SYNTHESIS OF NEW FUSED BENZOPYRANO-BENZODIAZEPINONES

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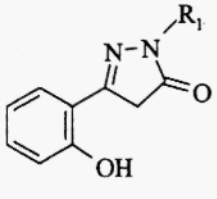
Abstract : The synthesis of a new series of compounds, the [1]benzopyrano[4,3-*c*]1,5-benzodiazepin-2(3*H*)-ones **7a-d** by condensation of 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-ones **4a**-d with *N,N*-dimethylformamide dimethylacetal (DMFDMA) **5** in good yields is reported.

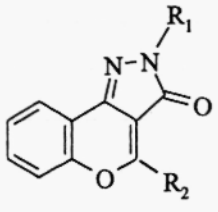
Introduction

A number of studies have been carried out on the reaction of 4-hydroxycoumarin with nitrogen nucleophiles such as amines (1), diamines (2,3) and hydrazines (4,5). Thus, it was reported that the reaction between 4-hydroxycoumarin **1** and methylhydrazine or arylhydrazines gives the 3-(2-hydroxyphenyl)-1-methyl-2-pyrazolin-5-one **2a** and the 1-aryl-3-(2-hydroxyphenyl)-2-pyrazolin-5-ones **2b** respectively. Compounds **2a,b** treated with triethyl orthoacetate and diethoxymethyl acetate were then converted to the corresponding [1]benzopyrano[4,3-*c*]pyrazolin-5(2*H*)-ones **3a-c** (4,5). We also noticed that the reaction between chromone-3-carboxylic acid and phenylhydrazine has been shown to be an efficient way to 2-phenyl-[1]benzopyrano[4,3-*c*]pyrazol-3(2*H*)-one **3d** (6). Another but, lengthier, route to **3c** and **3d** was published by Colotta *et al* (7) and involved reaction of 3-ethyl-(1-benzyloxyphenyl)-3-oxopropanoate and arylhydrazines.

On another hand, the reaction of 4-hydroxycoumarin with 1,2-phenylenediamines has been found to give rise to 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-ones 4 after the opening of the coumarin ring (2) (figure 1).



2a R_1=Me
2b R_1=Ar



3a R_1=Me R_2=H
3b R_1=Me R_2=Me
3c R_1=Ar R_2=H
3d R_1=Ar R_2=Me

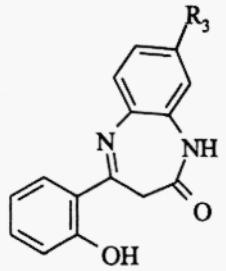


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Figure 1 : structures of compounds **2**, **3** and **4**

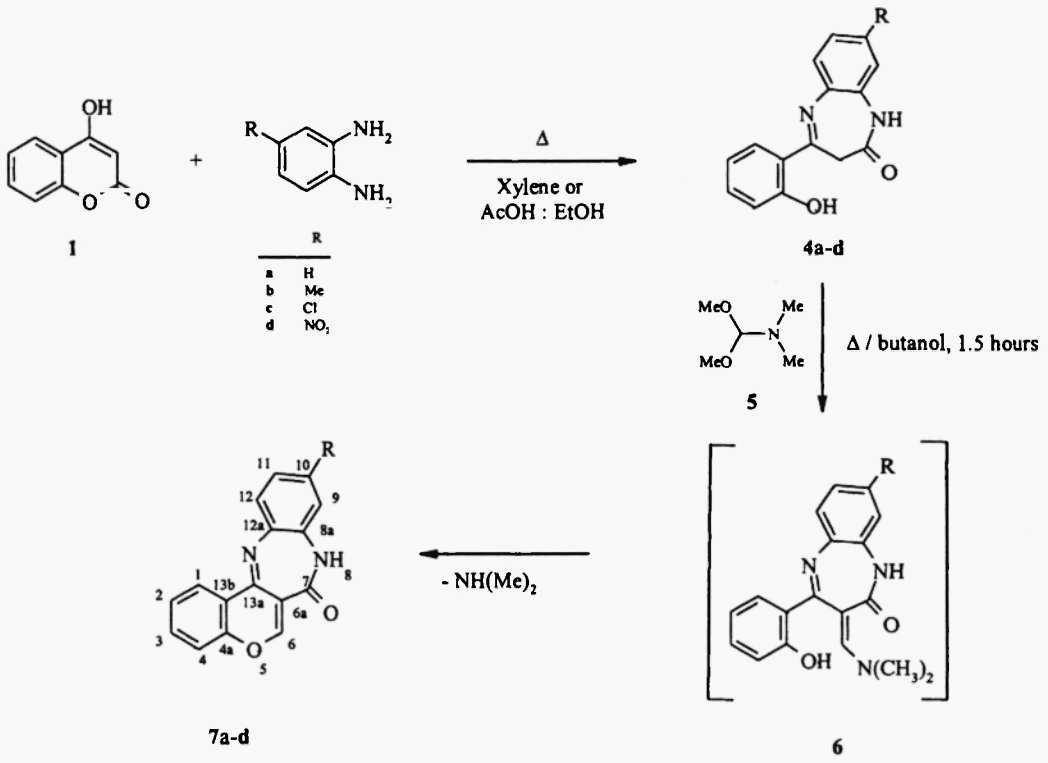
Results and Discussion

In the search of routes to new polycyclic heterocycles of biological interest from 4-hydroxycoumarin (8-10), we report here a simple preparation of 13-substituted [1]benzopyrano[4,3-*c*]1,5-benzodiazepin-2(3*H*)-ones **7a-d** from the reaction of *N,N*-dimethylformamide dimethylacetal (DMFDMA) **5** and 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-ones **4a-d**. Thus we have found that refluxing a solution of the benzodiazepinone 4 and 3 equivalents of DMFDMA in butanol for 1.5 hours, led to a series of the hitherto unreported compounds **7a-d**. A control by thin layer chromatography, (eluent: chloroform-ethyl acetate, 8:2) showed in all cases that the reaction gave rise to a single product that precipitate in the reactional mixture while hot. It is believed that under reaction conditions, the 3-dimethylaminomethylen-2-(2-hydroxyphenyl)-1,5-benzodiazepin-7-one **6** (non isolable) undergoes further cyclisation *via* loss of dimethylamine to yield final isolable product (scheme 1).

Trials for the preparation of compounds **7** using other routes failed, thus refluxing an equimolar ratio of 1,5-benzodiazepin-2-one 4 and aniline in the presence of excess ethyl orthoformate does not give any product (7). On another hand, we have projected to reach heterocycles **7** from the reaction of *o*-phenylenediamines with chromones bearing a functional group in 3-position. Nevertheless, we found that the direct reaction between the diamine and chromone-3-carboxylic acid and related esters has been recently investigated (11) and gave a variety of products other than the aforementioned compounds **7**.

All the products were obtained as solids, and their structures were elucidated by ir measurements, mass spectrometry, and nmr experiments: mono-dimensional: ^{1}H, ^{13}C; two-dimensional homonuclear ^{1}H-^{1}H (COSY) and two-dimensional heteronuclear ^{1}H-^{13}C (HMQC, HMBC).

Inspection of compound 7a ^{1}H nmr spectrum at (400 MHz, DMSO-*d*) showed the presence of a singlet at δ=10.15 ppm corresponding to the lactamic proton H_8. The spectrum, also, displayed a multiplet around 8.30 ppm due to overlapped signals relatives to protons H_6 and H_1. The chemical shifts δ=8.29 ppm and δ=8.30 ppm were, then, attributed to H_6 and H_1 respectively, on the basis of the direct correlation cross peaks (H_6-C_6, δC_6=157.2 ppm) and (H_1-C_1, δC_1=125.8 ppm) deduced from the HMQC spectrum. The set of peaks between δ=7.01 ppm and δ=7.60 ppm was attributed to the aromatic protons of both the benzopyrane and the benzodiazepinone moieties. Inspection of the HMBC spectrum showed that protons H_6 and H_8 both correlate with the quaternary carbon C_{6a} at δ=114.0 ppm and the one of the carbonyl at δ=163.8, consequently, this indicates a C_6-C_{6a}-C_7-N linkage. We also underscored correlation cross peaks of H_6 and H_1 with a same quaternary carbon C_{13b} at δ=145.2 ppm suggesting a C_1-C_{13b}-C_{13a}- C_{6a}-C_6 connection. Thus, the use of 2D nmr experiments permits unambiguous and complete ^{1}H and ^{13}C nmr assignments for compounds **7a-d** and an establishing of a whole set of linkages that confirms the molecular skeleton.



Scheme 1 : synthesis of compounds **7a-d**

Conclusion

On the basis of the above-described results, we developed a route to new fused Benzopyrano-Benzodiazepinones from 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-ones and *N,N*-dimethylformamide dimethylacetal. Unambiguous elucidation of the molecular skeleton was performed using 2D nmr spectroscopic methods. The synthesis has the advantage of simplicity, it is also selective as only a single product is formed in good yield. Moreover, tetracyclic heterocycles **7** contain both benzopyrane and 1,5-benzodiazepin-2-one frameworks and may exhibit biological activity.

Experimental

Melting points were taken on a Buchi-510 capillary melting point apparatus. Infrared spectra (potassium bromide) were run on a Perkin-elmer IR-197 infrared spectrometer. The mass spectra were measured using an AEI MS-50 mass spectrometer operating in electron impact mode at 70 eV. ^{1}H and ^{13}C nmr spectra were recorded on a Brüker spectrometer AC-300 using TFA-*d* (all the samples have been found to be very soluble in this solvent) whereas 2D experiments were performed on an AM-400 Bruker spectrometer in DMSO-*d* thus to observe peaks relative to exchangeable protons.

The starting materials **4a-d** were prepared according to the literature (2) by refluxing, for 3 hours, a solution of 4-hydroxycoumarin **1** and a series of selected various commercially available substituted 1,2-phenylenediamines in xylene or acetic acid-ethanol (*v:v*). The precipitate, that formed while hot or on cooling at room temperature, was washed with ether before recristallization in the appropriate solvent.

General Procedure for the preparation of compounds 7a-c..

A stirred solution of 4-(2'-hydroxyphenyl-1,5-benzodiazepin-2-ones) **4** (1 mmol) and *N,N*-dimethylformamide dimethylacetal **5** (0.42 ml, 3 mmol), in butanol (15 ml) was refluxed for 1.5 hours. The precipitate generally formed while hot, was filtered, washed with ether then recristallized in the suitable solvent.

Benzopyrano-Benzodiazepinone 7a (R=H).
Compound **7a** was crystallized from toluene as yellow crystals (yield = 75 %), m.p. 272 °C, MS (IE), m/z 262.9 [M^+], IR (cm^{-1}) $\nu_{C=N}$=1620, $\nu_{C=O}$=1678, ν_{N-H}=3207, ^{1}H nmr (TFA-*d*), δ(ppm) : 8.68 (d, 1H, H_1, *J*= 8.0 Hz), 8.05 (m, 1H, H_2), 8.30 (m, 1H, H_3), 8.05 (m, 1H, H_4), 9.50 (s,1H, H_6), 7.34 (d, 1H, H_9, *J*= 7.4 Hz), 7.62 (m, 1H, H_{10}), 7.46 (m, 1H, H_{11}), 7.66 (m, 1H, H_{12}), ^{13}C nmr , δ(ppm) : C_1=125.3, C_2=132.4, C_3=141.5, C_4=122.3, C_{4a}=157.3, C_6=169.5, C_{6a}=111.2, C_7=165.9, C_{8a}=128.9, C_9=124.5, C_{10}=134.1, C_{11}=129.4, C_{12}=127.0, C_{12a}=128.1, C_{13a}=156.9, C_{13b}=116.8.

Benzopyrano-Benzodiazepinone 7b (R=Me).
Compound **7b** was crystallized from DMF as yellow crystals (yield = 78%), m.p. 349 °C, MS (IE), m/z 276.1 [M^+], IR (cm^{-1}) $\nu_{C=N}$=1620, $\nu_{C=O}$=1677, ν_{N-H}=3204, ^{1}H nmr (TFA-*d*), δ (ppm): 8.57 (d, 1H, H_1, *J*= 8.1 Hz), 7.95 (m, 1H, H_2), 8.22 (dd, 1H, H_3, *J*= 7.6, 7.7 Hz), 7.95 (m, 1H, H_4), 9.38 (s,1H, H_6), 2.43 (s, 3H, Me), 7.35 (brs, 1H, H_9), 7.35 (brs, 1H, H_{11}), 7.12 (d, 1H, H_{12}, *J*= 8.4 Hz), ^{13}C nmr , δ(ppm) : C_1=125.1, C_2=132.4, C_3=141.3, C_4=122.2, C_{4a}=157.1, C_6=169.4, C_{6a}=111.0, C_7=165.6, C_{8a}=127.7, C_9=126.9, C_{10}=141.1, C-Me=20.9, C_{11}=134.8, C_{12}=124.4, C_{12a}=126.2, C_{13a}=156.7, C_{13b}=116.7.

Benzopyrano-Benzodiazepinone 7c (R=Cl).
Compound **7c** was crystallized from DMF as yellow crystals (yield =87%), m.p. 329 °C, MS (IE), m/z 296.1 [M^+], IR (cm^{-1}) $\nu_{C=N}$=1620, $\nu_{C=O}$=1681, ν_{N-H}=3201, ^{1}H nmr (TFA-*d*), δ(ppm) : 8.65 (d, 1H, H_1, *J*= 8.7 Hz), 8.03 (dd, 1H, H_2, *J*= 8.7, 7.1 Hz), 8.30 (d, 1H, H_3, *J*=8.0, 7.1 Hz), 8.04 (d, 1H, H_4, *J*= 8.0 Hz), 9.50 (s,1H, H_6), 7.66 (brs, 1H, H_9), 7.52 (brd, 1H, H_{11}, *J*= 8.5 Hz), 7.25 (d, 1H, H_{12}, *J*= 8.5 Hz), ^{13}C nmr , δ(ppm) : C_1=125.5, C_2=132.6, C_3=141.8, C_4=122.4, C_{4a}=157.4, C_6=170.1, C_{6a}=111.3, C_7=165.7, C_{8a}=129.1, C_9=126.7, C_{10}=135.6, C_{11}=133.8, C_{12}=125.7, C_{12a}=127.6, C_{13a}=157.9, C_{13b}=116.7.

Benzopyrano-Benzodiazepinone 7d (R=NO_2).
Compound **7d** was cristallized from dioxane as yellow crystals (yield = 45 %), m.p. 252 °C, MS (IE), m/z 307.1 [M^+], IR (cm^{-1}) $\nu_{C=N}$=1620, $\nu_{C=O}$=1679, ν_{N-H}=3203, ^{1}H nmr (TFA-*d*), δ(ppm) : 9.04 (d, 1H, H_1, *J*= 8.1 Hz), 8.37 (m, 1H, H_2), 8.62 (t, 1H, H_3, *J*=7.8 Hz), 8.38 (m, 1H, H_4), 9.90 (s,1H, H_6), 8.53 (brs, 1H, H_9), 8.53 (brs, 1H, H_{11}), 8.21 (d, 1H, H_{12}, *J*= 9.1 Hz), ^{13}C nmr , δ(ppm) : C_1=125.8, C_2=133.1, C_3=142.5, C_4=122.6, C_{4a}=157.9, C_6=170.5, C_{6a}=111.7, C_7=165.5, C_{8a}=130.5, C_9=120.0, C_{10}=150.6, C_{11}=123.6, C_{12}=128.6, C_{12a}=133.7, C_{13a}=158.8, C_{13b}=116.9.

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