The Synthesis and Transformations of 2*H*-Naphtho-[1,2-*b*]pyran-2-one Derivatives. Naphtho[2',1':5,6]-pyrano[3,4-*d*][1,3]oxazines and Naphtho[1',2':5,6]pyrano[3,4-*d*]-pyrimidines, Derivatives of Two New Heterocyclic Systems

Simona Fajgelj, Branko Stanovnik* and Miha Tišler

Department of Chemistry, Edvard Kardelj University,
61000 Ljubljana, Yugoslavia

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1,4-Naphthoquinone (**1**) was transformed with alkyl 2-aminofumarates **2** into 2*H*-naphtho[1,2-*b*]pyran-2-ones **3** and **4**, which served as intermediates in the synthesis of **7**, **8** and **13**, which are derivatives of two new heterocyclic systems: naphtho[2',1':5,6]pyrano[3,4-*d*][1,3]oxazine and naphtho[1',2':5,6]pyrano[3,4-*d*]pyrimidine.

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Several methods for the preparation of isomeric naphthopyrans are described in the literature. They include the preparation of derivatives of five isomeric systems: 2*H*-naphtho[1,2-*b*]pyran, 3*H*-naphtho[2,1-*b*]pyran, 2*H*-naphtho[2,3-*b*]pyran, naphtho[1,8-*bc*]pyran, and 1*H*,3*H*-naphtho[1,8-*cd*]pyran [1]. In connection with our studies in the field of heterocyclic amino acids and peptides, we have described recently a new method for the preparation of substituted 3-amino-2*H*-naphtho[1,2-*b*]pyran-2-ones and 2-amino-3*H*-naphtho[2,1-*b*]pyran-3-ones from the corresponding 1- and 2-naphthol and methyl 2-benzoylamino-3-dimethylaminopropenoate, a reagent which has been successfully employed also for construction of other heterocyclic systems [2]. On the other hand, inspite of the frequent use of 1,4-naphthoquinones as the building blocks in the synthesis of fused heterocyclic systems [3], their reaction with 2-aminofumarates has not been described so far.

In this communication we report the synthesis and some transformations of substituted 2*H*-naphtho[1,2,-*b*]pyran-2-ones **3** and **4**. They were prepared from 1,4-naphthoquinone (**1**) and dimethyl (**2**, R = Me) or diethyl 2-aminofumarate (**2**, R = Et) in acetic acid at room temperature in essentially the same way as it has been reported for the corresponding 2*H*-1-benzopyran-2-one derivatives [4,5]. Since these compounds contain an amino group at position 3 and an ester group at position 4 in the pyranone ring, we tried to transform them into derivatives of some novel heterocyclic systems according to the procedures we have described in the preceding paper [5].

In the reaction of compounds **3** and **4** with benzoyl chloride in pyridine at room temperature, only benzoylation of the hydroxy group at position 6 was observed which gave the compounds **5** and **6** in 64% and 51% yield, respectively. On the other hand, when compounds **3** and **4** were heated in pyridine under reflux with benzoyl chloride in a molar ratio of 1:2, benzoylation of the amino group at position 3 and the hydroxy group at position 6 took place, followed by cyclization involving the 3-benzoylamino group and the *ortho* ester functionality to give compound **7**, a derivative of a new heterocyclic system, naphtho[1',2':-5,6]pyrano[3,4-*d*][1,3]oxazine. Another derivative of the same heterocyclic system was obtained from the 6-methoxy compound **9** by treatment with benzoyl chloride in refluxing pyridine in 50% yield.

When the compounds **3** and **4** were heated with *N,N*-dimethylacetamide dimethyl acetal (DMADMA) a selective methylation of the hydroxy group at position 6 was observed to afford the 6-methoxy derivatives **9** and **10** in 45% and 57% yield, respectively. This is similar to our previous observations with 6-hydroxy-2*H*-1-benzopyran-2-one derivatives [5]. On the other hand, when *N,N*-dimethylformamide dimethyl acetal (DMFDMA) was used instead of DMADMA, methylation of the 6-hydroxy group in compound **4** as well as *N,N*-dimethylaminomethylation of the 3-amino group took place to give compound **11** in 68% yield. The formamidine part of the molecule was then further transformed quantitatively with hydroxylamine hydrochloride into the corresponding formamide oxime **12**. When the latter compound was heated at 170° or above, the cyclization occured to give compound **13**, a derivative of another new heterocyclic system: 2*H*,6*H*-naphtho[1',2':-5,6]pyrano[3,4-*d*]pyrimidine, in near quantitative yield.

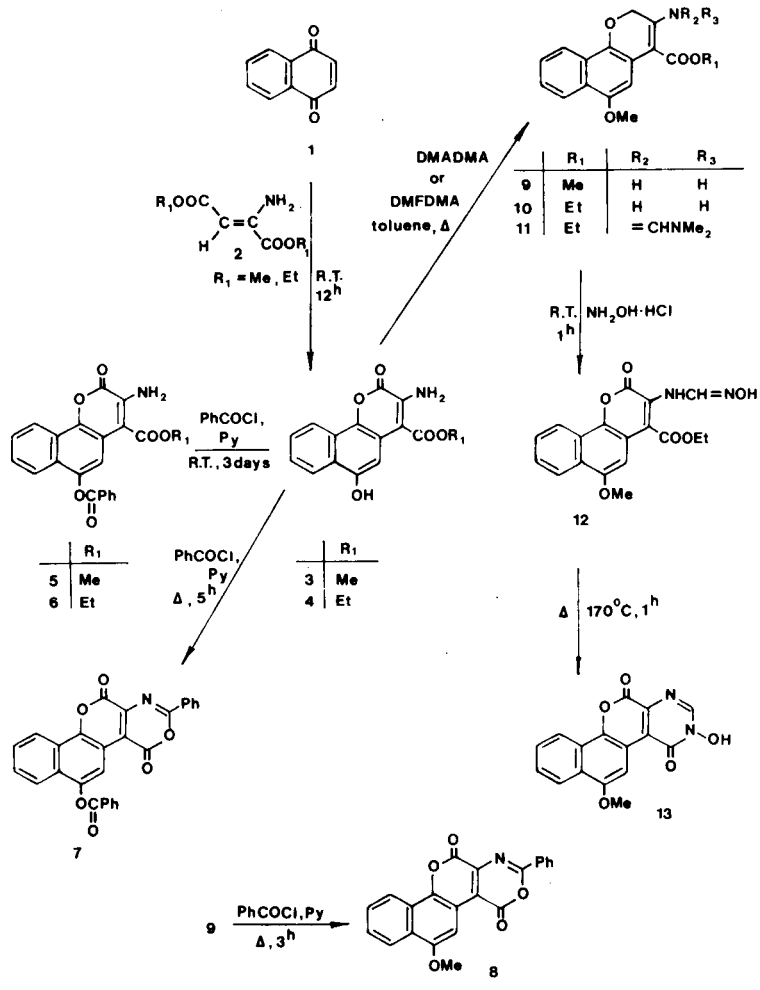
The structures of the compounds were established on the basis of their ir and ^{1}H nmr spectra, and by microanalyses for C, H, and N. The compounds **3** and **4** show in the ^{1}H nmr spectra two peaks around δ = 7.15 ppm integrat-

Table 1

^{1}H NMR and IR Data for the NH and OH Group of Compounds **3-6** and **9, 10**

Compound		^{1}H NMR, δ ppm	IR [cm^{-1}]		^{1}H NMR, δ ppm	IR [cm^{-1}]
3	NH_2	7.15	3490, 3370	OH	10.1	3300
4	NH_2	7.18	3530, 3400	OH	9.95-10.4	~3370
5	NH_2	6.96-7.42	3470, 3350		-	
6	NH_2	6.95-7.24	3550, 3410		-	
9	NH_2	7.00-7.39	3490, 3370		-	
10	NH_2	6.67-7.22	3500, 3380		-	

Scheme 1



ing for two protons and $\delta \simeq 10$ ppm integrating for one proton, corresponding to the amino and hydroxy group. The ir spectrum of compound **3** exhibits three bands at $\nu = 3530$ cm^{-1} and $\nu = 3400$ cm^{-1} for the amino group and a broad and stronger band at $\nu = 3300$ cm^{-1} corresponding to the hydroxy substituent. For compound **4**, the band for the hydroxy group is superimposed on the lower band of the amino group. On the other hand, compounds **5**, **6**, **9** and **10** show only two bands of equal intensity in the region $n = 3470$-3350 cm^{-1} for the free amino group (Table 1). On this basis, one can conclude that in all these examples the reactions are taking place at the hydroxy group at position 6. The evidence, that only the substituted amino group and the *ortho* ester functionality are involved in the cyclization to form the compounds **7**, **8**, and **13** follows from ^{1}H nmr spectra, since ester groups are no longer present in the ^{1}H nmr spectra of cyclized products.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on Jeol 60 HL or 90 Q FT spectrometers with TMS as an internal standard. The ir spectra were recorded on a Perkin-Elmer 1310 spectrometer, and elemental analyses for C, H, and N on a Perkin-Elmer CHN Analyser 240 C.

3-Amino-6-hydroxy-4-methoxycarbonyl-2*H*-naphtho[1,2-*b*]pyran-2-one (**3**).

A suspension of **1** (474 mg, 0.003 mole) in acetic acid (2 ml) was added slowly to stirred dimethyl 2-aminofumarate (**2**, R = CH_3, 500 mg, 0.00314 mole) at 0°. The mixture was left for 12 hours at room temperature, the precipitate was collected by filtration and washed with 1-propanol to give **3** (240 mg, 28%), mp 230, dec (from a mixture of DMF and ethanol); ^{1}H nmr (DMSO-d_6): δ 3.95 (s, MeO), 7.18 (br s, NH_2), 7.40-7.70 (m, 3H, arom), 8.00-8.25 (m, 2H, arom), 10.1 (br s, OH).

Anal. Calcd. for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; N, 4.91. Found: C, 63.27; H, 3.78; N, 4.63.

3-Amino-4-ethoxycarbonyl-6-hydroxy-2*H*-naphtho[1,2-*b*]pyran-2-one (**4**).

A suspension of **1** (12 g, 0.076 mole) in acetic acid (50 ml) was added dropwise to **2** (R = C_2H_5, 14.8 g, 0.079 mole) at 0°. The mixture was left for 12 hours at room temperature. The precipitate was collected by filtration and washed with 1-propanol to give **4** (4.8 g, 21%), mp 224-234° (from 1-propanol); ^{1}H nmr (DMSO-d_6): δ 1.45 (t, *Me*CH_2O), 4.45 (q, MeCH_2O), 7.15 (s, NH_2), 7.35-7.70 (m, 3H, arom), 8.0-8.3 (m, 2H, arom), 9.95-10.4 (br s, OH).

Anal. Calcd. for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.29; H, 4.46; N, 4.51.

3-Amino-6-benzoyloxy-4-methoxycarbonyl-2*H*-naphtho[1,2-*b*]-pyran-2-one (**5**).

A mixture of **3** (571 mg, 0.002 mole) and benzoyl chloride (295 mg, 0.0021 mole) in pyridine (5 ml) was left at room temperature for 3 days. The precipitate was collected by filtration to give **5** (495 mg, 64%), mp 265-268° (from DMF); ^{1}H nmr (DMSO-d_6): δ 4.05 (s, OMe), 6.96-7.42 (br s, NH_2), 7.55-8.10 (m, 5H, arom), 8.29-8.61 (m, 5H, arom).

Anal. Calcd. for $C_{22}H_{15}NO_6$: C, 67.87; H, 3.88; N, 3.60. Found: C, 67.40; H, 3.80; N, 3.62.

3-Amino-6-benzoyloxy-4-ethoxycarbonyl-2*H*-naphtho[1,2-*b*]pyran-2-one (**6**).

A mixture of **4** (599 mg, 0.002 mole) and benzoyl chloride (295 mg, 0.0021 mole) in pyridine (5 ml) was left at room temperature for 3 days. The crude product (410 mg, 51%) was collected by filtration to give **6**, mp 207-209° (from a mixture of chloroform and methanol); ^{1}H nmr (deuteriochloroform): δ 1.49 (t, *Me*CH_2O), 4.58 (q, MeCH_2O), 6.95-7.24 (br s, NH_2), 7.57-8.22 (m, 6H, arom), 8.35-8.90 (m, 4H, arom), (J_{CHCH} = 7.0 Hz).

Anal. Calcd. for $C_{23}H_{17}NO_6$: C, 68.48; H, 4.25; N, 3.47. Found: C, 68.83; H, 4.27; N, 3.20.

8-Benzoyloxy-4-phenyl-naphtho[2′,1′:5,6]pyrano[3,4-*d*][1,3]oxazin-2,6(2*H*,6*H*)-dione (**7**).

A solution of **4** (299 mg, 0.001 mole) and benzoyl chloride (295 mg, 0.0021 mole) in pyridine (3 ml) was heated under reflux for 5 hours. The precipitate was, after cooling, collected by filtration to give **7** (55 mg, 12%), mp 322-324° (from DMF); ^{1}H nmr (DMSO-d_6): δ 7.55-8.78 (m, 14H, arom), 8.87 (s, H_7).

Anal. Calcd. for $C_{28}H_{15}NO_6$: C, 72.88; H, 3.28; N, 3.04. Found: C, 72.44; H, 3.28; N, 3.48.

Compound **7** was obtained from **3** in 28% yield under the essentially the same reaction conditions.

8-Methoxy-4-phenyl-naphtho[2′,1′:5,6]pyrano[3,4-*d*][1,3]oxazin-2,6(2*H*,6*H*)-dione (**8**).

A mixture of **9** (200 mg, 0.00064 mole) and benzoyl chloride (230 mg, 0.00164 mole) in pyridine (5 ml) was heated under reflux for 3 hours. The precipitate was, after cooling, collected by filtration to give **8** (120 mg, 50%); ^{1}H nmr (DMSO-d_6): δ 4.18 (s, OMe), 7.74-7.93 (m, 5H, arom), 8.32-8.61 (m, 5H, arom).

Anal. Calcd. for $C_{22}H_{13}NO_5$: C, 71.16; H, 3.53; N, 3.77. Found: C, 70.78; H, 3.50; N, 4.09.

3-Amino-6-methoxy-4-methoxycarbonyl-2*H*-naphtho[1,2-*b*]pyran-2-one (**9**).

A mixture of **3** (285 mg, 0.001 mole) and DMADMA (200 mg, 0.0015 mole) in toluene (3 ml) was heated under reflux for 3 hours. The precipitate was, after cooling, collected by filtration to give **9** (135 mg, 45%), mp 213-218° (from toluene); ^{1}H nmr (DMSO-d_6): δ 3.06 (s, OMe), 4.07 (s, MeOCO), 7.00-7.39 (br s, NH_2), 7.56-7.98 (m, 3H, arom), 8.21-8.50 (m, 2H, arom).

Anal. Calcd. for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.08. Found: C, 64.31; H, 4.45; N, 4.40.

3-Amino-4-ethoxycarbonyl-6-methoxy-2*H*-naphtho[1,2-*b*]pyran-2-one (**10**).

A mixture of **4** (50 mg, 0.00017 mole) and DMADMA (50 mg) in toluene (1 ml) was heated under reflux for 3 hours. The precipitate was, after cooling, collected by filtration to give **10** (30 mg, 57%), mp 210° (from toluene); ^{1}H nmr (deuteriochloroform): δ 1.52 (t, *Me*CH_2O), 4.02 (s, OMe), 4.50 (q, MeCH_2O), 6.67-7.22 (br s, NH_2), 7.55-7.71 (m, 2H, arom), 7.77 (s, H_5), 8.19-8.55, (m, 2H, arom), (J_{CHCH} = 7.0 Hz).

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.16; H, 4.94; N, 4.40.

3-(*N,N*-Dimethylaminomethyleneamino)-4-ethoxycarbonyl-6-methoxy-2*H*-naphtho[1,2-*b*]pyran-2-one (**11**).

A mixture of **4** (150 mg, 0.0005 mole) and DMFDMA (150 mg, 0.00126 mole) in toluene (3 ml) was heated under reflux for 5 hours. The precipitate was, after cooling, removed by filtration, the filtrate was evaporated *in vacuo* to give **11** (125 mg, 68%), mp 158-160° (from a mixture of chloroform and cyclohexane); ^{1}H nmr (deuteriochloroform): δ 1.45 (t, *Me*CH_2O), 2.95 and 3.00 (2s, NMe_2), 3.98 (s, OMe), 4.43 (q, MeCH_2O), 6.37 (s, H_5), 7.20-7.50 (m, 2H, arom), 7.90-8.30 (m, 2H, arom), 8.60 (s, CH=N).

Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.40; H, 5.55; N, 7.49.

4-Ethoxycarbonyl-3-hydroxyiminomethylamino-6-methoxy-2*H*-naphtho[1,2-*b*]pyran-2-one (**12**).

To a solution of **5** (340 mg, 0.00092 mole) in ethanol, hydroxylaminehydrochloride (100 mg, 0.00143 mole) was added and the mixture was stirred for one hour at room temperature. The precipitate was collected by filtration and washed with ethanol to give **12** (355 mg, quantitative). The product was crystrallized from a mixture of DMF and ethanol. Above 170°, the compound was transformed into **13**. Compound **12** had ^{1}H nmr (trifluoroacetic acid): δ 1.60 (t, *Me*CH_2O), 4.0 (s, *Me*O), 4.75 (q, MeCH_2O), 7.15 (s, H_5), 7.40-7.90 (m) and 7.95-8.45 (m), (H_7,H_8,H_9,H_{10}), N*H*, and O*H* exchanged.

Anal. Calcd. for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.98; H, 4.62; N, 7.90.

5-Hydroxy-8-methoxy-2-naphtho[1′,2′:5,6]pyrano[3,4-*d*]pyrimidin-5,6(5*H*,6*H*)-dione (**13**).

Method A.

The solid **12** (100 mg) was heated for one hour at 170° or above, to give **13** quantitatively, mp >300° (from DMF). The compound was not soluble in organic solvents and therefore the ^{1}H nmr spectrum could not be obtained.

Method B.

The same compound was obtained when **12** (55 mg) was heated in hydrochloric acid (18%, 2 ml) under reflux for one hour. The precipitate was, after cooling, collected by filtration to give **13** in quantitative yield.

Anal. Calcd. for $C_{16}H_{10}N_2O_5$: C, 61.94; H, 3.25; N, 9.03. Found: C, 61.71; H, 3.46; N, 8.98.

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