# SYNTHESIS OF 11H-FURO[3',2':7,8]BENZOPYRANO[3,4-*c*]PYRIDIN-11-ONE AND 6,8-DIMETHYL-10H-PYRANO[2',3':4,5]-BENZOFURO[3,2-*c*]PYRIDIN-10-ONE (PYRIDOANGELICINS)

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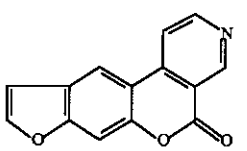
**Abstract** - 11*H*-Furo[3',2' : 7,8]benzopyrano[3,4-*c*]pyridin-11-one (**3**) was synthesized from 1-benzyl-3-ethoxycarbonylpiperidin-4-one and 2,3-dihydro-4-hydroxybenzofuran (**5**) by a von Pechmann reaction and subsequent aromatization of the hexahydro derivative (**6**). 6,8-Dimethyl-10*H*-pyrano[2',3' : 4,5] benzofuro-[3,2-*c*]pyridin-10-one (**4a**) was obtained by dehydrogenation of the tetrahydro derivative (**10b**). This compound was prepared from piperidinone-O-(4,6-dimethylcoumarin-7-yl) oxime (**9b**) using acid catalyzed Fischer indole-like reaction. Are also reported and compared the results of the reactions of piperidinone-O-(coumarin-7-yl) oxime (**9d**) and the corresponding 5-methyl (**9e**) derivative, in which the rearrangement occurs at both the 8 and the 6 positions.

We previously described pyridopsoralens (**1**) and (**2**).[1] These compounds exhibit high affinity toward DNA, and upon UV irradiation of the dark complex give rise to monofunctional adducts.[2] Now as a further extension of this study we report the preparation of their angular isomers, pyridoangelicins (**3**) and (**4a**).



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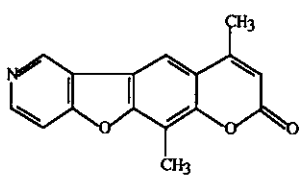

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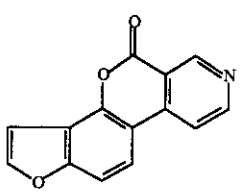

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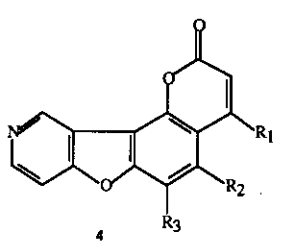


**4**

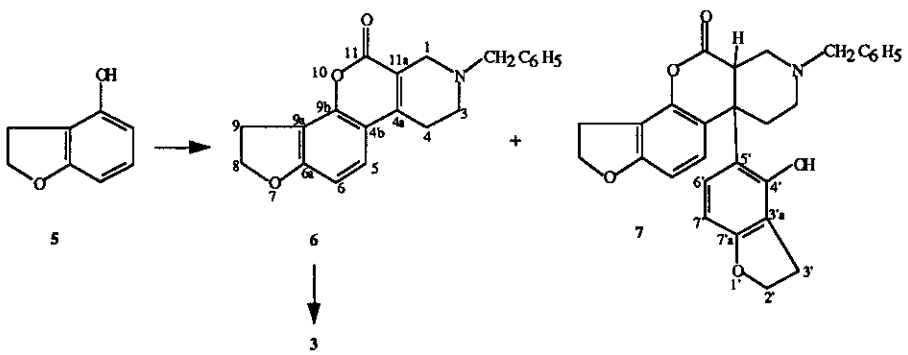
**a** : $R_2 = H$ ; $R_1 = R_3 = CH_3$

**Synthesis of 11*H*-furo[3',2':7,8]benzopyrano[3,4-*c*]pyridin-11-one (3) (Scheme 1) :**

A von Pechmann reaction of 1-benzyl-3-ethoxycarbonylpiperidin-4-one with 2,3-dihydro-4-hydroxybenzofuran (**5**) using hydrogen chloride in acetic acid as condensing agent as previously described for (**1**), gave the expected hexahydropyridoangelicin (**6**) in low yield (17 %) and compound **7** (7 %). The yield of **6** was slightly improved (30 %) when the reaction was performed in a mixture of sulfuric acid and phosphorus oxychloride.

The structure of **7** was determined on the basis of spectroscopic data. Its ir spectrum showed absorptions of hydroxyl and carbonyl groups at 3.400 $cm^{-1}$ and 1745 $cm^{-1}$. The chemical ionisation mass spectra revealed a ($MH^+$) ion peak at m/z 470 which was compatible with an adduct of **5** with **6**. The $^1$H-Nmr spectrum showed signals corresponding to four characteristic methylene triplets at δ 2.99, 3.24, 4.54 and 4.65 ppm and four one-proton aromatic doublets at δ 6.05, 6.13, 6.66 and 6.98 ppm, confirming the occurrence of two disubstituted dihydrobenzofuran units in the molecule. A double doublet signal at δ 4.22 was assigned to the 11a-H proton ; the coupling constants (J = 9.07 and 4.08 Hz) indicated a trans relationship with one of the 1H-protons. These data, together with the presence in the DEPT $^{13}$C-Nmr spectrum of one $sp^3$ methine carbon at δ 43.92 ppm and one $sp^3$ quaternary carbon at 42.25 ppm attributed to 11a-C and 4a-C respectively, suggested that the additional dihydrobenzofuran unit was attached to the 4a-C through a 4a-C, 5'-C carbon carbon bond. All the chemical shifts and coupling constants in the $^1$H and $^{13}$C the 2D COSY fully support this structure. A precedent for formation of such a compound is found in the von Pechmann condensation of resorcinol and methylmethoxyacetate.[3]

Simultaneous N-debenzylation and dehydrogenation of compound (**6**) with palladium on charcoal gave the pyridoangelicin (**3**).




Scheme 1

**Synthesis of 6,8-dimethyl-10H-pyrano[2',3':4,5]benzofuro[3,2-*c*]pyridin-10-one (4a) (Scheme 2) :**

The synthetic route to pyridoangelicin (**4**) is based on a Fischer-indole like reaction of O-8-unsubstituted coumaryl oximes (**9b-e**) followed by aromatization of the resulting tetrahydropyridoangelicin.

Oximes (**9b-c**) owing the presence of a methyl group at the 6-C position would be expected to rearrange exclusively to the tetrahydropyridoangelicins (**10b**) and (**10c**). Whereas oximes (**9d**) and (**9e**) would give both angular and linear tetrahydropyridofurocoumarins (**10d**), (**12d**) and (**10e**), (**12e**) respectively. As already described,[1] O-coumaryl oximes (**9b-e**) were synthesized from piperidin-4-one or 1-methyl piperidin-4-one and the appropriate O-coumaryl hydroxylamines (**8b-e**) which were prepared from the corresponding coumarins. Hydrogen chloride in acetic acid was used as catalyst for rearrangement of oximes (**9b-e**).

Treatment of oximes (**9b**) and (**9c**) afforded the expected tetrahydropyridoangelicins (**10b** ; 29 %) and (**10c** ; 31 %) and compounds (**11b** ; X = O) (6.6 %) and (**11c** ; X = O) (14 %) respectively. The rearrangement of oxime (**9d**) gave a mixture of linear **12d** and angular **10d** isomers (44.5 %) in a 3/7 ratio and compound (**11d** ; X = O) (6.4 %). In contrast, in the case of oxime (**9e**), no linear isomer (**12e**) was detected. The angular isomer (**10e** ; 17 %) was isolated along with compounds (**11e** ; X = O) (7.15 %), (**13e** ; X = O) (22.5 %) and a small amount of **14e** (3.5 %).

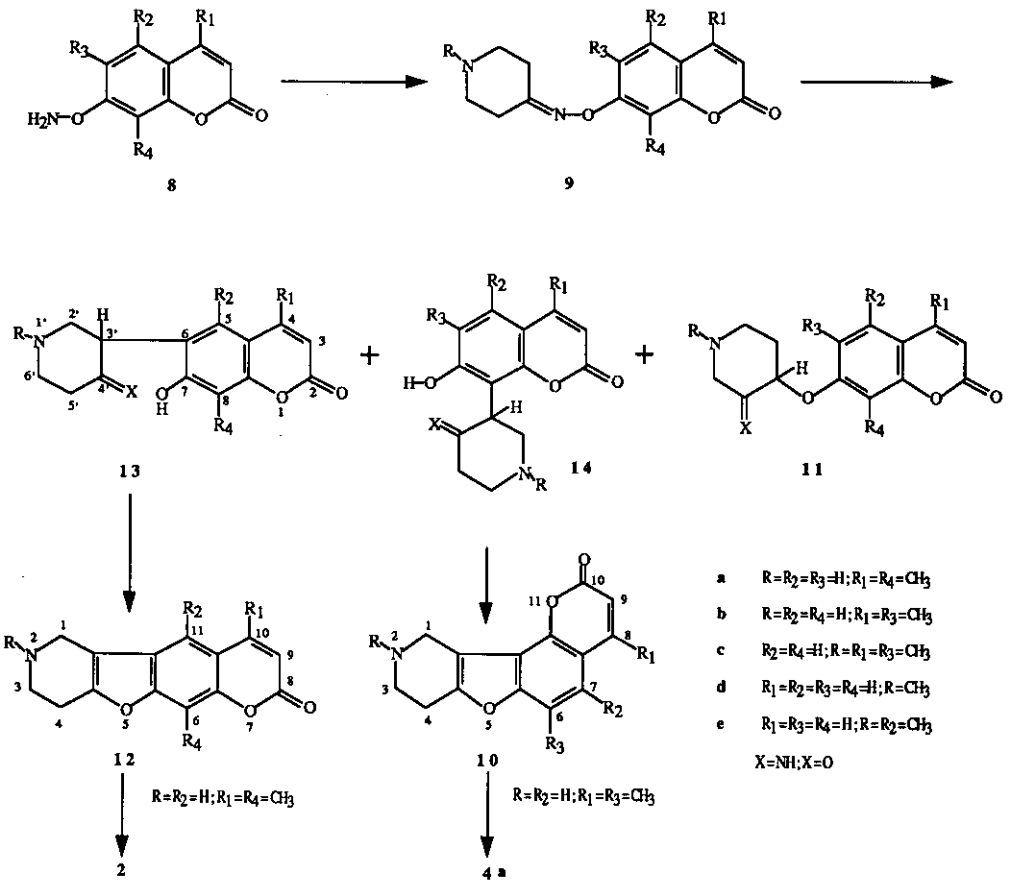
Compounds (**11b-e** ; X = O) are analogous to compound (**11a**) isolated previously as by-product from the rearrangement of **9a**.[1] They probably arose from hydrolysis of the imino-intermediates (**11b-e** ; X = NH) during work-up.[4] Compound (**13e** ; X = O) was also presumably formed by hydrolysis of the imino group of the postulated intermediate (**13e** ; X = NH) in the Fischer indole-like rearrangement of **9e**.

The structural determination of the ketone (**13e** ; X = O) was made on the basis of spectroscopic data as well as chemical transformation. Thus in the aromatic region the $^1$H-Nmr spectra exhibited an absorption at $\delta$ 6.69 which was assigned to the 8-H proton on the basis of a small coupling constant to the 4-H proton. In the aliphatic region we observed three one-proton resonances overshadowed by the methyl absorptions and four distinct one-proton resonances centered at $\delta$ 3.38, 3.15, 2.85 and 1.62 ppm. Homonuclear decoupling experiments showed that the three one-proton resonances at $\delta$ 3.38, 3.15 and 1.62 are part of an ABX system and were assigned to the 3'-H, 2'-H equatorial and 2'-H axial protons respectively. The 3'-H proton should be in an axial configuration on the basis of the coupling constants (J = 6.8 and 10.0 Hz). A long range coupling constant (J = 2.4 Hz) was observed between the 2'-H protons at $\delta$ 3.15 and the proton at 2.85 which was assigned to the 6'-H

equatorial proton. The 1.52 ppm chemical shift difference between axial and equatorial protons 2'-H implies that there is a highly preferred conformation of the piperidino moiety with the substituent in the C-3' equatorial. Comparison of the spectra of (**13e** ; X = O) and (**11e** ; X = O) in the aliphatic region showed a very similar spin-spin system for the 3'-H, 2'-H and 6'-H equatorial protons, suggesting the same stereochemistry for these protons in compounds (**13e** ; X = O) and (**11e** ; X = O) and the same dominant conformation in which the 3'-C substituent is equatorial.

Ring closure of **13e** (X = O) to the corresponding tetrahydropsoralen (**12e**) was effected by treatment with sulfuric acid.

The target compound (**4a**) was obtained by palladium charcoal dehydrogenation of the tetrahydro derivative (**10b**).




Scheme 2

We have not attempted to optimize the yields of the isolated compounds in the reactions described above. However it seems that there is a preference for rearrangement to 6-C for oxime (**9d**) ; (the 6-C/8-C ratio was 7/3). In the case of oxime (**9e**), the presence of a 5-C methyl group does not prevent the rearrangement to 6-C (the 6-C/8-C ratio was approximately 1/1), but in the reaction conditions, sterically hinders the ring closure of the imino intermediate (**13e** ; X = NH) to the tetrahydropyridopsoralen (**12e**).

## EXPERIMENTAL

All melting points were determined with a Reichert hot-stage microscope and are uncorrected. Ir spectra were recorded on a Nicolet X-S spectrophotometer. $^1$H-Nmr spectra were recorded on a Varian XL100 or on a Bruker AC200 spectrometer. Mass spectra were obtained with a Ribermag spectrometer ICMO Université de Paris XI 91405 Orsay. Elemental analyses were performed at the ICSN, CNRS 91190 Gif sur Yvette.

2-Benzyl-1,2,3,4,8,9-hexahydro-11*H*-furo [3',2':7,8][1]benzopyrano[3,4-*c*]pyridin-11-one (**6**) and compound (**7**). Method A. A solution of 4-hydroxy-2,3-dihydrobenzofuran (**5**) (obtained by dehydrogenation of 4-hydroxybenzofuran ; mp 80°C) (1.46 g, 10.73 mmol) and 1-benzyl-3-ethoxycarbonylpiperidin-4-one hydrochloride (3 g, 10.10 mmol) in glacial acetic acid (14 ml) containing 6 % of hydrogene chloride, was kept at room temperature for 6 days. The resulting precipitate was filtered off and the filtrate was evaporated. The residue and the precipitate were taken up in water, basified with 1N sodium hydroxide solution and extracted with dichloromethane. The combined organic extracts were evaporated and the residue was recrystallized from methanol to afford **6** (572 mg, 17 %) ; mp 170°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.83 (m, 4H, 3-$CH_2$, 4-$CH_2$), 3.38 (t, J = 8.8 Hz, 2H, 9-$CH_2$), 3.54 (s, 2H, 1-$CH_2$), 3.78 (s, 2H, $CH_2$Ar), 4.74 (t, J = 8.8 Hz, 2H, 8-$CH_2$), 6.75 (d, J = 8.6 Hz, 1H, 6-H), 7.30-7.40 (m, 6H, Ar, 5-H). $^{13}$C-Nmr ($CDCl_3$, 50 MHz) δ 26.90 (4-C), 26.64 (9-C), 49.09 (3-C), 50.80 (1-C), 62.26 ($CH_2$-Ar), 7.27 (8-C), 106.32 (6-C), 113.35 (4b-C), 113.42 (9a-C), 117.54 (11a-C), 123.82 (5-C), 137.32, 128.9, 128.3, 127.2 ($CH_2$Ar), 146.44 (4a-C), 149.41 (9b-C), 160.31 (11-C), 163.18 (6a-C). Anal. Calcd for $C_{21}H_{19}NO_3$ : C, 75.65 ; H, 5.74 ; N, 4.20. Found : C, 75.27 H, 5.48 ; N, 4.11.

The mother liquor was concentrated and the residue was column chromatographed on a silica gel eluting with dichloromethane-ethanol (97 : 3) to afford **7** (340 mg, 7 %) after recrystallisation from ethanol ; mp 220°C. Ir (Nujol) 3370, 1740, 1633, 1604 $cm^{-1}$. $^1$H-Nmr ($CDCl_3$, 100 MHz). δ 2.25 (m, 2H, 4-$CH_2$), 2.77 (m, 2H, 3-$CH_2$), 2.88 (m, 2H, 1-$CH_2$), 2.99 (m, 2H, 3'-$CH_2$), 3.24 (t, J = 8.9 Hz, 2H, 9-$CH_2$), 3.48 (m, 2H, $C\underline{H_2}Ar$), 4.22 (dd, J = 4.1, 9.9 Hz, 1H, 11a-H), 4.54 (t, J = 9 Hz, 2H, 2'-$CH_2$), 4.65 (t, J = 8.9 Hz, 2H, 8-$CH_2$), 6.05 (d, J = 8.4 Hz, 1H, 7'-H), 6.13 (d, J = 8.4 Hz, 1H, 6'-H), 6.66 (d, J = 8.3 Hz, 1H, 5-H), 6.98 (d, J = 8.3 Hz, 1H, 6-H), 7.28 (m, 5-H, Ar). $^{13}$C-Nmr ($CDCl_3$, 50 MHz) δ 26.42 (4-C), 27.11 (9-C), 29.85 (3-C), 42.25 (4a-C), 43.92 (11a-C), 49.43 (3-C), 50.53 (1-C), 62.18 ($\underline{C}H_2Ar$), 71.53 (2'-C), 72.16 (8-C), 107.74 (7'-C), 113.80 (3'a-C), 114.90 (9a-C), 116.7 (4b-C), 118.60 (5-C), 127.50 (5-C), 127.72 (6'-C), 137.21, 129.6, 128.36, 127.3 ($CH_2\underline{Ar}$), 148.11 (9b-C), 152.44 (4'-C), 158.60 (7'-C), 161.15 (6a-C), 169.7 (11-C). Cims ($NH_3$) m/z : 470 ($MH^+$, 100 %).

11*H*-Furo[3',2':7,8]benzopyrano[3,4-*c*]pyridin-11-one (**3**). A mixture of **6** hydrochloride (800 mg, 2.168 mmol), 10 % palladium on charcoal (800 mg) and diphenyl ether (8 ml) was refluxed for 7 h. After cooling, the reaction mixture was diluted with hexane. The solids were filtered off, washed with hexane and extracted with hot ethanol. The solvent was evaporated and the residue was recrystallized from ethanol to afford **3** (108 mg, 21 %). Recrystallization from acetonitrile gave an analytical sample, mp 240-241°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ : 7.20 (dd, J = 2.3, 1 Hz, 1H, 9-H), 7.50 (dd, J = 8.7, 1 Hz, 1H, 6-H), 7.74 (d, J = 2.3 Hz, 1H, 8-H), 7.92 (d, J = 5.5 Hz, 1H, 4-H), 7.99 (d, J = 8.7 Hz, 1H, 5-H), 8.96 (d, J = 5.5 Hz, 1H, 3-H), 9.59 (s, 1H, 1-H). Anal. Calcd for $C_{14}H_7NO_3$ : C, 70.89 ; H, 2.97 ; N, 5.91. Found : C, 70.61 ; H, 2.86 ; N, 5.82.

Method B. A stirred mixture of dihydrobenzofuran (**5**) (1.46 g, 10.73 mmol) and 1-benzyl-3-ethoxycarbonylpiperidin-4-one hydrochloride (3.18 g, 10.7 mmol), $H_2SO_4$ (6 ml), $POCl_3$ (2 ml, 7.9 mmol) was kept at room temperature overnight. The mixture was poured into ice-water, neutralized by cautions addition of solid sodium hydrogen carbonate. The resulting suspension was extracted with dichloromethane. The dried combined extracts were evaporated and the residue was recrystallized from methanol to afford **6** (1,3 g, 30 %) identical in all respects to the sample obtained in A.

7-Aminooxycoumarins (**8b-e**) were prepared from appropriate coumarins following the same general procedure described for (**8a**).[1]

7-Aminooxy-4,6-dimethylcoumarin (**8b**) ; mp 170°C (methanol). $^1$H-Nmr ($CDCl_3$) δ 2.22 (s, 3H, 6-$CH_3$), 2.39 (d, J = 1.2 Hz, 3H, 4-$CH_3$), 6.00 (s, 2H, $ONH_2$), 6.13 (q, J = 1.2 Hz, 3-H), 7.27 (s, 1H, 5-H), 7.46 (br s, 1H, 8-H). Anal. Calcd for $C_{11}H_{11}NO_3$ ; C, 64.38 ; H, 5.40 ; N, 6.83. Found : C, 64.37 ; H, 5.44 ; N, 6.95.

7-Aminooxy-coumarin (**8d**) ; mp 180°C (methanol). $^1$H-Nmr ($CDCl_3$) δ 6.80 (br s, 2H, $ONH_2$), 6.25 (d, J = 9.5 Hz, 1H, 3-H), 7.0 (dd, J = 8.7, 2.2 Hz, 1H, 6-H), 7.23 (d, J = 2.2 Hz, 1H, 8-H), 7.36 (d, J = 8.7 Hz, 1H, 5-H), 7.63 (d, J = 9.5 Hz, 1H, 4-H). Anal. Calcd for $C_9H_7NO_3$ : C, 61.01 ; H, 3.98 ; N, 7.91. Found : C, 61.01 ; H, 3.99 ; N, 8.15.

7-Aminooxy-5-methylcoumarin (**8e**) ; mp 169-171°C (methanol). $^1$H-Nmr ($CDCl_3$) δ 2.47 (s, 3H, 5-$CH_3$), 5.97 (br s, 2H, $ONH_2$), 6.25 (d, J = 9.6 Hz, 1H, 3-H) ; 6.80 (m, 1H, 6-H), 7.08 (d, J = 2.4 Hz, 1H, 8-H), 7.82 (d, J = 9.6 Hz, 1H, 4-H). Anal. Calcd for : $C_{10}H_9NO_3$ : C, 62.82 ; H, 4.75 ; N, 7.33. Found : C, 62.68 ; H, 4.70 ; N, 7.44.

O-Coumaryloximes (**9b-e**) were prepared from 7-aminooxycoumarins (**8b-e**) following the same general procedure described for **9a**.[1] They were identified by $^1$H nmr spectroscopy and were used in the next step without further purification.

Piperidin-4-one O-7-(4,6-dimethylcoumaryl)oxime (**9b**) ; mp 200°C (ethanol). $^1$H-Nmr ($CDCl_3$) δ 1.75 (br s, 1H, NH), 2.28 (d, J = 0.4 Hz, 3H, 6-$CH_3$), 2.39 (d, J = 1 Hz, 3H, 4-$CH_3$), 2.47 and 2.80 (2m, 2 x 2H, 3'-$CH_2$ and 5'-$CH_2$), 3.06 (m, 4H, 2'-$CH_2$ and 6'-$CH_2$), 6.12 (d, J = 0.6 Hz, 1H, 3-H), 7.30 (s, 1H, 5-H), 7.40 (s, 1H, 8-H).

1-Methylpiperidin-4-one O-7-(4,6-dimethylcoumaryl)oxime (**9c**) ; mp 125-126°C (methanol). $^1$H-Nmr ($CDCl_3$) δ 2.29 (s, 3H, 6-$CH_3$), 2.38 (1, 3H, N-$C\underline{H}_3$), 2.39 (d, J = 1 Hz, 3H, 4-$CH_3$), 2.60 and 2.86 (2 x m, 6H and 2H, 2',3',5' and 6'-$CH_2$), 6.13 (d, J = 1 Hz, 1H, 3-H), 7.31 (s, 1H, 5-H), 7.40 (s, 1H, 8-H).

1-Methylpiperidin-4-one O-(coumarin-7-yl)oxime(**9d**) ; mp 130°C (ethanol). $^1$H-Nmr ($CDCl_3$) δ 2.36 (s, 3H, N-$CH_3$), 2.58 and 2.84 (2m, 6H and 2H, 2',3',5' and 6'-$CH_2$), 6.26 (d, J = 9.5 Hz, 1H, 3-H), 7.07 (dd, J = 2.3, 8.6 Hz, 1H, 6-H), 7.21 (d, J = 2.3 Hz, 1H, 8-H), 7.39 (d, J = 8.6 Hz, 1H, 5-H), 7.64 (d, J = 9.5 Hz, 1H,
4-H).

1-Methylpiperidin-4-one O-7-(5-methylcoumaryl)oxime (**9e**) ; mp 140-141°C (methanol). $^1$H-Nmr ($CDCl_3$) δ 2.36 (s, 3H, N-$CH_3$), 2.49 (s, 3H, 5-$CH_3$), 2.58 and 2.79 (2m, 6H and 2H, 2',3',5' and 6'-$CH_2$), 6.26 (d, J = 9.7 Hz, 1H, 3-H), 6.93 (m, 1H, 6-H), 7.05 (m, 1H, 8-H), 7.89 (dd, J = 9.7, 0.7 Hz, 1H, 4-H).

General procedure for the rearrangement of O-coumaryloximes (**9b-e**). A suspension of the oxime hydrochloride (1 mmol) in glacial acetic acid (13 ml) containing 6 % of hydrogen chloride was stirred at 80°C and dry hydrogen chloride was passed through the mixture. After 7 h the reaction was allowed to cool. Usually a precipitate was obtained except in the case of **9e**. The different products from the reaction were separated as described for each example.

Rearrangement of oxime (**9b**). 6,8-Dimethyl-1,2,3,4-tetrahydro-10*H*-pyrano[2',3' : 4,5]benzofuro[3,2-*c*] pyridin-10-one (**10b**) and compound (**11b**, X = O). From **9b** hydrochloride (1.49 g, 4.62 mmol) there was obtained a precipitate which was filtered off. The solid was taken up in water, basified with 1N sodium hydroxide solution and extracted with dichloromethane. The combined extracts were evaporated to give a residue of crude **10b**, 360 mg (29 %). A sample (100 mg) was recrystallized from ethyl acetate to give pure **10b** (75 mg ; 75 %) ; mp 202-204°C. $^1$H-Nmr ($CDCl_3$) δ 1.68 (s, 1H, NH), 2.46 (d, J = 1 Hz, 3H, 8-$CH_3$), 2.54 (d, J = 0.8 Hz, 3H, 6-$CH_3$), 2.84 and 3.27 (2m, 2 x 2H, 3-$CH_2$, 4-$CH_2$), 4.28 (m, 2H, 1-$CH_2$), 6.21 (d, J = 1 Hz, 1H, 9-H), 7.19 (s, 1H, 7-H). Anal. Calcd for $C_{16}H_{15}NO_3$ : C, 71.36 ; H, 5.61 ; N, 5.20. Found : C, 71.42 ; H, 5.54 ; N, 5.05.

Removal of acetic acid from the mother liquor gave a residue which was taken up in 1N sodium hydroxide solution and extracted with dichloromethane. Evaporation of the solvent left a residue which was recrystallized from ethyl acetate, then from ethanol to give **11b** (X = O) (88 mg, 6.6 %) ; mp 176-178°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.33 (d, J = 0.7 Hz, 3H, 6-$CH_3$), 2.39 (d, J = 0.7 Hz, 3H, 4-$CH_3$), 2.50-2.65 (m, 2H, 5'-H),

4.30-3.40 (m, 3H, 2'-Hax, 2 x 6'-H), 3.62 (ddd, J = 12.7, 5.4, 1.3 Hz, 1H, 2Heq), 4.71 (dd, J = 5.4, 8.3 Hz, 1H, 3'-Hax), 6.13 (d, J = 0.7 Hz, 1H, 3-H), 6.62 (s, 1H, 8-H), 7.35 (d, J = 0.7 Hz, 1H, 5-H). Anal. Calcd for $C_{16}H_{17}NO_4$ : C, 66.88 ; H, 5.96 ; N, 4.88. Found : C, 66.32 ; H, 5.96 ; N, 4.67.

Rearrangement of oxime (**9c**). 2,6,8-Trimethyl-1,2,3,4-tetrahydro-10*H*-pyrano[2',3' : 4,5]benzofuro[3,2-*c*]pyridin-10-one (**10c**) and compound (**11c**, X = O). The reaction of oxime hydrochloride **9c** (1.565 g, 4.64 mmol) was worked up as described above. The base liberated from the precipitate was recrystallized from ethyl acetate to provide **10c** (337 mg, 25.65 %). Recrystallization from ethanol gave an analytical sample ; mp 187-189°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.46 (d, J = 1.1 Hz, 3H, 8-$CH_3$), 2.53 (d, J = 1.2 Hz, 3H, 6-$CH_3$), 2.58 (s, 3H, N-$CH_3$), 2.90 (br s, 4H, 3-$CH_2$, 4-$CH_2$), 3.90 (s, 2H, 1-$CH_2$), 6.21 (d, J = 1.1 Hz, 1H, 9-H), 7.18 (s, 1H, 7-H). Anal. Calcd for $C_{17}H_{17}NO_3$ : C, 72.06 ; H, 6.05 ; N, 4.94. Found : C, 71.99 ; H, 6.04 ; N, 5.26.

The liberated base from the acetic acid mother liquor was recrystallized from ethanol to give **11c** (X = O) (164 mg, 11.75 %). Recrystallization from ethyl acetate gave analytical sample ; mp 206-207°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.30 (s, 3H, 6-$CH_3$), 2.37 (d, J = 1 Hz, 3H, 4-$CH_3$), 2.49 (s, 3H, N-$CH_3$), 2.10-2.90 (m, 4H, 6'-Hax, 2 x 5'-H, 2'-Hax), 3.10 (m, 1H, 6'-Heq), 3.46 (m, 1H, 2'-H), 4.94 (dd, J = 6.0, 10 Hz, 1H, 3'-H), 6.12 (d, J = 1 Hz, 1H, 3-H), 6.56 (s, 1H, 8-H), 7.33 (s, 1H, 5-H). Anal. Calcd for $C_{17}H_{19}NO_4$ ; C, 67.76 ; H, 6.36 ; N, 4.65. Found : C, 67.52 ; H, 6.26 ; N, 4.92.

Chromatography of the combined mother liquors on neutral $Al_2O_3$ column using dichloromethane as eluent gave an additional 71 mg (5.4 %) of **10c** and 30 mg (2.15 %) of **11c** (X = O). Total yields of isolated compound, **10c** (31 %), **11c** (X = O) (14 %).

Rearrangement of oxime (**9d**). 2-Methyl-1,2,3,4-tetrahydro-10*H*-pyrano[2',3' : 4,5]benzofuro[3,2-*c*]pyridin-8-one (**10d**). 2-Methyl-1,2,3,4-tetrahydro-8*H*-pyrano[3',2' : 5,6]benzofuro[3,2-*c*]pyridin-8-one (**12d**) and compound (**11d**) (X = O). The reactions of oxime hydrochloride **9d** (3.5 g, 11.36 mmol) was worked-up as usual. $^1$H-Nmr spectral analysis of the liberated base from the precipitate (1.2 g, 44.5 %) indicated a 3 : 7 mixture of compounds (**10d**) and (**12d**). This mixture was recrystallized four times from ethyl acetate to afford pure **12d** (372 mg, 12.84 %) ; mp 142-143°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.57 (s, 3H, N-$CH_3$), 2.90 (br s, 4H, 3-$CH_2$, 4-$CH_2$), 3.60 (s, 2H, 1-$CH_2$), 6.35 (d, J = 9.5 Hz, 1H, 9-H), 7.40 (br s, 2H, 6-H, 11-H), 7.77 (d, J =

9.5 Hz, 1H, 10-H). Anal. Calcd for $C_{15}H_{13}NO_3$ : C, 70.58 ; H, 5.13 ; N, 5.49. Found : C, 70.56 ; H, 5.14 ; N, 5.27.

The combined mother liquors from the recrystallization of **12d** were column chromatographed on silica gel using dichloromethane-ethanol (9/1) as eluent. The first fractions were recrystallized from ethyl acetate to give pure **10d** (114 mg, 3.93 %) ; mp 180°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.59 (s, 3H, N-$CH_3$), 2.90 (br s, 4H, 3-$CH_2$, 4-$CH_2$), 3.90 (br s, 2H, 1-$CH_2$), 6.35 (d, J = 9.5 Hz, 1H, 9-H), 7.80 (m, 2H, 6-H, 7-H), 7.77 (d, J = 9.5 Hz, 1H, 8H). Anal. Calcd for $C_{15}H_{13}NO_3$ : C, 70.58 ; H, 5.13 ; N, 5.49. Found : C, 70.37 ; H, 5.05 ; N, 5.50.

The liberated base from acetic acid mother liquor was recrystallized from ethanol to give **11d** (X = O) (197 mg, 6.4 %) ; mp 178°C. $^1$H-Nmr ($CDCl_3$, 100 MHz), δ 2.48 (s, 3H, N-$CH_3$), 2.94-2.34 (m, 4H, 2 x 5'-H, 2'-H, 6'-H), 3.08 (ddd, J = 9.5, 4.5, 2.4 Hz, 1H, 6'-H), 3.34 (ddd, J = 11.25, 6.1, 2.4 Hz, 1H, 2'-H), 4.90 (dd, J = 10, 6.1 Hz, 1H, 3'-H), 6.25 (d, J = 9.5 Hz, 1H, 3-H), 6.76 (m, 1H, 8-H), 6.82 (dd, J = 8.3, 2.5 Hz, 1H, 6-H), 7.36 (d, J = 8.3 Hz, 1H, 5-H), 7.62 (d, J = 9.5 Hz, 1H, 4-H). Anal. Calcd for $C_{15}H_{15}NO_4$ : C, 65.92 ; H, 5.53 ; N, 5.13. Found : C, 65.90 ; H, 5.35 ; N, 5.09.

Rearrangement of oxime (**9e**). 2-6-Dimethyl-1,2,3,4-tetrahydro-10*H*-pyrano[2',3' : 4,5]benzofuro[3,2-*c*]-pyridin-8-one (**10e**). Compound (**11e**) (X = O), compound (**13e**) (X = O) and compound (**14e**) (X = O). The mixture resulting from the reaction of **9e** hydrochloride (11 g, 3.416 mmol) was concentrated and the residue was recrystallized from ethanol to give **10e** hydrochloride (200 mg). The liberated base was recrystallized from ethanol to yield **10e** (106 mg, 11.53 %) ; mp 197-198°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.58 (s, 6H, N-$CH_3$, 7-$CH_3$), 2.87 (br s, 4H, 3-$CH_2$, 4-$CH_2$), 3.87 (br s, 2H, 1-$CH_2$), 6.35 (d, J = 9 Hz, 1H, 9-H), 7.17 (d, J = 0.8 Hz, 1H, 6-H), 7.97 (d, J = 9 Hz, 1H, 8-H). Anal. Calcd for $C_{16}H_{15}NO_3$ : C, 71.36 ; H, 5.61 ; N, 5.20. Found : C, 71.05 ; H, 5.43 ; N, 5.18.

The mother liquor from the first recrystallization was evaporated, the liberated base was recrystallized twice from ethyl acetate to afford **13e** (X = O) (137 mg, 13.97 %) ; mp 195-196°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 1.62 (dd, J = 11.25, 10 Hz, 1H, 2'-Hax), 2.29 (s, 3H, N-$CH_3$), 2.42 (s, 3H, 5-$CH_3$), 2.10-2.40 (m, 3H, 6'-Hax, 2 x 5'-H), 2.85 (ddd, J = 9, 5, 2.4 Hz, 1H, 6'-Heq), 3.15 (ddd, J = 11.25, 6.8, 2.4 Hz, 1H, 6'-Heq), 3.38 (dd, J = 10, 6.8 Hz, 1H, 3'-Hax), 6.2 (d, J = 9.7 Hz, 1H, 3-H), 6.69 (s, 1H, 8-H), 7.78 (d, J = 9.7 Hz, 1H, 4-H). Anal. Calcd for $C_{16}H_{17}NO_4$. 1/2$H_2O$ : C, 62.94 ; H, 6.27 ; N, 4.59. Found : C, 62.75 ; H, 6.13 ; N, 4.02.

The mother liquors from the recrystallization of **13e** (X = O) were evaporated. Repeated recrystallization from ethanol furnished **11e** (X = O) (20 mg, 2 %) ; mp 184-185°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.47 (s, 3H, N-$CH_3$), 2.49 (d, J = 0.5 Hz, 3H, 5-$CH_3$), 2.50-3.00 (m, 4H, 2 x 5'-H, 1 x 6'-H, 1 x 2'-H), 3.13 (ddd, J = 9.5, 4.95, 2.4 Hz, 1H, 6'-Heq), 3.37 (ddd, J = 11.25, 6.1, 2.4 Hz, 1H, 2'-H), 4.93 (dd, J = 10, 6.1 Hz, 1H, 3'-Hax), 6.28 (d, J = 9 Hz, 1H, 3-H), 6.58 (d, J = 2.5 Hz, 1H, 6-H), 6.71 (dd, J = 2.5, 0.5 Hz, 1H, 8-H), 7.82 (d, J = 9.5 Hz, 1H, 4-H). Anal. Calcd for $C_{16}H_{17}NO_4$ : C, 66.88 ; H, 5.96 ; N, 4.88. Found : C, 66.40 ; H, 5.96 ; N, 4.93.

All the combined mother liquors were column chromatographed over neutral $Al_2O_3$ using dichloromethane as eluent. The initial fractions (100 mg) were a 1/1 mixture of **11e** (X = O) and **10e**. Separation of them was not attempted. The latter fractions were rechromatographed on silica gel using dichloromethane-ethanol (9/1) as eluent, to yield additional **13e** (X = O) (84 mg, 8.56 %) and **14e** (35 mg, 3.5 %) ; mp 224°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.42 (d, J = 0.7 Hz, 3H, 5-$CH_3$), 2.57 (s, 3H, N-$CH_3$), 2.45-3.40 (br s, or m, 6H, 2'-$CH_2$, 5'-$CH_2$, 6'-$CH_2$), 4.64 (br m, 1H, 3'-H), 6.18 (d, J = 10 Hz, 1H, 3-H), 6.68 (br s, 1H, 6-H), 7.79 (d, J = 10 Hz, 1H, 4-H).

Overall yield **10e** (17 %), **11e** (7,15 %), **13e** (22.5 %), **14e** (3.5 %).

6,8-Dimethyl-10*H*-pyrano[2',3' : 4,5]benzofuro[3,2-*c*]pyridin-10-one (**4a**). A mixture of compound **10b** hydrochloride (260 mg, 0.855 mmol), 10 % palladium on charcoal (250 mg) and decalin (12 ml) was refluxed for 1 h. After cooling the reaction mixture was diluted with hexane. The solids were filtered off, washed with hexane, and extracted with hot ethanol, and the extract was filtered whilst hot. The solvent was evaporated and the residue was recrystallized from ethanol to afford **4a** (85 mg, 37.8 %) ; mp 238-239°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.53 (d, J = 1.3 Hz, 3H, 8-$CH_3$), 2.66 (s, 3H, 6-$CH_3$), 6.34 (d, J = 1.3 Hz, 1H, 9-H), 7.54 (s, 1H, 7-H), 7.57 (d, J = 5.6 Hz, 1H, 4-H), 8.75 (d, J = 5.6 Hz, 1H, 3-H), 9.64 (s, 1H, 1-H). Anal. Calcd for $C_{16}H_{11}NO_3$ 1/2 $H_2O$ : C, 70.03 ; H, 4.41 ; N, 5.11. Found : C, 70.03 ; H, 4.45 ; N, 5.26.

11-Methyl-1,2,3,4-tetrahydro-8*H*-pyrano[3',2' : 5,6]benzofuro[3,2-*c*]pyridin-8-one (**12e**). A solution of **13e** (35 mg, 0.12 mmol) in conc. sulfuric acid (0.5 ml) was kept at room temperature for 24 h. The mixture was treated with ice-water, neutralized with solid sodium hydrogen carbonate and extracted with dichloromethane. The combined extracts were evaporated and the residue was recrystallized from ethyl acetate to yield **12e** (20 mg,

62 %) ; mp 214-215°C. $^1$H-Nmr ($CDCl_3$, 100 MHz) δ 2.59 (s, 3H, N-$CH_3$), 2.65 (s, 3H, 11-$CH_3$), 2.88 (s, 4H, 3-$CH_2$, 4-$CH_2$), 3.81 (s, 2H, 1-$CH_2$), 6.35 (d, J = 10 Hz, 1H, 9-H), 7.24 (s, 1H, 6-H), 8.0 (d, J = 10 Hz, 1H, 8-H). Anal. Calcd for $C_{16}H_{15}NO_3 \cdot 1/2H_2O$ : C, 69.05 ; H, 5.79 ; N, 5.03. Found : C, 68.83 ; H, 5.41 ; N, 5.13.

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