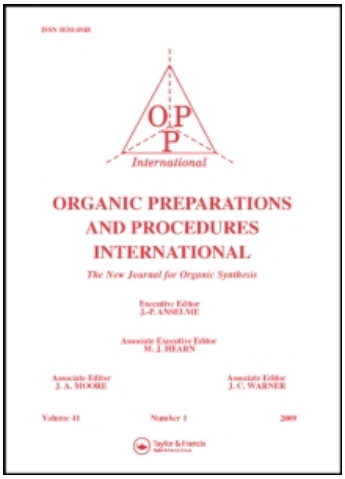

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SYNTHESES OF FURO-, PYRROLO- AND THIENO[3,2-c]COUMARINS

M. Trkovnik[a]; R. Djudić[a]; I. Tabaković[a]; M. Kuleš[a]
[a] Laboratory of Organic Chemistry and Biochemistry Technological Faculty, "Djuro Pucar Stari" University, Banja Luka, YUGOSLAVIA

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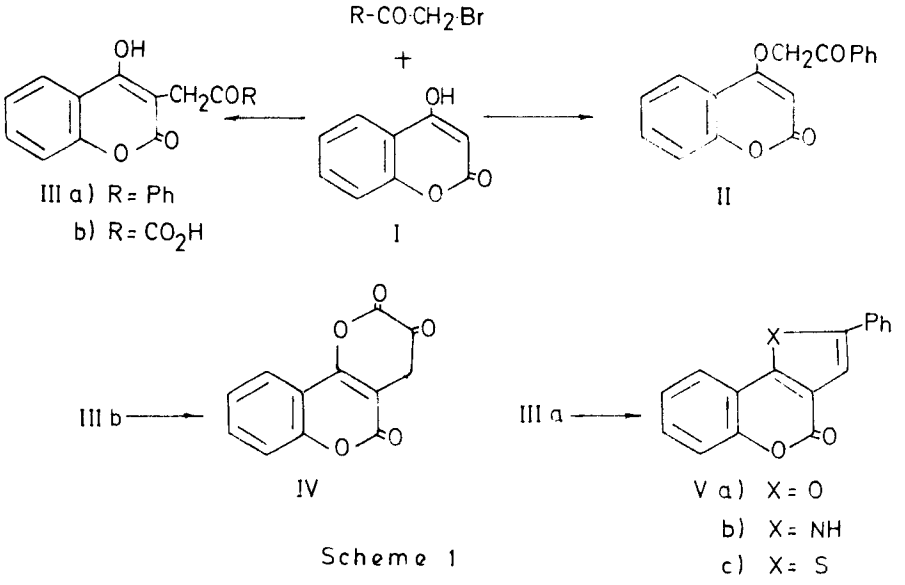
SYNTHESES OF FURO-, PYRROLO- AND THIENO[3,2-c]COUMARINS

M. Trkovnik*, R. Djudjić, I. Tabaković and M. Kuleš

Laboratory of Organic Chemistry and Biochemistry
Technological Faculty, "Djuro Pucar Stari" University
78000 Banja Luka, YUGOSLAVIA

Coumarins with additional rings condensed at the 3,4-position have been reported to exhibit potent biological activity.[1-3] We now report the synthesis several novel representatives of this class of compounds.

Treatment of 4-hydroxycoumarin (I) with phenacyl bromide in basic medium afforded the O- and C-alkylated derivatives II



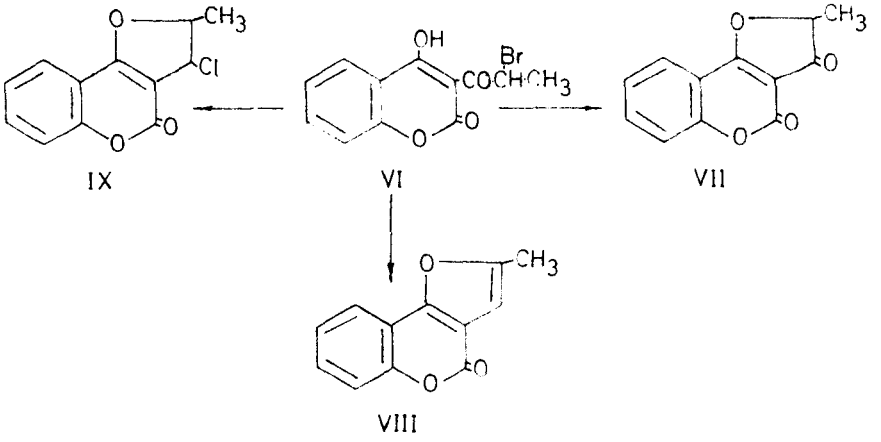
Scheme 1

and IIIa. The former, 4-phenacyloxycoumarin (II), was generated in dimethylformamide (DMF) with potassium carbonate as the base, while the latter, 3-phenacyl-4-hydroxycoumarin (IIIa), resulted when the reaction was carried out in dimethylsulfoxide (DMSO) with triethylamine as the base. Similar treatment of 4-hydroxycoumarin with α-bromopyruvic acid (DMSO/Et_3N) gave β-(4-hydroxycoumarin-3-yl)pyruvic acid (IIb) which was easily converted to its methyl ester. Heating of IIIb in polyphosoporic acid (PPA) resulted in ring closure and gave the cyclic keto-dilactone IV.

Although the synthesis of thieno[3,2-c]coumarin derivatives is reported to be difficult[3], having to be performed under an inert argon atmosphere, we succeeind in obtaining a derivative (Vc) by simple treatment of IIIa with P_2S_5 in dioxane with no special precautions. Similar products with other hetero atoms in the additional ring, namely the furo- and pyrrolo[3,2-c]coumarin derivatives (Va and Vb) were obtained from 3-phenacyl-4-hydroxycoumarin by ring closure in PPA and in acetic acid/ammonium acetate, respectively. In all cases, the yields ranged from good to excellent (59-82%) and the time required were quite short (1-2 hrs).

The furo[3,2-c]coumarin derivatives VII-IX were obtained by dehydrobromination of 3-α-bromopropionyl-4-hydroxycoumarin (VI) with amines or by sodium borohydride reduction in tetrahydrofuran (THF). The treatment of VI with amines was carried out under various conditions in the hope of obtaining a substi tution of bromine with an amino residue, but these attempts failed: the reaction product was always 2-methyl-4H-furo

[3,2-c][1]benzopyran 3[2H],4-dione (VII). The treatment of VI with $NaBH_4$ in THF resulted not only in reduction but also in cyclization. Treatment of either VI or VII resulted in the reduction of the ketonic carbonyl group. Take-up of the dry products in 50% acetic acid resulted in elimination of water and the final product was in both cases 2-methyl-4H-furo[3,2-c][1] benzopyran-4-one (VIII). An identical product was obtained by the Claisen rearrangement of 4-allyloxycoumarin followed by dehydrogenation over Pd/C[4]. When the dry residues after $NaBH_4$ reduction of VI and VII were taken up into dilute HCl (1:1) instead of into 50% acid, the final product was 2-methyl-3-chloro-2,3-dihydro-4H-furo[3,2-c][1] benzopyran-4-one (IX).



Scheme 2

EXPERIMENTAL

All mps are uncorrected. The spectra were recorded on the following instruments: Perkin-Elmer M-377 infrared spectrometer (KBr pellets); Perkin-Elmer B-12 nmr spectrometer (solvents DMSO d-6, $CDCl_3$).

4-Phenacyloxycoumarin (II).-4-Hydroxycoumarin (2 g, 13.2 mmoles) and potassium carbonate (1.82 g, 13.2 mmoles) were dissolved in DMF (10 ml) and the solution stirred 1 hr at 90°. An equimolar amount of phenacyl bromide (2.61 g) was added and stirring at 90° was continued for one additional hour. The mixture was allowed to cool whereupon (15 ml) of a saturated aqueous solution of $NaHCO_3$ was added to precipitate the product which separated in the form of a gray tarry crystalline mass. Recrystallisation from 96% ethanol gave 3.0 g (82%) of white woolly crystals, mp.192-194°.

IR (cm^{-1}): 3090 (CH, arom.), 1710, 1640 (CO); NMR δ (DMSO d-6, ppm); 6.05 (s, CH_3), 5.95 (s, CH_2), 7.5-8.2 (m, 4H, arom.).

Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85, H, 4.28.

Found: C, 73.21, H, 4.53.

3-Phenacyl-4-hydroxycoumarin (IIIa).-4-Hydroxycoumarin (3 g, 19.7 mmoles) was dissolved in DMSO (5 ml) and the solution mixed with 0.5 ml of triethylamine, then stirred 5 min at 50°. A solution of phenacyl bromide (3.93 g, 19.7 mmoles) in 3 ml of DMSO was poured and the mixture stirred at 50°. After having been left standing for 45 min, the reaction mixture was poured into cold water, the precipitated product collected, dried and recrystallized from 96% ethanol to yield 3.25 g (59%) of pink crystals, mp.182-185°.

IR (cm^{-1}): 3390 (OH), 3080 (CH, arom.), 1660, 1640 (CO).

Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85, H, 4.28.

Found: C, 73.18, H, 4.47.

α-(4-Hydroxycoumarin-3-yl)pyruvic acid (IIIb).-4-Hydroxycoumarin (2g, 13.2 mmoles) was dissolved in DMSO (4 ml) and solu-

tion mixed with 0.5 ml of triethylamine then stirred and heated at 40-50° for 10 min. A solution of phenacyl bromide (2.15 g, 13.2 mmoles) in 3 ml of DMSO was poured and the mixture stirred 30 min. During this period the product deposited as pale yellow plate-like crystals. Recrystallisation from 96% ethanol gave 1.48 g (46%) of pure product, mp. 216-218°.

IR (cm^{-1}): 3420 (carboxyl-OH), 3005, 2910, (CH, arom.), 1717, 1640 (CO), 1600 (C=C, arom.).

Anal. Calcd for $C_{12}H_8O_6$: C, 58.06, H, 3.22.

Found: C,58.63, H, 3.44.

Methyl ester of IIIb.-Compound IIIb (0.5 g, 2.0 mmoles) was dissolved in methanol (20 ml), the solution acidified with one drop of concentrated sulfuric acid, and heated 2 hr on a water bath. On cooling the product separated in crystalline form. Recrystallisation from 96% ethanol gave 0.25 g (48%) of pale yellow crystals mp.170-172°.

IR (cm^{-1}): 3385 (OH), 3010, 2930 (CH, arom.), 1760, 1640 (CO), 1605 (C=C, arom.).

Anal. Calcd for $C_{13}H_{10}O_6$: C, 59.54, H, 3.84.

Found: C, 60.09, H, 3.82

2H,3H,4H,5H-Pyrano[3,2-c][1]benzopyran-2,4,6-trione (IV).-Compound IIIb (0.5 g, 2.0 mmoles) was heated with PPA (5 ml) for 1 hr on a water bath. The resulting dark mass was poured onto ice whereupon small yellow crystals of the keto-dilactone separated; they were collected and recrystallised from 96% etanol yield 0.29 g (63%), mp.222-224°.

IR (cm^{-1}): 3115, 3060 (CH, arom.), 1735, 1685 (CO), 1590 (C=C, arom.).

Anal. Calcd for $C_{12}H_6O_5$: C, 62.60, H, 2.60.
Found: C, 62.13, H, 2.88.

2-Phenacyl-4H-furo[3,2-c][1]benzopyran-4-one (Va).-A mixture of compound IIIa (0.5 g, 1.8 mmole) and PPA (5 ml) was heated 1 hr on a water bath then poured into cold water to yield 0.37 g (68%). Recrystallisation from 96% ethanol gave a crystalline product, mp.171-173°.

IR (cm^{-1}): 3130, 3030 (CH, arom.), 1740 (CO), 1630 (C=C, arom.)
NMR δ (DMSO d-6, ppm): 7.30-8.00 (m, 9H, arom.), 8.25 (s, CH).

Anal. Calcd for $C_{17}H_{10}O_3$: C, 77.86, H, 3.81.
Found: C, 77.71, H, 4.02.

2-Phenyl-4H-pyrrolo[3,2-c][1]benzopyran-4-one (Vb).-Compound IIIa (0.5 g, 1.8 mmole) was dissolved in acetic acid (20 ml) containing ammonium acetate (0.27 g, 3.6 mmoles) and the solution was refluxed for 2 hrs. During this period the product (0.38 g, 83%) deposited as yellow crystals and was collected after cooling. Recrystallisation from 96% ethanol gave the pure product, mp.305-307°.

IR (cm^{-1}): 3295 (NH), 3060, 3005 (CH, arom.), 1680 (CO), 1620 (C=C, arom.); NMR δ(DMSO d-6, ppm). 7.12 (s, 3-CH), 7.30-8.04 (m, 9H arom.), 11.00 (s, NH).

Anal. Calcd for $C_{17}H_{11}NO_2$: C, 78.16, H, 4.21, N, 5.26.
Found: C, 78.52, H, 4.46, N, 5.05.

2-Phenyl-4H-thieno[3,2-c][1]benzopyran-4-one (Vc).- A solution of compound IIIa (0.5 g, 1.8 mmole) in dioxane (7 ml), to which was added P_2S_5 (0.3 g, 1.4 mmole), was refluxed for 2 hrs. The hot reaction mixture was poured into cold water and the resulting colloidal solution extraeted with ether. Removal of

the ether from the extract left 0.3 g (75%) of yellow crystals. After recrystallisation from 96% ethanol the mp. was 173-175°.
IR (cm^{-1}): 3040, 2910 (CH, arom.), 1700 (CO), 1605 (C=C, arom.)
Anal. Calcd for $C_{17}H_{10}O_2S$: C, 73.38, H, 3.60.
Found: C, 72.95, H, 3.42.

2-Methyl-4H-furo[3,2-c][1]benzopyran-3[2H],4-dione (VII).- A solution of VI[5] (2 g, 6.7 mmoles) and diethylamine or n-propyl amine(2 ml) in 96% ethanol (50 ml) was refluxed 3 hrs then concentrated to a small (cca 10 ml) volume. The separated solid was collected and recrystallised from methanol to afford a nearly quantitative yield of pure product as needle-like crystals, mp.227°, lit.[6] 227.5-228.5°.
IR (cm^{-1}): 3080 (CH, arom.), 1735 1700 (CO): NMR δ ($CDCl_3$, ppm: coupling const's, Hz): 1.66 (d, 3H, J, 7), 4.99 (q, 1H, J_1, J_2, 15 and 7, resp.), 7.30-8.10 (m, 4H, arom.).
Anal. Calcd for $C_{12}H_8O_4$: C, 66.66, H, 3.73.
Found: C, 66,42, H, 3.91.

2-Methyl-4H-furo[3,2-c][1]benzopyran-4-one (VIII).
Route A(from VI).- A solution of VI (2.0 g, 6.7 mmoles) and $NaBH_4$ (0.133 g, 3.5 mmoles) in THF (30 ml) was stirred 3 hrs at room temperature, after which the solvent was removed under reduced pressure. The dry residue was with 50% acetic acid (30 ml), to give 1.05 g (78%) of needle-like crystals, mp.174° after recrystallisation from methanol, lit.[4] 174°; lit.[7] 175-176°.
IR (cm^{-1}): 3130 (CH, arom.), 1725 (CO): NMR δ ($CDCl_3$, ppm): 2.46 (s, 3H, CH_3), 6.53 (s, 1H, 3-CH), 7.15-7.90 (m, 4H, arom.).
Anal. Calcd for $C_{12}H_8O_3$: C, 71.99, H, 4.02.

Found: C, 72.27, H, 3.78

Route B(from VII).-A solution of VII (0.5 g, 2.3 mmoles) and $NaBH_4$ (0.04 g, 1.1 mmoles) in THF (30 ml) was refluxed 3 hrs after which the reaction mixture was treated as desoribed above to yield 0.34 g (74%), mp. 174°.

2-Methyl-3-chloro-2,3-dihydro-4H-furo[3,2-c][1]benzopyran-4-one (IX).- A solution of VI (2.0 g, 6.7 mmoles) and $NaBH_4$ (0.133 g, 3.5 mmoles) in THF (50 ml) was treated as in the preparation of compound IX up to the removal of solvent. The dry residue was then worked up with dilute hydrochloric acid (1:1, 50 ml), which left 1.5 g (94%) of crystals, mp 183° after recrystallisation from methanol.

IR (cm^{-1}): 1782 (CO); NMR δ ($CDCl_3$, ppm; coupling const's, Hz): 1.70 (d, 3H, CH_3; J=7), 5.33 (q, 1H, 2-CH_3; J_1, J_2, 13 and 7, respectively), 7.30-8.40 (m, 5H, arom. and 3-CH).

Anal. Calcd for $C_{12}H_9O_3Cl$: C, 60.90, H, 3.83, Cl, 15.01.

Found: C, 60.64, H, 3.75, Cl, 15.24.

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