Pergamon

Tetrahedron, Vol. 53, No. 47, pp. 16185-16194, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10077-1

Synthesis of [1]Benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones

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Abstract. 2-N-(Acylmethyl)aminochromones were prepared from 2-chlorochromone and α-amino ketones (hydrochloride or ketal derivatives) in ethanol/triethylamine. Their treatment with acetic acid/pyrrolidine led to [1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones, which were subsequently functionalized in C2 by aromatic electrophilic substitution (acetylation, bromination or nitration).

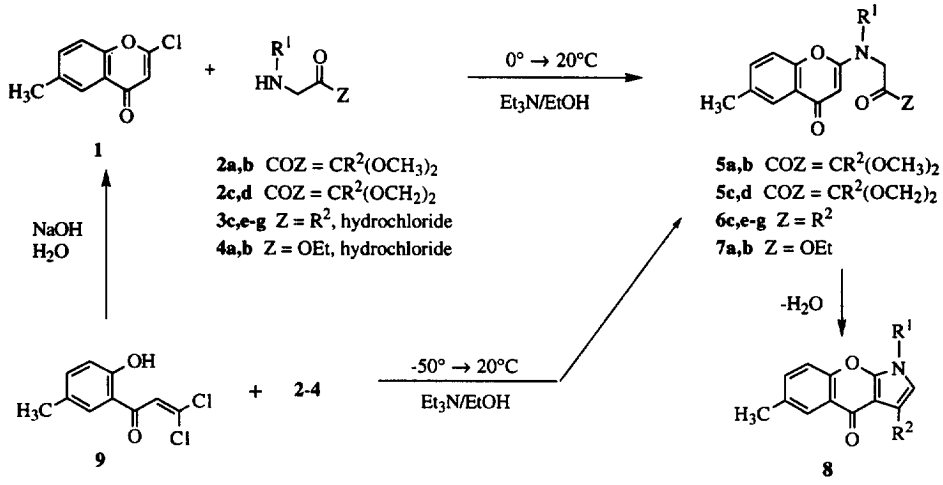
Introduction

Although the synthesis and pharmacological properties of [1]benzopyran-4(1*H*)-ones[2,3]condensed with numerous nitrogen-containing heterocycles have been the object of extensive studies, there are relatively few references when the fused heterocycle is a pyrrole. Only several natural [1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones, antibiotics TAN-876A[1] and pyralomicins,[2-4] have been isolated from culture broth and characterized. Herein we describe the first synthetic method to obtain [1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones **8** from 2-chlorochromones **1**[5] and α-aminocarbonyl compounds (acetal and ketal **2**, or hydrochloride **3**, **4** derivatives).

Synthesis of [1]Benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones

Our synthetic procedure involves two steps: first a 1,4 addition followed by elimination, that is a substitution of Cl by N, to obtain the 2-aminochromone derivatives **5-7**, and, secondly, their subsequent cyclization to give **8** (Scheme 1).

This method is a modification of the Knorr reaction, where the intermediate enamines **5-7** formed during these processes do not arise from the attack of the amines **2-4** to a ketone, but to the synthetic equivalent of a carboxylic function. Morever, the high reactivity in C2 of the intermediate 2-aminochromones **5-7** does not allow a generalization of the procedures usually employed for the cyclization of N-acylmethyl-β-aminoenones, and the fusion of a pyrrole can be achieved only for some specific R^1 and Z groups.



a: $R^1 = R^2 = H$; **b**: $R^1 = CH_3$, $R^2 = H$; **c**: $R^1 = H$, $R^2 = CH_3$; **d**: $R^1 = R^2 = CH_3$; **e**: $R^1 = H$, $R^2 = Ph$;

f: $R^1 = CH_3$, $R^2 = Ph$; **g**: $R^1 = H$, $R^2 = 4\text{-}NO_2\text{-}Ph$.

Scheme 1: General procedures to obtain [1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones **8**.

Table 1: Preparation of Compounds **5-7** from **1** or **9**.

Start	Amine	R^1	Z	Method[c]	Time (h)	Product	Yield (%)
1	**2a**	H	$CH(OCH_3)_2$	A	18	**5a**	89
1	**2b**	CH_3	$CH(OCH_3)_2$	A	24	**5b**	92
1	**2c**	H	$CCH_3(OCH_2)_2$	A	72	**5c**	82
1	**2d**	CH_3	$CCH_3(OCH_2)_2$	A	120	**5d**	70
1	**3c**[a]	H	CH_3	A	24	**6c**	—[b]
1	**3e**[a]	H	Ph	A	25	**6e**	89
1	**3f**[a]	CH_3	Ph	A	96	**6f**	70
1	**3g**[a]	H	4-NO_2-Ph	A	24	**6g**	—[b]
1	**4a**[a]	H	OEt	A	25	**7a**	69
1	**4b**[a]	CH_3	OEt	A	24	**7b**	87
10	**2a**	H	$CH(OCH_3)_2$	B	98	**5a**	86
10	**2b**	CH_3	$CH(OCH_3)_2$	B	96	**5b**	76
10	**2d**	CH_3	$CCH_3(OCH_2)_2$	B	96	**5d**	58
10	**3e**[a]	H	Ph	B	150	**6e**	60
10	**3f**[a]	CH_3	Ph	B	145	**6f**	65
10	**4a**[a]	H	OEt	B	120	**7a**	56
10	**4b**[a]	CH_3	OEt	B	96	**7b**	78

(a) Hydrochloride derivative. (b) **3** autocondensed. (c) Method A: Et_3N/EtOH, 0°→ 20°C. Method B: Et_3N/EtOH, -50°→ 20°C.

The addition-elimination step gives satisfactory results when **1** is treated with ethyl glycinate hydrochlorides **4a,b** in ethanol/triethylamine.[6] However, important limitations were observed for α-aminocarbonyl hydrochlorides due to their easy autocondensation. Among all the studied substrates only **6e** and **6f** could be obtained from their respective phenacyl derivatives **3e** and **3f** (Table 1).

The acetalic or ketalic derivatives **2** are used as an alternative to those hydrochlorides which show a greater tendency to autocondense. Their reaction with **1** in ethanol/triethylamine leads to **5** in excellent yields (Table 1).

The aminochromones **5-7** can also be prepared from **9**,[7] which is precursor of **1**.[5] The reactions of **9** with the amines **2-4** are more complex than those using **1** as starting material, being the overall yields usually lower than those found in the two steps method (Scheme 1, Table 1).

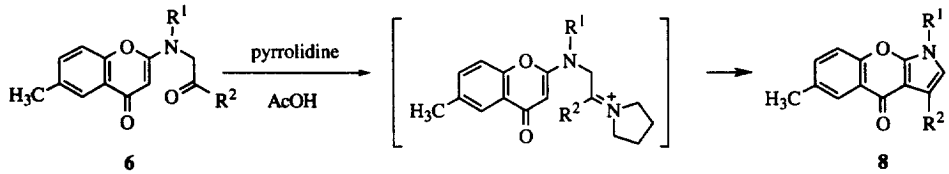
Table 2: Cleavage of acetals and ketals **5**.

Start	Deprotecting Agent	T(°C)	Time (h)	Product	Yield (%)
5a	(a)	—	—	**6a**	—
5b	$AcOH/H_2O$ (4:1)	reflux	15	**8b**	85
5b	$TFA/H_2O/CHCl_3$ (1:1:1)	20	24	**6b** + **8b**	(b)
5c	(a)	—	—	**6c**	—
5d	$TFA/H_2O/CHCl_3$ (1:1:1) 20	20	24	**6d**	56

(a) A variety of deprotecting agents were employed ($AcOH/H_2O$, CF_3CO_2H, $ISiMe_3$, $TiCl_4$). (b) Total yield: 83%, ratio **6b/8b**: variable.

The success of the selective deprotection of the acetal or ketal in the presence of the enamine to obtain **6** from **5** depends strongly on the substituent R^1 (Table 2). When R^1 = H (**5a** and **5c**), the cleavage of the acetal or ketal is always accompanied by degradation of the molecule , regardless of the deprotecting agent employed ($AcOH/H_2O$, CF_3CO_2H, $ISiMe_3$, $TiCl_4$).[8] However, when R^1 = CH_3 (**5b** and **5d**), the molecule is more stable, and either acetic or trifluoroacetic acids give satisfactory results when used as deprotecting agents. These deprotection processes occur with total or partial simultaneous cyclization to **8**; in the latter case no attempts were made to isolate **6** from the reaction mixture and the processes were continued in order to obtain a complete transformation to **8**.

When the cyclization processes are carried out from aldehydes or ketones, the results obtained depend not only on the nature of R^2 but also of R^1 (Table 3). Degradation products were formed, when starting from **6e** (R^1 = H), regardless of the conditions used (heating, AcOH, H_3PO_4, SiO_2, NEt_3, EtONa). However, the



6 **8**

Scheme 2: Cyclization of **6** when R^1 = CH_3

pyrroles **8b,d,f** ($R^1 = CH_3$) were readily obtained when their respective precursors were heated in pyrrolidine/acetic acid (1/1). In this case, the pyrrolidine probably activates the electrophilicity of the carbonylic function through an iminum salt as intermediate (Scheme 2), since other acidic or basic conditions do not lead to these results.

Table 3 shows how the yields are higher as the electrophilicity of the carbonyl increases ($R^3 = H > CH_3 > Ph$), and thus the higher reactivity of the aldehyde allows the deprotection of **5b** in acetic acid/water (4/1) with total cyclization to **8b**.

Table 3: Cyclization from **5** or **6** to **8**

Start	Conditions	Time (h)	Product	R^1	R^2	Yield (%)
5b	AcOH/H_2O (4:1), reflux	24	**8b**	CH_3	H	85
6d	AcOH/pyrrolidine (1:1), reflux	24	**8d**	CH_3	CH_3	70
6e	(a)	—	**8e**	H	Ph	—
6f	AcOH/pyrrolidine (1:1), reflux	48	**8f**	CH_3	Ph	65

(a) A variety of methods were used: heating, AcOH, pyrrolidine, pyrrolidine/AcOH, H_3PO_4, SiO_2, Et_3N, EtONa.

Although there are some precedents in the literature of 2*H*-3-pyrrolones[9] obtained from α-aminoesters, we could not achieve [1]benzopyrano[2, 3-*b*]pyrrol-3,4(1*H*, 2*H*)-diones when the esters **7a** and **7b** were used as starting materials.

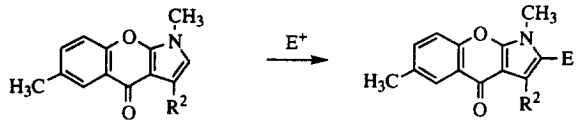
Aromatic Electrophilic Substitution

Oxygenated electron-donating substituents at the α–C increase the chemical unstability of pyrroles towards Lewis acids. In [1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones **8**, such effect decreases due to the presence of an electron-withdrawing substituent at the β–C, and because both substituents are fused between two aromatic cycles. We have verified that this tricyclic system is reasonably stable in the conditions usually employed for the aromatic electrophilic substitutions of pyrroles, and new functionalized groups can be incorporated to the molecule (Scheme 3, Table 4).

The nitration with nitric acid/acetic anhydride must be carried out without any excess of acid and at low temperature (-5°C), otherwise degradation processes occur. The acetylation with acetic anhydride/titatium tetrachloride requires a lower control of the reaction conditions, and it can be carried out at 70°C. In both cases the substitution takes place exclusively at the 2-C, since all direct effects, i.e. the heteroatom, the donating substituent at the α–C, and the withdrawing substituent at the β–C, coincide in this position.

The pyrroles **8** are not sufficiently activated to be formilated with the Vilsmeier reagent ($POCl_3$/DMF, 50°C) and the starting product was recovered after 3h of heating.

The bromations with N-bromosuccinimide/acetic acid are cleaner than those with Br_2/AcOH. Polibromation in **8b** is observed, as often occur in pyrroles, and we were not able to control the process to obtain exclusively the 2-bromo derivative. The only monobromo derivative was obtained from **8d**, as it has only one available position.



8 **10-16**

Scheme 3: Aromatic electrophilic subtitution on **8**.

Table 4: Aromatic electrophilic substitution.

Start	Reactant-Solvent	T (°C)	Time (h)	Product	R^2	E	Yield (%)
8b	$TiCl_4/Ac_2O$	70	17	**10**	H	Ac	70
8b	HNO_3/Ac_2O	-5	2	**11**	H	NO_2	50
8b	NBS/AcOH	20	2	**12**	H	Br	37
				13	Br	Br	35
8d	$TiCl_4/Ac_2O$	70	2	**14**	CH_3	Ac	57
8d	NBS/AcOH	20	2	**15**	CH_3	Br	60
8f	HNO_3/Ac_2O	-5	2	**16**	Ph	NO_2	58

EXPERIMENTAL

Mps were measured on a Leit Laborlux D microscope with a heating device and are uncorrected. NMR spectra were recorded on Bruker AC300 spectrometer, and chemical shifts are given downfield from $SiMe_4$ as internal standard; ^{13}C NMR spectra were carried out with complete ^1H decoupling and the assignments were made by additional DEPT experiments. Mass spectra and elemental analyses were measured on a Hewlett-Packard 5988 A mass spectrometer and on a Perkin Elmer 2400B CHN analyzer respectively.

The starting compounds were purchased from the usual suppliers or synthesized by literature procedures (**1**,[5] **2c**,[10] **2d**,[11] **3c**,[12] **3f**,[13,14] **3g**,[14] **9**[7]).

Preparation of 5-7 from 1. General Procedure. To a chilled (0°C) solution of **1** (1.94 g, 10 mmol), Et_3N (1.67 ml, 1.21 g, 12 mmol) in EtOH (80 ml) was added hydrochloride **2-4** (12 mmol). The temperature was allowed to rise 20°C and the mixture was stirred for the times given on the table 1. At the end of the reaction, monitored by tlc, the solution was concentrated *in vacuo*. The hydrochlorides present in the mixture were removed by succesive washings with water when the residue was a solid. Otherwise, when an oil was obtained, the residue was dissolved in dry THF, filtered, and evaporated to dryness. The product was recrystallized from toluene, or chromatographed on silica gel using AcOEt as eluent.

The compounds **5a-d**, **6e-f** and **7a-b** were thus preparated. The chemical yields and the physical and spectral characteristics of these product are given below.

2-(2,2-Dimethoxy-ethylamino)-6-methyl-4H-1-benzopyran-4-one (**5a**): 89%, mp. 120°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 3.39 (m, 2H), 3.41 (s, 6H), 4.58 (t, J = 5.2, 1H), 5.46 (s, 1H), 6.21 (br, NH), 7.11 (d, J = 8.4, 1H), 7.30 (dd, J = 8.4, J=1.4, 1H), 7.91 (d, J = 1.4, 1H); ^{13}C NMR (75.4 MHz,

$CDCl_3$) δ = 20.8 (CH_3), 43.0 (CH_2), 54.3 ($2CH_3$), 85.8 (CH), 101.6 (CH), 116.0 (CH), 122.6 (C), 125.1 (CH), 133.1 (CH), 134.4 (C), 151.8 (C), 163.2 (C),177.1 (C); MS: m/z 263 (M^+, 1), 75 (100). (Found: C, 63.96; H, 6.48; N, 5.29. $C_{14}H_{17}NO_4$ requires C, 63.86; H, 6.51; N, 5.32%).

2-(2,2-Dimethoxy-N-methyl-ethylamino)-6-methyl-4H-1-benzopyran-4-one (**5b**): 92%, mp. 97°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.41 (s, 3H), 3.10 (s, 3H), 3.44 (s, 6H), 3.56 (d, J = 5.2, 2H), 4.54 (t, J = 5.2, 1H), 5.42 (s, 1H), 7.19 (d, J = 8.4, 1H), 7.34 (dd, J = 8.4, J=1.4, 1H), 7.95 (d, J=1.4, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.8 (CH_3), 37.6 (CH_3), 51.9 (CH_2), 54.9 ($2CH_3$), 86.3 (CH), 103.0 (CH), 116.0 (CH), 122.5 (C), 125.1 (CH), 133.0 (CH), 134.5 (C), 151.8 (C), 162.3 (C), 176.8 (C); MS: m/z 277 (M^+, 5), 75 (100). (Found: C, 64.92; H, 6.88; N, 5.03. $C_{15}H_{19}NO_4$ requires C, 64.96; H, 6.91; N, 5.05%).

2-(2,2-Ethylenedioxy-propylamino)-6-methyl-4H-1-benzopyran-4-one (**5c**): 82%, mp. 152°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.35 (s, 3H), 2.34 (s, 3H), 3.35 (d, J = 6.2, 2H), 3.95 (s, 4H), 5.45 (s, 1H), 5.93 (br, NH), 7.08 (d, J = 8.4, 1H), 7.26 (dd, J = 8.4 and 1.9, 1H), 7.88 (d, J = 1.9, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.7 (CH_3), 22.4 (CH_3), 47.6 (CH_2), 65.1 (2 CH_2), 85.9 (CH), 107.9 (C), 115.9 (CH), 122.7 (C), 125.0 (CH), 132.8 (CH), 134.1 (C), 151.7 (C),163.5 (C), 176.9 (C); MS: m/z 275 (M^+, 20), 87 (100). (Found: C, 65.25; H, 6.26; N, 5.11. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09%).

2-(2,2-Ethylenedioxy-N-methyl-propylamino)-6-methyl-4H-1-benzopyran-4-one (**5d**): 70%, mp. 102°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.32 (s, 3H), 2.40 (s, 3H), 3.09 (s, 3H), 3.63 (s, 2H), 3.93 (m, 4H), 5.48 (s, 1H), 7.19 (d, J = 8.4, 1H), 7.35 (dd, J = 8.4, J=1.4, 1H), 7.94 (d, J=1,4, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.6 (CH_3), 22.3 (CH_3), 37.5 (CH_3), 54.7 (CH_2), 64.7 (2 CH_2), 86.2 (CH), 109.0 (C), 115.8 (CH), 122.2 (C), 124.8 (CH), 132.8 (CH), 134.1 (C),151.5 (C), 162.7 (C), 176.6 (C); MS: m/z 289 (M^+, 4), 87 (100). (Found: C, 66.34; H, 6.61; N, 4.82. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%).

2-Phenacylamino-6-methyl-4H-1-benzopyran-4-one (**6e**): 89%, mp. 242°C. ^1H NMR (300 MHz, DMSO-d_6) δ = 2.37 (s, 3H), 4.91 (d, J = 5.9, 2H), 5.30 (s, 1H), 7.29-8.11 (8H Ar, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.5 (CH_3), 47.7 (CH_2), 85.1 (CH), 116.4 (CH), 122.7 (C), 124.3 (CH), 128.1 (CH), 128.9 (CH), 133.0 (CH), 133.9 (CH), 134.6 (C),151.4 (C), 163.7 (C), 171.3 (C), 174.5 (C), 194.8 (C); MS: m/z 293 (M^+, 26), 105 (100). (Found: C, 73.66; H, 5.15; N, 4.80. $C_{18}H_{15}NO_3$ requires C, 73.71; H, 5.15; N, 4.78%).

2-(N-Methyl-phenacylamino)-6-methyl-4H-1-benzopyran-4-one (**6f**): 70%, mp. 190°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.40 (s, 3H), 3.16 (s, 3H), 4.93 (s, 2H), 5.47 (s, 1H), 7.04-7.99 (8H Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.7 (CH_3), 37.6 (CH_3), 56.0 (CH_2), 86.7 (CH), 116.0 (CH), 122.3 (C), 125.0 (CH), 127.8 (CH), 128.9 (CH), 132.9 (CH), 134.1 (CH), 134.3 (C), 134.4 (C), 151.7 (C), 162.9 (C), 176.9 (C), 193.1 (C); MS: m/z 307 (M^+, 7), 68 (100). (Found: C, 74.19; H, 5.59; N, 4.57. $C_{19}H_{17}NO_3$ requires C, 74.24; H, 5.58; N, 4.56%).

2-(Ethoxycarbonil-methylamino)-6-methyl-4H-1-benzopyran-4-one (**7a**): 69%, mp. 141°C. ^1H NMR (300 MHz, DMSO-d_6) δ = 1.32 (t, J=7.1, 3H), 2.40 (s, 3H), 4.01 (d, J=4.9, 2H), 4.27 (q, J=7.1, 2H), 5.37 (s, 1H), 6.00 (br, NH), 7.15 (d, J=8.3, 1H), 7,33 (d.d, J=8.3, J=1.4, 1H), 7.92 (d, J=1.4, 1H) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 14.1 (CH_3), 20.8 (CH_3), 43.2 (CH_2), 62.0 (CH_2), 86.3 (CH), 116.2 (CH), 122.6 (C), 125.1 (CH), 133.3 (CH), 134.6 (C), 151.9 (C), 162.9 (C),169.0 (C), 177.3 (C); MS: m/z 261 (M^+, 65), 188 (100). (Found: C, 64.26; H, 5.81; N, 5.38. $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36%).

2-(Ethoxycarbonil-N-methyl-methylamino)-4H-1-benzopyran-4-one (**7b**): 87%, mp. 130°C. ^1H NMR (300 MHz, DMSO-d_6) δ = 1.28 (t, J=7.1, 3H), 2.40 (s, 3H), 3.12 (s, 3H), 4.23 (m, 4H), 5.44 (s, 1H), 7.17 (d,

J=8.4, 1H), 7,33 (d.d, J=8.4, J=1.3, 1H), 7.94 (d, J=1.3, 1H) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 14.2 (CH_3), 20.8 (CH_3), 37.4 (CH_3), 51.3 (CH_2), 61.7 (CH_2), 86.9 (CH), 116.1 (CH), 122.3 (C), 125.1 (CH), 133.2 (CH), 134.6 (C), 151.9 (C), 162.8 (C), 168.6 (C), 177.1 (C); MS: m/z 275 (M^+, 27), 68 (100). (Found: C, 65.36; H, 6.25; N, 5.06. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09%).

Cleavage-Cyclization of 2-(2,2-dimethoxy-N-methyl-ethylamino)-6-methyl-4*H*-1-benzopyran-4-one (5b) to *1,6-dimethyl-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one* (8b). The compound **5b** (0.20 g, 0.72 mmol) was refluxed in 10 ml of AcOH/H_2O (4/1) for 12 h. The mixture was poured into water, extracted with CH_2Cl_2, and the organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated under reduced pressure to yield 0.13 g (85%) of highly pure **8b** as a pale yellow solid. mp. 148°C (from toluene). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.40 (s, 3H), 3.70 (s, 3H), 6.45 (d, J = 3.5, 1H), 6.80 (d, J = 3.5, 1H), 7.50 (s, 1H), 7.50 (d, J=1.3, 1H), 7.92 (d, J=1.3, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ = 20.4 (CH_3), 31.3 (CH_3), 100.8 (CH), 105.6 (C), 117.3 (CH), 120.2 (CH), 122.3 (C), 125.4 (CH), 133.7 (CH), 133.7 (C), 148.9 (C), 151.7 (C), 171.7 (C); MS: m/z 213 (M^+, 100). (Found: C, 73.15; H, 5.23; N, 6.58. $C_{13}H_{11}NO_2$ requires C, 73.22; H, 5.20; N, 6.57%).

Cleavage of 2-(2,2-ethylenedioxy-N-methyl-propylamino)-6-methyl-4*H*-1-benzopyran-4-one (5d) to *2-(N-methyl-2-oxo-propylamino)-6-methyl-4H-1-benzopyran-4-one* (6d). A solution of **5d** (0.10 g, 0.34 mmol) in 6 ml of $CHCl_3$/H_2O/TFA (1/1/1) was vigorously stirred for 24 h ar r.t., and then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on silica gel using AcOEt as eluant, to yield 0.58 g (56%) of **6d**. mp. 143°C (from toluene). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.23 (s, 3H), 2.39 (s, 3H), 3.08 (s, 3H), 4.32 (s, 2H), 5.53 (s, 1H), 7.13 (d, J = 8.4, 1H), 7.33 (dd, J = 8.4, J=1.4, 1H), 7.88 (d, J=1.4, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.8 (CH_3), 26.9 (CH_3), 37.5 (CH_3), 59.4 (CH_2), 86.4 (CH), 116.1 (CH), 121.5 (C), 124.9 (CH), 133.6 (CH), 135.0 (C), 151.7 (C), 163.1(C), 176.5 (C), 202.2 (C); MS: m/z 245 (M^+, 5), 68 (100). (Found: C, 68.63; H, 6.16; N, 5.70. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71%).

Cyclization of 6 to 8. General procedure. A solution of **6** (0.22 mmol) in 5 ml of pyrrolidine/AcOH (1/1) was refluxed for 24-48 h (Table 3). The volatiles compounds (pyrrolidine, AcOH and $AcN(CH_2)_4$ were then removed under reduced pressure, and the residue was chromatographed on silica gel using CH_2Cl_2 as eluant. The following compounds were thus prepared.

1,3,6-Trimethyl-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one **(8d):** 70%, mp. 184°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.44 (s, 3H), 2.46 (s, 3H), 3.65 (s, 3H), 6.24 (s, 1H), 7.33 (d, J = 8.4, 1H), 7.40 (d.d, J=8.4, J=1.9, 1H), 8.12 (d, J=1.9, 1H) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 11.6 (CH_3), 20.9 (CH_3), 31.0 (CH_3), 105.5 (C), 115.2 (C), 115.8 (CH), 116.7 (CH), 123.3 (C), 126.2 (CH), 133.2 (CH), 133.8 (C), 149.5 (C), 152.2 (C), 174.2 (C); MS: m/z 227 (M^+, 53), 42 (100). (Found: C, 74.11; H, 5.74; N, 6.13. $C_{14}H_{13}NO_2$ requires C, 73.99; H, 5.77; N, 6.16%).

1,6-Dimethyl-3-phenyl-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one **(8f)**: 65%, mp. 170°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.42 (s, 3H), 3.62 (s, 3H), 6.57 (s, 1H), 7.20-8.20 (8H, Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.9 (CH_3), 31.4 (CH_3), 103.6 (C), 116.3 (CH), 116.6 (CH), 121.1 (C), 123.2 (C), 126.5 (CH),

126.6 (CH), 128.1 (2 CH), 128.3 (2 CH), 133.4 (CH), 133.6 (C), 134.0 (C), 150.3 (C), 151.6 (C), 173.2 (C); MS: m/z 289 (M^+, 100). (Found: C, 78.89; H, 5.24; N, 4.86. $C_{19}H_{15}NO_2$ requires C, 78.87; H, 5.23; N, 4.84%).

Acetylation of 1,6-Dimethyl-[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones (8b) and 1,3,6-Trimethyl-[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (8d). A solution of **8b** or **8d** (0.5 mmol) in 2 ml of Ac_2O was added to a solution of 0.17 (1.5 mmol) ml of $TiCl_4$ in 4 ml of Ac_2O and the mixture was heated to 80°C under nitrogen. When the reaction was completed, monitored by tlc, the mixture was hydrolized and neutralized with NaOH/ice/water, and then extracted with AcOEt. The extract, after drying Na_2SO_4, was evaporated and chromatographed on silica gel, using CH_2Cl_2/hexane (1/2) as eluant (Table 4). The following compounds were thus prepared.

2-Acetyl-1,6-dimethyl-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one **(10):** 70%, mp. 260°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.46 (s, 3H), 2.49 (s, 3H), 4.00 (s, 3H), 7.40 (d, J=8,4, 1H), 7.48 (s, 1H), 7.49 (dd, J=8.4, J=1.1, 1H), 8.10 (d, J = 1.1, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.8 (CH_3), 26.7 (CH_3), 31.6 (CH_3), 106.1 (C), 113.0 (CH), 117.1 (CH), 122.5 (C), 126.4 (CH), 127.1 (C), 134.4 (CH), 134.8 (C), 152.2 (C), 152.5 (C), 173.7 (C), 189.6 (C); MS: m/z 255 (M^+, 54), 240 (100). (Found: C, 70.56; H, 5.13; N, 5.46. $C_{15}H_{13}NO_3$ requires C, 70.58; H, 5.13; N, 5.49%).

2-Acetyl-1,3,6-trimethyl-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one **(14):** 57%, mp. 227°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.44 (s, 3H), 2.50 (s, 3H), 2.84 (s, 3H), 3.90 (s, 3H), 7.34 (d, J=8.3, 1H), 7.41 (dd, J=8.3, J=1.1, 1H), 8.05 (d, J=1.1, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.0 (CH_3), 20.8 (CH_3), 31.1 (CH_3), 32.0 (CH_3), 105.4 (C), 116.9 (CH), 123.0 (C), 125.1 (C), 126.2 (CH), 126.6 (C), 134.1 (CH), 134.5(C), 151.4 (C), 152.1 (C), 175.0 (C), 190.0 (C); MS: m/z 269 (M^+, 100). (Found: C, 71.40; H, 5.02; N, 5.22. $C_{16}H_{15}NO_3$ requires C, 71.37; H, 5.61; N, 5.2%).

Bromination of 1,6-Dimethyl-[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (8b) and 1,3,6-Trimethyl-[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (8d). To a solution of **8b** or **8d** (0.2 mmol) in 1 ml of glacial acetic acid was added dropwise with stirring at r.t. under nitrogen a solution of N-bromosuccinimide (0.035 g, 0.2 mmol) in 4 ml of anhydrous glacial acetic acid. After 2 h. the solution was poured into a mixture of ice-water (9 ml) and sodium hidroxide (3.5 g). The solution was decanted and extracted with ethyl acetate.The organic layer, after drying over sodium sulfate, was concentrated at room temperature. The concentrate was chromatographed on silica gel, using CH_2Cl_2 as eluent. The following compounds were thus prepared.

2-Bromo-1,6-dimethyl-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one **(12):** 37%, mp. 148°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.49 (s, 3H), 3.67 (s, 3H), 6.73 (s, 1H), 7.35 (d, J = 8.6, 1H), 7.43 (dd, J = 8.6, J=1.6, 1H), 8.12 (d, J = 1.6, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.8 (CH_3), 30.3 (CH_3), 102.7 (C), 104.3 (CH), 106.9 (C), 116.9 (CH), 122.9 (C), 126.3 (CH), 133.7 (CH), 134.3 (C), 149.1 (C), 152.0 (C), 172.0 (C); MS: m/z 291 (M^+, 100), 293 (M+2, 98). (Found: C, 53.45; H, 3.46; N, 4.79. $C_{13}H_{10}NO_2Br$ requires C, 53.46; H, 3.45; N, 4.79%).

2,3-Dibromo-1,6-dimethyl-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one **(13):** 35%, mp. 220°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.44 (s, 3H), 3.69 (s, 3H), 7.31 (d, J = 6.8, 1H), 7.41 (d, J = 6.8, 1H), 8.05 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.9 (CH_3), 31.2 (CH_3), 93.0 (C), 104.5 (C), 104.7 (C), 116.9 (CH), 122.4

(C), 125.9 (CH), 133.9 (CH), 134.4 (C), 148.0 (C), 151.5 (C), 170.9 (C); MS: m/z 369 (M^+, 50), 371 (M+2, 100), 373 (M+4, 51). (Found: C, 42.14; H, 2.45; N, 3.78. $C_{13}H_9NO_2Br_2$ requires C, 42.08; H, 2.45; N, 3.78%).

2-Bromo-1,3,6-trimethyl-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one (**15**): 60%, mp. 142°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.38 (s, 3H), 2.44 (s, 3H), 3.60 (s, 3H), 7.28 (d, J = 8.4, 1H), 7.39 (dd, J = 8.4, J=1.1, 1H), 8.07 (d, J=1.1, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 11.3 (CH_3), 20.9 (CH_3) , 30.1 (CH_3), 101.4 (C), 105.5 (C), 114.7 (C), 116.7 (CH), 123.1(C), 126.0 (CH), 133.3 (CH), 134.1 (C), 148.9 (C), 151.8 (C), 172.8 (C); MS: m/z 305 (M^+, 22), 307 (M+2, 22), 91 (100). (Found: C, 54.99; H, 3.95; N, 4.56. $C_{14}H_{12}NO_2Br$ requires C, 54.93; H, 3.95; N, 4.57%).

Nitration of 1,6-Dimethyl-[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (8b) and 1,6-Dimethyl-3-phenyl-[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (8f). The pyrrol **8b** or **8f** (0.5 mmol) was dissolved in 4 ml of acetic anhydride and chilled to -5°C. To this was added under nitrogen a cold mixture of nitric acid (0.062 ml) in 2 ml of acetic anhydride at such a rate as to prevent the temperature from rising above 0°C. When the reaction, which was monitored by tlc, was completed (2h), the mixture was poured into ice-water and extracted with ethyl acetate. The extract was evaporated to dryness at room temperature and the solid taken up in ethyl acetate, washed with sodium bicarbonate solution, and dried (Na_2SO_4). The solution was concentrated and chromatographed on silica gel, using CH_2Cl_2 as eluent. The following compounds were thus prepared.

1,6-Dimethyl-2-nitro-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one (**11**): 50%, mp. 250°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.48 (s, 3H), 4.08 (s, 3H), 7.43 (d, J = 8.5, 1H), 7.52 (d.d, J = 8.5, J=1.5, 1H), 7.65 (s, 1H), 8.08 (d, J = 1.5, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.9 (CH_3), 32.2(CH_3) , 105.8 (C), 107.8 (CH), 117.3 (CH), 122.5 (C), 126.6 (CH), 134.6 (C), 135.1 (CH), 135.6 (C), 150.0 (C), 152.6 (C), 173.3 (C); MS: m/z 258 (M^+, 100). (Found: C, 60.43; H, 3.90; N, 10.87. $C_{13}H_{10}N_2O_4$ requires C, 60.47; H, 3.90; N, 10.85%).

1,6-Dimethyl-2-nitro-3-phenyl-[1]benzopyrano[2,3-b]pyrrol-4(1H)-one (**16**): 58%, mp. 222°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.43 (s, 3H), 4.07 (s, 3H), 7.39-7.53 (m, 7H), 7.99 (d, J = 1.3, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.8 (CH_3), 32.3 (CH_3) , 104.3 (C), 116.9 (CH), 123.0 (C), 125.3 (C), 126.0 (CH), 127.6 (2 CH), 128.7 (CH), 129.6 (C), 130.2 (2 CH), 134.8 (CH), 135.4 (C), 149.3 (C), 152.1 (C), 173.0 (C); MS: m/z 334 (M^+, 100). (Found: C, 68.18; H, 4.22; N, 8.38. $C_{19}H_{14}N_2O_4$ requires C, 68.26; H, 4.22; N, 8.38%).

Acknowledgement: Thanks are due to the Junta de Castilla y León for financial support.

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(*Received in UK* 18 *July* 1997; *revised* 16 *September* 1997; *accepted* 18 *September* 1997)