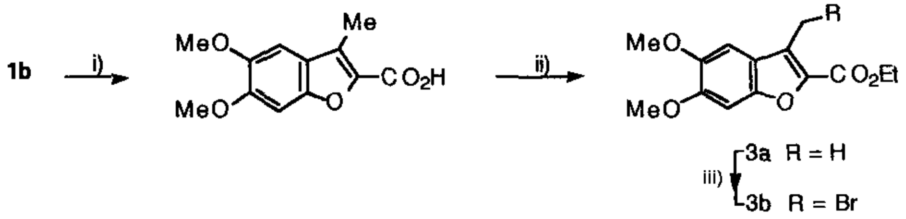
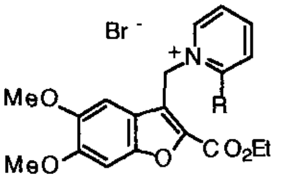
We have synthesized 2-carboethoxy-5,6-dimethoxy-3-methylbenzofuran (**3a**),[3] and have investigated reaction of 3-bromomethyl-2-carboethoxy-5,6-dimethoxybenzofuran (**3b**)[3] with pyridine and with 2-aminopyridine. We also report the synthesis of a novel amide salt (**12**).

Compound (**3a**), available by the method of Whalley *et al.*,[4] was more easily obtained by refluxing 3-bromo-6,7-dimethoxy-4-methylcoumarin (**1b**)[5] with 5 molar equivalents of sodium hydroxide in ethanol, followed by esterification of the carboxylic acid formed (Scheme 1). Compound (**1b**) was prepared by methylation of commercially available 6,7-dihydroxy-4-methylcoumarin followed by treatment with bromine (3 moles) in chloroform. Compound (**3a**) was then converted to 2-carboethoxy-3-bromomethyl-5,6-dimethoxybenzofuran (**3b**) by reaction with NBS in CCl_4 under irradiation. Unlike the case of **1a**, reaction of compound (**3b**) with phenoxides was found to take place efficiently to provide ethers (**3**) (R = 3-methoxyphenoxy, 1-naphthyloxy etc.) in yields of over 80%.[3]

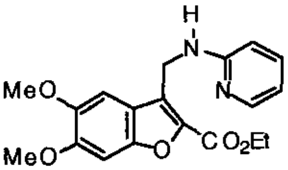


Scheme 1 *Reagents and conditions* i) NaOH in EtOH, reflux; ii) K_2CO_3, EtI; iii) NBS, CCl_4, hv

When compound (**3b**) was treated with pyridine in dry chloroform at room temperature, the pyridinium salt (**4a**) was produced in 90% yield. With 2-aminopyridine in refluxing chloroform, however, both the pyridinium salt (**4b**) and the secondary amine (**5**) were produced in 42% and 23% yields, respectively. The multiplicity and chemical shift of the methylene group which is *alpha* - to the nitrogen, were, in both cases, ready evidence of the position at which alkylation had occurred. The ^1H NMR spectrum of **4b** showed these protons as a singlet at δ 5.88, whereas in **5** they resonated as a doublet at δ 4.98 which collapsed to a singlet on D_2O exchange.



4a R = H
4b R = NH_2



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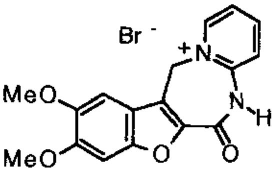
2-Aminopyridine (**2**) is tautomeric, therefore, the amino form exists in equilibrium with the pyridone-imine form (**2a**).[6] The spectroscopic characteristics of 2-aminopyridine, however, indicate that the amino form (**2**) greatly predominates over the imino form (**2a**) and that the ratio of **2** to **2a** is greater than 1000 : 1.[7-9] In the absence of added base, alkylation of 2-aminopyridines at the ring nitrogen is normally preferred over alkylation of the exocyclic nitrogen since the ring nitrogen is more basic. However, if the exocyclic amino group is first deprotonated, the alkylation occurs at this position.[6] It was expected that refluxing compound (**3b**) with 2-aminopyridine would provide the salt (**4b**). Formation of **5** as well, indicated that alkylation of 2-aminopyridine had occurred at the amino group without previous deprotonation.

It was envisaged that the novel tetracyclic salt (**6**) could be prepared from **4b** by nucleophilic attack of the amino group on the carboethoxy functionality. However, compound (**4b**) proved resistant to cyclization by refluxing in triethylamine or in 2,4,6-trimethylpyridine for 6 hours, or refluxing in *m*-xylene for 10 hours. In all cases starting material was recovered unchanged. This is probably due to the contribution of the canonical form (**7**) which has a positively charged exocyclic nitrogen. Attempts to obtain **6** by converting the ester functionality of **4b** to the acyl halide would no doubt lead to protonation of the amino group, rendering it non-nucleophilic.



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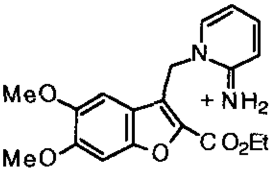

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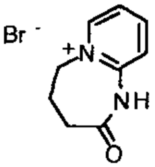

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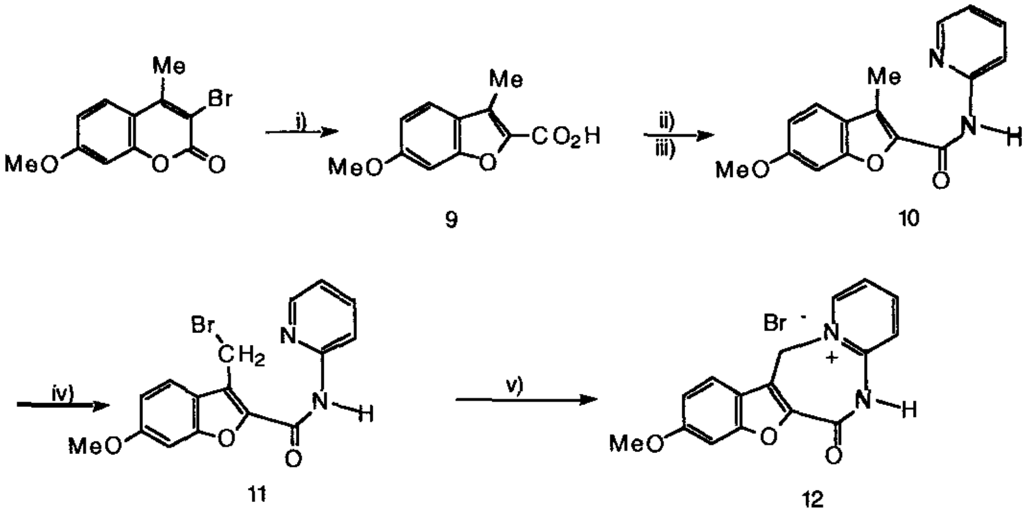
We now wish to report the successful synthesis of the novel tetracyclic salt (**12**). Fozard and Jones[10] synthesized the analogous amide (**8**) by treating 2-aminopyridine with γ-bromobutanoyl bromide. The yield of the amide (**8**), however, was only 7%. Their work also showed that the amino group exhibited a tendency to undergo acylation whereas the pyridinium nitrogen preferentially undergoes alkylation.

We investigated the alternative pathway to the tetracyclic salt (**12**) (Scheme 2) using compound (**9**) since it was more readily available than its dimethoxy analogue. The electronic characteristics of both sets of compounds should be quite similar. Treatment of the acid (**9**) with thionyl chloride followed by 2-aminopyridine produced the amide (**10**) in 53% yield. Irradiation (using high intensity visible light) of **10** with NBS in CCl_4 for 2 hours, produced **11** (83%) which was converted to the tetracyclic salt (**12**) (85%) by refluxing in acetone for 20 hours. The salt (**12**) was also obtained directly, but in lower yield, when the reaction time of amide (**10**) with NBS in CCl_4 was prolonged for 24 hours.



Scheme 2 *Reagents and conditions* i) NaOH, EtOH, reflux; ii) $SOCl_2$, py; iii) 2-aminopyridine; iv) NBS,CCl_4, hν; v) acetone, reflux

One very prominent and, in fact, distinguishing feature in the ^1H NMR spectra of compounds (**10**), (**11**) and (**12**) was the position of the methyl or methylene protons attached to the benzofuran system. The spectrum of **10** showed these methyl protons resonating at δ 3.90. In compound (**11**), the corresponding methylene protons were further downfield at δ 5.15, emphasizing the influence of the bromine substituent. The methylene protons of the salt (**12**) were deshielded even further, and resonated at δ 6.12. On cyclization of **11** to **12** also, the δ-value of the proton adjacent to the nitrogen atom of the pyridine ring showed a distinct shift downfield from 8.32 to 9.15, the latter confirming the cyclization to a pyridinium salt.

EXPERIMENTAL

General. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Unless otherwise stated, ^1H and ^{13}C NMR spectra were obtained in deuteriochloroform solutions on a Bruker AC 200 instrument using tetramethylsilane as an internal standard. Mass spectral data were obtained using a VG Auto Spec spectrometer. Infrared spectra were obtained on a Perkin Elmer 735B-model or Perkin Elmer 1600 FTIR spectrophotometer and are for KBr discs. Elemental analyses were performed by Butterworth Labs., Middlesex, UK. Column chromatography was carried out using silica gel.

2-Carboethoxy-5,6-dimethoxy-3-methylbenzofuran (**3 a**): A mixture of 5,6-dimethoxy-3-methylbenzofuran-2-carboxylic acid[4,5] (2.0 g, 8.5 mmol), ethyl iodide (3.5 mL, 43 mmol) and K_2CO_3 (5.9 g, 43 mmol) in acetone (200 mL) was stirred at reflux for 6 h. The mixture was filtered, the acetone removed *in vacuo*, and the resultant solid recrystallized from methanol to give **3 b** (1.80 g, 80%), mp 113-114^{0}C; ^{1}H NMR δ 1.42 (3H, t, J =7 Hz, $C\underline{H_3}CH_2$-), 2.53 (3H, s, $C\underline{H_3}$-C=C), 3.93 (6H, s, 2 x OMe), 4.42 (2H, q, J = 7 Hz, -$C\underline{H_2}CH_3$), 6.90 and 6.98 (each 1H, s); IR 1710 cm^{-1}. *Anal.* Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.55; H, 6.11.

3-Bromomethyl-2-carboethoxy-5,6-dimethoxybenzofuran (**3 b**): To a stirred solution of **3 a** (3.57 g, 13.6 mmol) in carbon tetrachloride (72 mL), *N*-bromosuccinimide (2.66 g, 15 mmol) was added, in portions. The mixture was irradiated (150 W tungsten lamp) for 4 h during which time the mixture refluxed gently. The suspension was then filtered and the filtrate was concentrated to give **3 b** (3.09 g, 66%), mp 134-136^{0}C (from MeOH); ^{1}H NMR δ 1.45 (3H, t, J = 7 Hz, - $CH_2C\underline{H_3}$), 3.93 and 3.95 (each 3H, s, OMe), 4.45 (2H, q, J = 7 Hz, -$C\underline{H_2}CH_3$), 4.95 (2H, s, -CH_2Br), 7.00 and 7.05 (each 1H, s); IR 1710 cm^{-1}.

This compound is unstable at room temperature and is best used within a few days of preparation.

2-Carboethoxy-5,6-dimethoxy-3-benzofuranmethylpyridinium bromide (4a): To a solution of compound (**3 b**) (145 mg, 0.42 mmol.) in dry chloroform (2.5 mL) was added dry pyridine (0.2 mL, 2.54 mmol) and the mixture was stirred overnight at room temperature. The resulting precipitate was collected by filtration, washed with carbon tetrachloride and recrystallized from 10% aqueous HBr. The recrystallized material was washed with acetone to yield the pyridinium salt (**4 a**) (160 mg, 90%), as fluffy white needles, mp 231.5-232.5^{0}C. ^{1}H NMR ($CDCl_3$ +TFA) δ 1.47 (3H, t, J =7 Hz), 4.03 (6H, s, 2 x OMe), 4.53 (2H, q, J =7 Hz), 6.38 (2H, s, -CH_2-py$^+$ Br$^-$), 7.25 (1H, s, H-7), 7.40 (1H, s, H-4), 8.00-8.88 (3H, m, H-3', -4', -5') and 9.03 (2H, m, H-2' and H-6'); IR 1703 cm^{-1}. *Anal.* Calcd for $C_{19}H_{20}NO_5Br$: C, 53.90; H, 4.76; N, 3.31; Br, 18.88. Found: C, 53.56; H, 4.80; N, 3.46; Br, 19.05.

2-Carboethoxy-5,6-dimethoxy-3-benzofuranmethyl-2'-aminopyridinium bromide (4b) and ***N*-(2-carboethoxy-5,6-dimethoxy-3-benzofuranmethyl)-*N*-2-pyridylamine (5):** 2-Aminopyridine (281 mg, 3.0 mmol) was added to a solution of compound (**3 b**) (410 mg, 1.2 mmol) in chloroform (5 mL) which had been dried over $CaCl_2$. The resulting solution was stirred at reflux for 4.5 h. After cooling, the formed precipitate was collected and recrystallized from 10% aqueous HBr to give shiny crystals of the salt (**4b**) (218 mg, 42%), mp 238^{0}C (decomp). ^{1}H NMR ($CDCl_3$ +TFA) δ 1.45 (3H, t, J=7 Hz, -CH_2-C$\underline{H_3}$), 3.92 and 4.02 (each 3H, s, OMe), 4.55 (2H, q, J =7 Hz, -C$\underline{H_2}$-CH_3), 5.88 (2H, s, -CH_2-py $^+$), 7.02 (1H, s, H-7), 7.22 (1H, s, H-4), 6.92-7.37 (2H, m) and 7.94 (2H, m); IR 1710 cm^{-1}. *Anal.* Calcd for $C_{19}H_{21}N_2O_5Br.H_2O$: C, 50.12; H, 5.09; N, 6.15; Br, 17.55. Found: C, 50.05; H, 5.14; N, 6.52; Br, 17.55.

The filtrate of the original reaction mixture - i.e., the chloroform solution - was evaporated and after PLC in chloroform-ethyl acetate (9:1), the amine (**5**) was obtained (98 mg, 23%), mp 147^{0}C. ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J=7 Hz, -CH_2C$\underline{H_3}$), 3.75 and 3.85 (each 3H, s, OMe), 4.42 (2H, q, J =7 Hz, -C$\underline{H_2}$$CH_3$), 4.98 (2H, d, J=6 Hz, collapses to singlet with D_2O, - C$\underline{H_2}$ - NH -), 5.48 (1H, bd, J =6 Hz, exchanges with D_2O, - CH_2 - N$\underline{H}$ -), 6.50 (2H, m, H-4' and H-5'), 6.93 (1H, s, H-7), 7.22 (1H, s, H-4) 7.36 (1H, m, H-3') and 8.10 (1H, m, H-2'); IR 3350 and 1690 cm^{-1}. *Anal.* Calcd for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.66; N, 7.86. Found: C, 64.24; H, 5.63; N, 7.92.

6-Methoxy-3-methylbenzofuran-2-carboxylic acid (9): A solution of sodium hydroxide (7.43 g, 186 mmol) in ethanol (364 mL) was added to 3-bromo-7-methoxy-4-methylcoumarin[1] (10.05 g, 37 mmol), and the mixture was refluxed for 2 h. The solution was then concentrated to give a white solid. A minimum volume of water (10 mL) was added to obtain a solution which was acidified with concentrated hydrochloric acid while cooling. The resultant precipitate was then filtered, dried and recrystallized from aqueous ethanol to give **9** (6.93 g, 90%), as a white powder, mp 183-185^{0}C, (lit.,[11] 186^{0}C, decomp).

***N*-2-Pyridyl-6-methoxy-3-methylbenzofuran-2-carboxamide (10):** Redistilled thionyl chloride (25 mL, 343 mmol) was added to the dry acid (**9**) (5.00 g, 24 mmol) and the mixture refluxed gently for 30 min. The excess thionyl chloride was distilled off. The residue in the flask was the acid chloride (5.2 g, 22 mmol) to which pyridine (20 mL) followed by 2-aminopyridine (2.27 g, 24.2 mmol) was added with stirring. The mixture was stirred at rt for 48 h. Toluene (80 mL) was then added, and the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (hexane:chloroform - 7:3 by volume) to give the amide (**10**) (3.64 g, 53%), as white crystals, mp 167-169^{0}C; ^{1}H NMR δ 2.65 (3H, s, $CH_3C=C$), 3.92 (3H, s, -OCH_3), 6.92 (2H, m, H-3' and H-5'), 7.08 (1H, m, H-7), 7.49 (1H, dd, J = 2 and 6 Hz, H-5), 7.75 (1H, dt, J = 2 and 8 Hz, H-4'), 8.35 (2H, m, H-4 and H-6'), 9.00 (1H, s, -NH-); ^{13}C NMR δ 9.15, 55.72, 95.40, 113.10, 113.96, 119.76, 121.31, 123.06, 124.98, 138.30, 141.33, 148.04, 151.19, 154.64, 158.18, 160.65; IR 1620, 1670, 3360 cm^{-1}; MS m/z (relative intensity) 282 (M$^+$, 100), 267 (10), 254 (12), 239 (26), 189 (73), 133 (23), 121 (11), 90 (11). *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.62; H, 5.09; N, 10.16.

***N*-2-Pyridyl-6-methoxy-3-bromomethylbenzofuran-2-carboxamide (11):** To a stirred solution of **10** (0.50 g, 1.7 mmol) in carbon tetrachloride (30 mL), *N*-bromosuccinimide (0.35 g, 1.9 mmol) was added, in portions. The mixture was irradiated (150 W tungsten lamp) for 2 h during which time the mixture refluxed gently. The suspension was then filtered and the filtrate was concentrated to give **11** (0.53 g, 83%), as a light brown powder, mp 285-286^{0}C (from CCl_4); ^{1}H NMR δ 3.99 (3H, s, $-OCH_3$), 5.20 (s, 2H, $-CH_2Br$), 6.90-7.10 (3H, m, H-7, H-3' and H-5'), 7.67 (1H, dd, J = 8 Hz, H-5), 7.75 (1H, dt, J = 2 and 4 Hz, H-4'), 8.35 (2H, m, H-4 and H-6'), 9.10 (1H, s, -NH-); ^{13}C NMR δ 20.80, 55.78, 95.61, 113.83, 114.21, 120.17, 120.58, 121.69, 124.57, 138.40, 141.43, 148.10, 150.73, 154.86, 157.25, 160.97; IR 1625, 1772, 3362 cm^{-1}.

This compound is not very stable and should be used within a few days of its preparation.

3-Methoxy-6,7,12-trihydro-6-oxo-[1]benzofurano[2,3-*c*]-1*H*-pyrido[1,2-*a*][1,3]-diazepinium bromide (12): Freshly distilled acetone (20 mL) was added to **11** (0.13 g, 2.6 mmol) and the mixture was heated at reflux for 20 h. The acetone was evaporated and the resultant solid was treated with hot ethanol. The hot suspension was filtered and the tetracyclic salt (**12**) (0.11 g, 85%) was obtained as a tan-colored powder, mp 260-262^{0}C(decomp); ^{1}H NMR δ 3.84 (3H, s, $-OCH_3$), 6.12 (2H, s, $-CH_2py^+-$), 7.16 (1H, dd, J = 2 and 10 Hz, H-2), 7.41 (1H, d, J = 2 Hz, H-4), 7.80 (2H, m, H-8 and H-10), 8.12 (1H, d, J = 10 Hz, H-1), 8.54 (1H, dt, J = 4 and 6 Hz, H-9), 9.15 (1H, d, J = 6 Hz, H-11); ^{13}C NMR δ 49.78, 55.98, 96.02, 114.61, 117.71, 121.44, 122.59, 122.85, 123.27, 143.17, 143.18, 146.50, 147.85, 156.79, 157.38, 161.18; IR 1620, 1705, 3447 cm^{-1}. *Anal.* Calcd for $C_{16}H_{13}N_2O_3Br.1/2H_2O$: C, 51.89; H, 3.78; N, 7.57. Found: C, 51.72; H, 3.62; N, 7.30.

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