SYNTHESIS OF A NEW PYRANOQUINOLONIC DERIVATIVE FROM COUMARIN.

Alex Sander D. da Matta, Cesar D. de Oliveira and Gilberto A. Romeiro*.
Universidade Federal Fluminense, Instituto de Quimica, Departamento de Quimica Orgânica, Campus do Valonguinho S/N, Niterói, CEP 24210-150, Rio de Janeiro, Brasil.

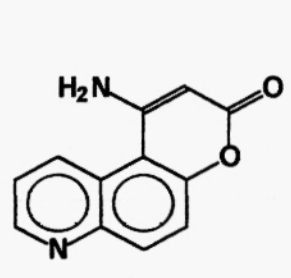
Abstract

Searching for new biological active compounds having the quinolonic system, the synthesis of new pyranoquinolonic compound, ethyl-7,10-dihydro-7-oxo-3H-pyrm[2,3-h]quinolin-3-one-8-carboxylate **14**, it was carried out by condensation of the appropriated 5-aminocoumarin **12**, with ethoxymethylenemalonate and subsequent cyclization reaction through Gould-Jacobs conditions.

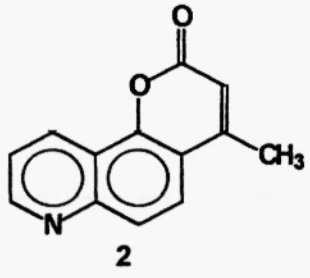
Introduction

The pyrane and benzopyrane moiety are present in several pharmacological compounds with important applications, *eg*: anticoagulant, antibiotics, dermal diseases, antibacterial and antiviral[1-6]. The tricyclics systems combined by pyrane, quinoline and quinolonic rings has received an enormous synthetic study due to their several biological activity, for example, 2-amino-3H-pyran[3,2-f]quinolin-3-one **1**; 2H-pyran[2,3-f]quinolin-2-one **2**; 3H-pyran[3,2-g]quinolin-3-one **3** and 3H-pyran[3,2-f]quinolin-9-carboxylic acid **4** showed antipiretic and antibacterials activity[7-10].

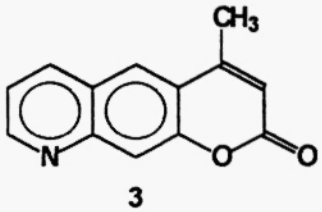
The new pyranequinolonic synthezised and reported in this paper as an angular structure was obtained from aminocoumarin using Gould-Jacobs[11] condensation conditions.



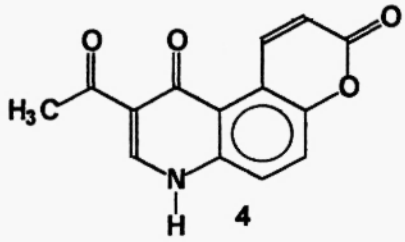
1



2



3



4

Experimental

Melting points wich were uncorrected, were determined using a Fisher-Johns melting point apparatus. The IR spectra were recorded on a Perkin-Elmer 1420 spectrometer using potassium bromide pellets. The ^1H and ^{13}C NMR spectra were recorded on a Varian Unity, frequency of 300 MHz for ^1H and 75.0 MHz for ^{13}C, spectrometer with TMS as an internal standard and the coupling constants were given in Hz. Low-resolution EI mass spectra were recorded on a MAT 711A Finnigan instrument. The ionization energy was 70 eV with the source at 200 °C and the accelerating voltage of 8 KV. The samples were heated and introduced directly into the source area. Analytical thin-layer chromatography (tlc) was performed on silica gel plates, 60F-254 (MERCK, 0.25mm), developed with different mixture of eluents. ***6-Nitrocoumarine*** **6**, ***6-acetamide-5-nitrocoumarine*** **9**, ***6-Aminocoumarine*** **7**, ***6-Acetamidocoumarine*** **8** and ***6-Amino-5-nitrocoumarin*** **10** were prepared as described in the literature.

5-aminocoumarine **12**. The nitro compound (0.5 mmol) in ethyl acetate (100 mL) was hydrogenated over 10% Pd-C (0.4 g) in ethyl acetate (50 mL) at 2 atm. The mixture was stirred for 30 min at room temperature. The catalyst was filtered and the filtrate was recrystalized from water affording 5-aminocoumarine, as yellow needles in 75% yield, mp 124 °C. IR (KBr) cm^{-1} 3400-3310, 1720 (CO); ^1H NMR ($CDCl_3$) δ 6.32 (1H, d, J= 9.9 Hz), 6.56 (1H, dd), 6.73 (1H, dt), 7.27(1H; dd) and 7.75 (1H, dd).

5-Nitrocoumarin **11**. A solution of **10** (0.01 mol), 20 mL of H_2SO_4 98% and 50 mL of water was externally cooled to 0 °C. Then 1g of $NaNO_2$ was added for 30 min portion wise. After this period of time stirring solution of H_3PO_2 50% (40 mL) was added slowly for 1h at 0 °C and kept in the refrigerator for 24h. Precipitated was filtered, dried and recrystalized from ethanol to give **11** as yellow needles in 69% yield. IR (KBr), 1730 (CO), 1530, 1300 (NO_2); ^1H NMR ($CDCl_3$) δ 6.65 (1H, d, J= 10.2 Hz), 7.62 (1H, dd), 7.66 (1H, dd), 8.02 (1H; dd) and 8.51 (1H, d, J= 10.2 Hz).

Diethyl (coumarin-5-yl) aminomethylene malonate **13**. A solution of **12** in 20 mL of ethanol and 2 mL (0.009 mol) of diethylethoxymethylene malonate was stirred under reflux for 2h. After cooling to room temperature a precipitated was formed and then filtered, dried and recrystalized from ethanol giving **13**, in 76% yield, mp 160 °C. IR (KBr), 1720 (CO), 1590 (CO), 1250 and 1210; ^1H NMR ($CDCl_3$) δ 1.37 ($2CH_3$, m), 4.31 ($2CH_2$, m), 6.51 (1H, d, J= 10.2 Hz), 7.15 (1H, dd), 7.55 (1H, dd), 7.9 (1H, dd), 8.55 (1H, d, J= 12.6 Hz) and 11.69 (1H, d, J= 12.6 Hz)

8-Carbethoxy-7,10-dihidro-7-oxo-3H-pyrane[2,3-h]quinolin-3-one **14**. A mixture of **13** (0.002 mol), 2.3 g of PPA and 8.2g of $POCl_3$ was stirred and refluxed for 4h at 100 °C. The resulting mixture was cooled and poured into water (20 mL) to give a precipitated which was washed with water, filtered, dried and recristalyzed from ethanol, 90% yield and mp 314 °C (dec.). IR (KBr), 3450 (NH), 1720 (CO), 1620 (CO), 1290; ^1H NMR (CF_3CO_2D) δ 0.97 (t, CH_3), 4.11 (CH_2, q), 6.40 (1H, d, J= 9.9 Hz), 7.36 (1H, d, J= 9.3 Hz),

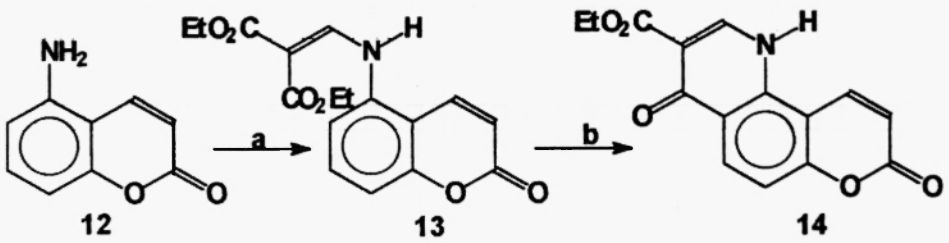
8.27 (1H, d, J= 9.3 Hz), 8.29 (1H, d, J= 9.9 Hz), 8.54 (1H, s); ^{13}C NMR (CF_3CO_2D) δ 13.6 (CH_3), 66.2 (CH_2), 107.6 (C10a), 112.8 (C4a), 118.3 (C3), 119.0 (C6), 121.6 (C9), 130.0 (C5), 138.4 (C10), 147.7 (C2), 160.7 (C10b), 163.2 (C6a), 168.6 (C8), 174.4 (COO), 174.6 (C4); EILRMS, 70 eV, *m/z*(%), 285 $[M]^+$, 239 (100), 213 (30), 211 (42).

Results and Discussions

In order to prepare the target compound **14**, the 5-aminocoumarin **12** was prepared from coumarin **5** in seven steps. The nitration in first step was performed by using a mixture of H_2SO_4 and HNO_3 (1:1) leading to 6-nitrocoumarin **6**. This nitro compound was reduced to 6-aminocoumarin **7** using catalytic hydrogenation with Pd/C (10%). The amino group of **7** was protected as an ester group and then the second nitro group was introduced using the same reaction conditions as previously described leading to **9**. With the nitro group in the appropriated position, the acyl group was removed by hydrolyses giving **10** which was converted to diazonium salt with subsequent hydrogenolise in H_3PO_3 leading to **11** in 65% yield. In the last step the nitro group was reduced with H_2 and Pd/C (10%) giving the desired 5-aminocoumarin **12** in 76% yield (mp 124 ° C). The compounds **6-12** had their structures confirmed by ^{1}H and IR spectra data.

Finally, to prepare the target compound **14**, the 5-amino coumarin **12** was condensed with diethylethoxymethylenemalonate using the Gould-Jacobs reaction[12], **Scheme 1**, producing the acrilate **13** in 76% yield. The ^{1}H RMN showed two signals at 1.37 (6H, m) and 4.31 (4H, m) ppm corresponding to the two ethyl groups and 6.51 (1H, d, J= 10.2), 7.15 (1H, 7.55 (1H, dd), 7.93 (1H, dd), 8.55 (1H, d, J= 10.2) and 11.69 (1H, dd, J= 12.6) ppm for the hydrogen of the aromatic region. Treatment of **13** with PPA/$POCl_3$ at 100 °C lead to 8-carbetoxi-7,10-dihidro-7-oxo-3H-pyran[2,3-h]quinolin-3-one **14** in 95% yield.

Scheme 1: Synthesis of the target pyranquinolone **14**.



a) Diethylethoxymethylenemalonate, EtOH, reflux, 2h; b) PPA/$POCl_3$, 100 °C, 4h.

By the data presented in experimental, we can observe doublets for the signals associated with protons of the positions 5 and 6 of **14**, in 7.36 and 8.27 ppm, J= 9.3 Hz in substitution to the signal in 7.55 ppm in compound **13**. To confirm the structure **14**, the mass spectrum

showed the molecular ion $[M]^{+\cdot}$ 285 (5) and the fragments *m/z* 256 (5) from the molecular ion. $[M - C_2H_5]^+$, *m/z* 239 (20) corresponding to $[M - C_2H_5O]^+$. *m z* 211 $[M - C_2H_5OH - CO]^+$ and others.

Conclusions

The new pyranoquinolonic derivative. 3-carbetoxi-7-oxopyran[2.3-h]quinolin-3-one 14 was obtained in good yield. This route constitutes an alternative. using Gould-Jacob reaction. for syntetize importants compounds like 4 with antipiretic and antibacterial activity.

Acknowledgments

We thanks the financial support from Conselho Nacional de Desenvolvimento Cientifico c Tecnológico - CNPq (PADCT) and to Fundaçao e Aperfeiçoamento de Pesquisa e Ensino (CAPES) for ASDM scholarship. Especial thanks to Institut für Organicshe Chemie. Universität Tübingen. Tübingen – Germany. with the Mass Spectra colaboration.

References

(1) S. Wawzonek. *Heterocyclic Compounds*. Ed Wiley. NY. 173. vol 2. 1977.

(2) L. S. Goodman and A. Gilman. *The Pharmacological Basis of Therapeutics*. The Macnillon Co., NY, 4th Ed., 1291 e 1451, 1970.

(3) H. Meyer. *Acta Chem. Scand*, B 29(1). 133. (1975).

(4) M. Jetter and N. Heindel, *J. Heterocycl. Chem.*, 27. 995. (1990).

(5) E. Lummey, S. Hagen, J. Domagala and C. Humblet. *J. Med. Chem.*, 37, 2664. (1994).

(6) K. Romines. K. Watenpaugh, P. Tomich and W. Hove, *J. Med. Chem.*, 38, 1884, (1995).

(7) D. Heber and Th. Berghaus. *J. Heterocycl. Chem.*,31, 1353, (1994).

(8) H. N. Gupta. *J. Indian Chem. Soc.*, 9, 371, (1932).

(9) R. Atkins and D. Bliss, *J. Org. Chem.*, 43 (10). 1975, (1978).

(10) G. Y. Lesher. U. S. Patent. 3, 313, 818. 1967 (C. A. 68. 68 968. 1968).

(11) R. Gould and W. Jacobs. *J. Am. Chem. Soc.*. 61, 2890. (1939).

(12) M. Khan and A. L. Gemal. *J. Heterocycl. Chem.*, 15. 159, 1978.

Received on October 10, 2000