MODIFIED COUMARINS. 26. SYNTHESIS OF ANGULAR DIHYDROOXAZINOCOUMARINS FROM 3-HYDROXY[*b,d*]PYRAN-6-ONE

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N-*Substituted angular pyranodihydrobenzoxazines were prepared by condensation of 3-hydroxydibenzo[*b,d*]pyran-6-one with various primary amines and two equivalents of formaldehyde in the presence of 4-N,N-dimethylaminopyridine as base.*

Key words: coumarins, dibenzo[*b,d*]pyran-6-ones, Mannich reaction, pyranodihydrobenzoxazines.

Dibenzo[*b,d*]pyran-6-ones form a unique group of coumarins that are isolated from plant and animal sources and are products of fungal and microorganism metabolism. Until now, about 30 compounds have been isolated from natural sources. These are based on the benzo[*c*]chromen-6-one system. 3-Hydroxydibenzo[*b,d*]pyran-6-one (**1**), also known as urolitin B, was isolated from latex of *Euphorbia royleana* [1], fruit of *Trapa natans* [2, 3], and metabolic products of *Trogopterus xanthipes* [4].

The goal of this work was to modify the stucture of dibenzo[*b,d*]pyran-6-one by annellating a 1,3-dihydrooxazine ring to it to form angular pyranobenzoxazines.

3-Hydroxydibenzo[*b,d*]pyran-6-one (**1**) that was required for further transformations was prepared by the Hurtley method, condensation of 2-bromobenzoic acid and resorcinol in NaOH solution using copper sulfate solution (10%) as catalyst [5].

It is known that several reaction products may be formed during the Mannich reaction depending on the substrate structures and equivalents of formaldehdye [6]. In particular, prolonged heating of equivalent amounts of primary amine, formaldehyde, and derivatives of 7-hydroxycoumarin forms 7-hydroxy-8-aminomethylcoumarins. Using equivalent amounts of primary amine and 7-hydroxycoumarin and two equivalents of formaldehyde or paraformaldehyde in the presence of catalytic amounts of KOH forms pyranodihydrobenzoxazines [7-12]. This condensation was also carried out in acetic acid [13]. Pyranodihydrobenzoxazines are also formed by the action of formalin on Mannich bases prepared from primary amines [7].

We proposed another approach to building the dihydrobenzoxazine ring. Obviously, the synthesis of pyranodihydrobenzoxazines is a two-step process. An *N,N*-di(hydroxymethyl)amine is formed in the first step by the reaction of a primary amine and two equivalents of formaldehyde. Then this reacts with a phenol in the presence of base in the second step to give simultaneously C- and O-alkylation. Therefore, we annellated a 1,3-oxazine ring to the coumarin system via the reaction of 7-hydroxycoumarin and previously prepared substituted *N,N*-di(hydroxymethyl)amine in the presence of an organic base.

Using **1** as the phenol in this synthesis produced substituted angular pyranodihydrobenzoxazines, 3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-ones **2-15**, i.e., the 1,3-oxazine ring was added exclusively to the 7,8-positions of the coumarin system. The structures of the products were confirmed by PMR spectroscopy. The spectra were simplified in the region of aromatic protons because H-2 was not coupled to the dibenzo[*b,d*]pyran-6-one system. The H-11 and H-12 protons of angular pyranodihydrobenzoxazines **2-15** resonated as doublets with SSCC 8.7-9.0 Hz at 7.80 and 6.80 ppm, respectively.

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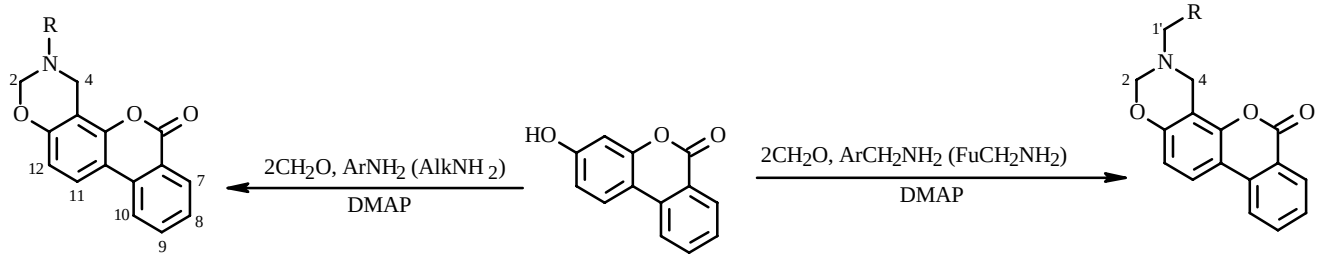
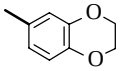
The highest yields were obtained using catalytic amounts of 4-*N*,*N*-dimethylaminopyridine (DMAP) or 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) as the base. Performing the reaction in the presence of triethylamine, pyridine, or inorganic bases (potash, NaOH, KOH) typically gave lower yields and side products.



2a - 9a, 13a - 15a **1** **10a - 12a**

R = **2a:** 4-F-C_6H_4- **7a:** 4-$CH_3O_2CC_6H_4$- **11a:** 3,4,5-$(OCH_3)_3$-C_6H_2-
3a: 4-Cl-C_6H_4- **8a:** 3-CF_3-C_6H_4- **12a:** 2-Fu-
4a: 4-C_4H_7O-C_6H_4- **9a:**  **13a:** *i*-C_3H_7-
5a: 4-CF_3-C_6H_4- **14a:** c-C_3H_5-
6a: 4-(CH_3-CONH)-C_6H_4- **10a:** 4-F-C_6H_4- **15a:** H_3CO-CH_2-CH_2-

Substituted anilines [4-fluoroaniline (**2**), 4-chloroaniline (**3**), 4-butoxyaniline (**4**), 4-(trifluoromethyl)-aniline (**5**), *N*-(4-aminophenyl)acetamide (**6**), methyl-4-aminobenzoate (**7**), 3-(trifluoromethyl)aniline (**8**), and 2,3-dihydro-1,4-benzodioxin-6-amine (**9**)], benzylamines [4-fluorobenzylamine (**10**) and 3,4,5-trimethoxybenzylamine (**11**)], 2-furylmethylamine (**12**), and aliphatic amines [isopropylamine (**13**), cyclopropylamine (**14**), and 2-methoxyethylamine (**15**)] were used as the amines in this condensation.

The 1,3-dihydroxazine ring was smoothly annellated to dibenzo[*b*,*d*]pyran-6-one using benzylamines, 2-furylmethylamine, and aliphatic amines regardless of the structure or the presence of substituents. If anilines were used as the amines, the experimental results showed that addition of the 1,3-dihydroxazine ring to the coumarin system depended strongly on the structures of the starting anilines. Pyranodihydrobenzoxazines did not form using anilines containing strong electron-accepting groups or bulky substituents in the position ortho to the amine. For example, we could not synthesize pyranodihydrobenzoxazines using methyl- and ethyl-2-aminobenzoates, 2-(trifluoromethyl)aniline, dimethyl-2-aminoterephthalate, and methyl-2-amino-4,5-dimethoxybenzoate as the amines. The presence of strong electron-accepting groups in the positions meta or para to the amine had little effect on the reaction. Pyranodihydrobenzoxazines were formed in satisfactory yields.

PMR spectra of **2a-15a** exhibited two 2H singlets for methylenes that were characteristic of an annellated 1,3-dihydroxazine ring. For *N*-aryl derivatives **2a-9a**, the CH_2-2 and CH_2-4 methylenes resonated at 5.35-5.48 and 4.73-4.93 ppm, respectively. However, PMR spectra of *N*-benzyl, *N*-furylmethyl, and *N*-alkylamine derivatives **10a-15a** showed singlets for CH_2-2 and CH_2-4 at stronger field of 4.91-5.03 and 4.21-4.32 ppm, respectively.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck 60 F254 plates with elution by $CHCl_3$:CH_3OH (9:1 and 19:1). Melting points were determined on a Kofler block. PMR spectra were recorded on Varian VXR-300 and Varian Mercury 400 spectrometers at 300 and 400 MHz, respectively, relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

The synthesis of 3-hydroxydibenzo[*b*,*d*]pyran-6-one (**1**) has been described [14,15].

3,4-Dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-ones 2a-15a. A solution of the appropriate primary amine (4.4 mmol) in dioxane (10 mL) was treated with formalin solution (35%, 0.9 mL, 10 mmol). The resulting mixture was held at room temperature and stirred vigorously for 1 h, treated with hydroxycoumarin **1** (0.85 g, 4 mmol) and a catalytic amount of DMAP (20 mg), and heated at 100°C for 2-10 h (course of reaction monitored by TLC). After the reaction was complete, solvent was removed in vacuo in a rotary evaporator. The oily residue was crystallized from propan-2-ol.

3-(4-Fluorophenyl)-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (2a). Yield 59%, $C_{21}H_{16}FNO_3$, mp 186-187°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.81 (2H, s, CH_2-4), 5.38 (2H, s, CH_2-2), 6.83 (1H, d, J = 9.0, H-12), 6.96 (2H, t, J = 8.4, H-2′, H-6′), 7.13 (2H, m, H-3′, H-5′), 7.50 (1H, t, J = 8.1, H-9), 7.78 (1H, t, J = 8.1, H-8), 7.83 (1H, d, J = 9.0, H-11), 7.98 (1H, d, J = 9.0, H-10), 8.38 (1H, d, J = 8.1, H-7).

3-(4-Chlorophenyl)-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (3a). Yield 77%, $C_{21}H_{16}ClNO_3$, mp 198-199°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.82 (2H, s, CH_2-4), 5.39 (2H, s, CH_2-2), 6.82 (1H, d, J = 8.7, H-12), 7.09 (2H, d, J = 9.0, H-3′, H-5′), 7.22 (2H, d, J = 9.0, H-2′, H-6′), 7.50 (1H, t, J = 8.1, H-9), 7.77 (1H, t, J = 8.1, H-8), 7.81 (1H, d, J = 8.7, H-11), 7.98 (1H, d, J = 8.7, H-10), 8.34 (1H, d, J = 8.1, H-7).

3-(4-Butoxyphenyl)-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (4a). Yield 72%, $C_{25}H_{23}NO_4$, mp 141-142°C.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95 (3H, t, J = 7.6, CH_3-4″), 1.47 (2H, m, CH_2-3″), 1.72 (2H, m, CH_2-2″), 3.89 (2H, t, J = 7.2, CH_3-1″), 4.79 (2H, s, CH_2-4), 5.37 (2H, s, CH_2-2), 6.82 (2H, d, J = 9.2, H-3′, H-5′), 6.84 (1H, d, J = 8.8, H-12), 7.12 (2H, d, J = 9.2, H-2′, H-6′), 7.51 (1H, t, J = 7.6, H-9), 7.78 (1H, t, J = 7.6, H-8), 7.80 (1H, d, J = 8.8, H-11), 7.97 (1H, d, J = 8.0, H-10), 8.34 (1H, d, J = 8.0, H-7).

3-[4-(Trifluoromethyl)phenyl]-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (5a). Yield 62%, $C_{22}H_{14}F_3NO_3$, mp 179-180°C.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.93 (2H, s, CH_2-4), 5.48 (2H, s, CH_2-2), 6.86 (1H, d, J = 8.8, H-12), 7.12 (2H, d, J = 8.8, H-2′, H-6′), 7.51 (1H, t, J = 7.6, H-9), 7.54 (2H, d, J = 8.8, H-3′, H-5′), 7.80 (1H, t, J = 7.6, H-8), 7.85 (1H, d, J = 8.8, H-11), 8.01 (1H, d, J = 8.0, H-10), 838 (1H, d, J = 7.6, H-7).

3-[4-(*N*-acetylamino)phenyl]-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (6a). Yield 66%, $C_{23}H_{18}N_2O_4$, mp 203-204°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.96 (3H, s, CH_3CON), 4.73 (2H, s, CH_2-4), 5.45 (2H, s, CH_2-2), 6.79 (1H, d, J = 9.0, H-12), 7.06 (2H, d, J = 8.7, H-2′, H-6′), 7.42 (2H, d, J = 8.7, H-3′, H-5′), 7.55 (1H, t, J = 7.5, H-9), 7.85 (1H, d, J = 7.5, H-8), 8.03 (1H, d, J = 9.0, H-11), 8.19 (1H, d, J = 8.1, H-10), 8.21 (1H, d, J = 8.1, H-7), 9.67 (1H, s, NH).

Methyl-4-(6-oxobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-3-yl)benzoate (7a). Yield 70%, $C_{23}H_{17}NO_5$, mp 201-202°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.86 (3H, s, COOMe), 4.92 (2H, s, CH_2-4), 5.47 (2H, s, CH_2-2), 6.84 (1H, d, J = 9.0, H-12), 7.15 (2H, d, J = 8.7, H-2′, H-6′), 7.51 (1H, t, J = 7.5, H-9), 7.81 (1H, t, J = 7.5, H-8), 7.96 (2H, d, J = 8.7, H-3′, H-5′), 7.98 (1H, d, J = 9.0, H-11), 8.19 (1H, d, J = 8.1, H-10), 8.36 (1H, d, J = 8.1, H-7).

3-[3-(Trifluoromethyl)phenyl]-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (8a). Yield 65%, $C_{22}H_{14}F_3NO_3$, mp 169-170°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.90 (2H, s, CH_2-4), 5.45 (2H, s, CH_2-2), 6.87 (1H, d, J = 9.0, H-12), 7.20 (1H, d, J = 7.5, H-6′), 7.30-7.39 (3H, m, H-2′, H-4′, H-5′), 7.51 (1H, t, J = 7.5, H-9), 7.79 (1H, t, J = 7.5, H-8), 7.84 (1H, d, J = 9.0, H-11), 7.99 (1H, d, J = 8.1, H-10), 8.36 (1H, d, J = 7.8, H-7).

3-(1,3-Benzodioxol-5-yl)-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (9a). Yield 79%, $C_{22}H_{15}NO_5$, mp 185-186°C.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.78 (2H, s, CH_2-4), 5.35 (2H, s, CH_2-2), 3.83 (2H, s, OCH_2O-2′), 6.63 (1H, dd, J = 2.0, 8.8, H-6′), 6.70 (1H, dd, J = 8.8, H-7′), 6.75 (1H, dd, J = 2.0, H-4′), 6.84 (1H, d, J = 8.8, H-12), 7.53 (1H, t, J = 8.0, H-9), 7.81 (1H, t, J = 8.0, H-8), 7.84 (1H, d, J = 8.8, H-11), 8.00 (1H, d, J = 8.0, H-10), 8.36 (1H, d, J = 8.0, H-7).

3-(4-Fluorobenzyl)-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (10a). Yield 85%, $C_{22}H_{16}FNO_3$, mp 129-130°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.89 (2H, s, CH_2-1′), 4.21 (2H, s, CH_2-4), 4.91 (2H, s, CH_2-2), 6.85 (1H, d, J = 8.7, H-12), 7.04 (2H, t, J = 9.0, H-3″, H-5″), 7.34 (2H, m, H-2″, H-6″), 7.50 (1H, t, J = 7.2, H-9), 7.78 (1H, t, J = 7.2, H-8), 7.84 (1H, d, J = 8.7, H-11), 8.00 (1H, d, J = 8.1, H-10), 8.34 (1H, d, J = 8.1, H-7).

3-(3,4,5-Trimethoxybenzyl)-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (11a). Yield 84%, $C_{25}H_{23}NO_6$, mp 158-159°C.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.82 (9H, s, OCH_3-3″, OCH_3-4″, OCH_3-5″), 3.88 (2H, s, CH_2-1′), 4.24 (2H, s, CH_2-4), 4.96 (2H, s, CH_2-2), 6.60 (2H, s, H-2″, H-6″), 6.86 (1H, d, J = 8.8, H-12), 7.50 (1H, t, J = 8.0, H-9), 7.78 (1H, t, J = 8.0, H-8), 7.85 (1H, d, J = 8.8, H-11), 8.01 (1H, d, J = 8.0, H-10), 8.34 (1H, d, J = 8.0, H-7).

3-(2-Furylmethyl)-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (12a). Yield 85%, $C_{20}H_{15}NO_4$, mp 143-144°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.94 (2H, s, CH_2-1′), 4.26 (2H, s, CH_2-4), 4.94 (2H, s, CH_2-2), 6.28 (1H, d, J = 3.3, H-3″), 6.34 (1H, s, H-4″), 6.84 (1H, d, J = 9.0, H-12), 7.42 (1H, s, H-5″), 7.49 (1H, t, J = 7.8, H-9), 7.78 (1H, t, J = 7.8, H-8), 7.81 (1H, d, J = 9.0, H-11), 7.99 (1H, d, J = 8.1, H-10), 8.34 (1H, d, J = 7.8, H-7).

3-Isopropyl-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (13a). Yield 65%, $C_{18}H_{17}NO_3$, mp 135-136°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.20 (6H, d, J = 7.2, two CH_3-1′), 3.14 (1H, m, H-1′), 4.28 (2H, s, CH_2-4), 5.03 (2H, s, CH_2-2), 6.78 (1H, d, J = 9.0, H-12), 7.49 (1H, t, J = 7.8, H-9), 7.78 (1H, t, J = 7.8, H-8), 7.81 (1H, d, J = 9.0, H-11), 7.99 (1H, d, J = 8.1, H-10), 8.35 (1H, d, J = 7.8, H-7).

3-Cyclopropyl-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (14a). Yield 72%, $C_{18}H_{15}NO_3$, mp 147-148°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm,J/Hz): 0.61 (4H, m, CH_2-2′, CH_2-3′), 2.40 (1H, m, H-1′), 4.32 (2H, s, CH_2-4), 4.96 (2H, s, CH_2-2), 6.85 (1H, d, J = 9.0, H-12), 7.50 (1H, t, J = 7.8, H-9), 7.78 (1H, t, J = 7.8, H-8), 7.82 (1H, d, J = 9.0, H-11), 7.99 (1H, d, J = 8.1, H-10), 8.35 (1H, d, J = 7.8, H-7).

3-(2-Methoxyethyl)-3,4-dihydrobenzo[3,4]chromeno[8,7-*e*][1,3]oxazin-6-one (15a). Yield 61%, $C_{18}H_{17}NO_4$, mp 129-130°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.99 (2H, d, J = 7.2, CH_2-2′), 3.41 (3H, s, CH_3O), 3.59 (2H, d, J = 7.2, CH_2-1′), 4.28 (2H, s, CH_2-4), 4.98 (2H, s, CH_2-2), 6.81 (1H, d, J = 9.0, H-12), 7.49 (1H, t, J = 7.8, H-9), 7.79 (1H, t, J = 7.8, H-8), 7.81 (1H, d, J = 9.0, H-11), 7.99 (1H, d, J = 8.1, H-10), 8.34 (1H, d, J = 7.8, H-7).

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