Preparation of 2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-1,5-dione Derivatives

Stephen P. Stanforth

School of Applied Sciences, University of Northumbria, Newcastle upon Tyne, NE1 8ST, UK

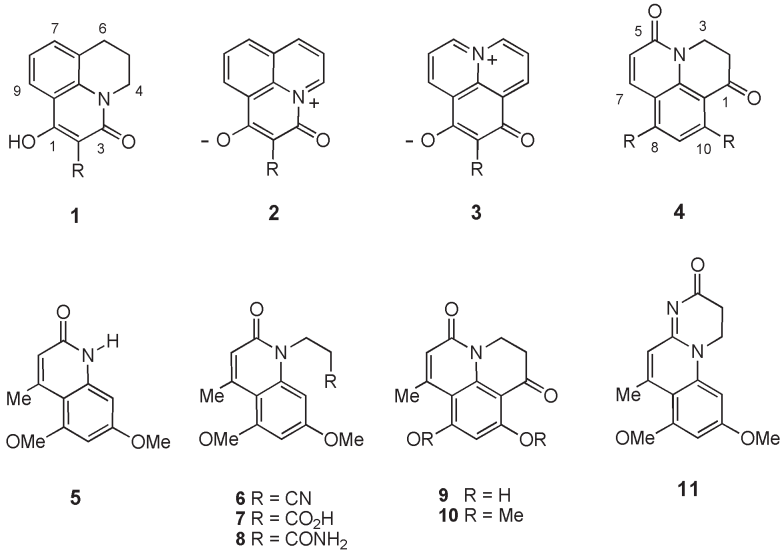
Received October 25, 2005

The 2,3-dihydro-7-methyl-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-1,5-dione derivatives **9** and **10** were prepared from 3-(5,7-dimethoxy-4-methyl-2-oxo-2*H*-quinolin-1-yl)propionitrile (**6**). Cyclodehydration of the amide **8** gave 1,2-dihydro-7,9-dimethoxy-6-methylpyimido[1,2-*a*]quinolin-3-one (**11**).

J. Heterocyclic Chem., **42**, 723 (2005).

We have previously reported the synthesis of the cross-conjugated heterocyclic mesomeric betaine, 3-oxo-2-phenyl-3aλ^5-azaphenalen-3a-ium-1-olate **2** (R = Ph) and described a dipolar cycloaddition of this compound [1]. The tricyclic system **1** (R = Ph) was readily constructed by heating 1,2,3,4-tetrahydroquinoline with diethyl phenylmalonate and the mesomeric betaine **2** (R = Ph) was subsequently obtained from compound **1** (R = Ph) in several steps. We were also interested in the preparation of other cross-conjugated mesomeric betaine isomers of the parent heterocycle **2** (R = H), for example derivatives of compound **3** (R = H). A potential synthetic route to derivatives of compound **3** (R = H) might involve the tricyclic system, 8,10-dimethoxy-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-1,5-dione (**4**) (R = OMe) in which the two methoxy groups would eventually provide the two oxygen atoms of the heterocyclic mesomeric betaine **3** (R = H). This paper describes the synthesis of 2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-1,5-dione derivatives **9** and **10**. 2,3-Dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-1,5-dione **4** (R = H) has been reported previously and this compound was obtained in moderate yield by heating 2-(2-carboxyethylamino)cinnamic acid with polyphosphoric acid [2]. The 6-(4-methoxyphenyl) derivative of heterocycle **4** (R = OMe) has been reported as part of a study of the anti-tumor activity of 3-aryl-2-quinolone derivatives [3].

Cyanoethylation of 5,7-dimethoxy-4-methylquinol-2-one **5** [4] using acrylonitrile in the presence of tetrabutylammonium hydroxide afforded the cyano derivative **6** in good yield (80 %). When compound **6** was heated with dilute sulphuric acid at 110°, the carboxylic acid derivative **7** was formed in 94 % yield rather than the tricyclic product **10**. It had been anticipated that the acid **7**, once formed, would undergo cyclisation onto the electron-rich dimethoxy-substituted ring but the proton nmr spectrum of the reaction product showed three aromatic signals indicating that cyclisation had not occurred. However, compound **10** could be prepared in 63 % yield from the acid derivative **7** when it was heated with a mixture of phosphoric acid and phosphorus pentoxide in hot toluene. Thus, the proton nmr spectrum of compound **10** showed only two aromatic signals indicating the desired reaction had occurred. Other cyclisation reagents were also investigated. In an attempt to induce cyclisation directly, compound **6** was heated with 49 % hydrobromic acid. However, under these conditions both cyclisation and demethylation occurred concomitantly and the phenolic derivative **9** was produced in 91 % yield. Milder conditions that might effect cyclisation were also



investigated. Thus, treatment of the cyano derivative **6** with a mixture of zinc dichloride and hydrogen chloride gas in acetic acid gave the amide **7** in 77 % yield rather than the tricyclic compound **10**. Amide **7** could be dehydrated with phosphorus pentoxide in boiling toluene giving the heterocyle **11** (36 % yield).

In conclusion, various conditions have been investigated in order to convert the cyano derivative **6** into the tricyclic derivatives **9** and **10**. The dimethoxy derivative **10** is available *via* the carboxylic acid **6** whereas the dihydroxy derivative **9** can be prepared directly from compound **6**. Cyclodehydration of the amide **8** afforded the 1,2-dihydropyimido[1,2-*a*]quinolin-3-one derivative **11**.

EXPERIMENTAL

3-(5,7-Dimethoxy-4-methyl-2-oxo-2*H*-quinolin-1-yl)propionitrile (**6**).

A mixture of 5,7-dimethoxy-4-methylquinolin-2-one (**5**) [4] (0.2 g, 0.9 mmol), acrylonitrile (0.4 mL, 6.0 mmol) and 40 % tetrabutylammonium hydroxide (2 drops) in dimethoxymethane (5 mL) was heated (0.5 hour) under reflux with stirring. After cooling to room temperature, the mixture was filtered and the white solid (0.3 g) was washed with ether and recrystallised from ethanol giving compound **6** (0.2 g, 80 %), mp 188°. Compound **6** had: ir (chloroform)1650 and 1610 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 6.94 (s, 2H, Ar-H), 6.79 (s, 1H, Ar-H), 5.01 (t, 2H, J = 7 Hz, $-CH_2-$), 4.07 (s, 6H, $-OCH_3$), 3.22 (t, 2H, J = 7 Hz, $-CH_2-$) and 2.96 (s, 3H, $-CH_3$).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.2; H, 5.9; N, 10.3. Found: C, 65.9; H, 5.6; N, 10.4.

3-(5,7-Dimethoxy-4-methyl-2-oxo-2*H*-quinolin-1-yl)propionic Acid (**7**) and 8,10-Dimethoxy-2,3-dihydro-7-methyl-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-1,5-dione (**10**).

A mixture of compound **6** (1.5 g, 5.5 mmol) and dilute sulphuric acid (5 *M*, 40 mL) was heated on a steam bath (2 hours) and then allowed to cool to room temperature. The colorless needles were collected and dried under high vacuum yielding compound **7** (1.5 g, 94 %), mp 116-119° (from acetic acid). Compound **7** had: ir (KBr) 2410 (broad) and 1735 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 7.03 (s, 1H, Ar-H), 6.98 (s, 1H, Ar-H), 6.68 (s, 1H, Ar-H), 5.05 (2H, t, J = 6 Hz, $-CH_2-$), 4.10 (s, 6H, $-OCH_3$), 3.18 (t, 2H, J = 6 Hz, $-CH_2-$) and 2.99 (s, 3H, $-CH_3$); ms: m/z 291 (50) and 219 (100). Compound **7** was cyclised directly to compound **10** as follows. Compound **7** (0.6 g, 2.1 mmol) was added to a mixture of phosphorus pentoxide (0.9 g) and phosphoric acid (4 mL). The mixture was heated (2 hours) at 100° (oil-bath) with protection from moisture (calcium chloride guard tube). The pale orange mixture was allowed to cool to room temperature and was then cooled in an ice-bath. Ice-cold dilute sodium hydroxide solution was then added cautiously and the cream coloured precipitate was collected and washed with water. The solid was partitioned between chloroform and dilute sodium hydroxide solution. The aqueous layer was extracted three times with chloroform and the combined chloroform extracts were washed with water, dried (magnesium sulfate) and evaporated giving compound **10** (0.35 g, 63 %) as a white solid, mp 259-261° (from acetone). Compound **10** had: ir (chloroform) 1680, 1660, 1580, 1470 and 1360 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 7.02 (s, 1H, Ar-H), 6.73 (s, 1H, Ar-H), 4.80 (t, 2H, J = 7 Hz, $-CH_2-$), 4.19 (s, 3H, $-OCH_3$), 4.17 (s, 3H, $-OCH_3$), 3.08 (t, 2H, J = 7 Hz, $-CH_2-$) and 2.89 (s, 3H, $-CH_3$); ms: m/z 273 (100).

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.9; H, 5.5; N, 5.1. Found: C, 65.7; H, 5.5; N, 4.8.

3-(5,7-Dimethoxy-4-methyl-2-oxo-2*H*-quinolin-1-yl)propionamide (**8**).

A suspension of compound **6** (0.85 g, 3.1 mmol) and zinc dichloride (0.85 g, 6.3 mmol) in acetic acid (10 mL) was saturated with hydrogen chloride gas. The mixture was allowed to stand at room temperature overnight, diluted with water and extracted four times with chloroform. The organic extracts were dried (sodium sulfate) and evaporated giving a yellow oil. Ether was added to the oil and compound **8** precipitated as a white solid (0.7 g, 77 %), mp 211-214°. Compound **8** had: ir (potassium bromide) 3410, 3130, 1690, 1640, 1610, 1590, 1395, 1270 and 1160 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 7.74 (broad s, 2H, $-CONH_2$), 7.04 (s, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 6.82 (s, 1H, Ar-H), 5.03 (t, 2H, J = 6 Hz, $-CH_2-$), 4.09 (s, 6H, $-OCH_3$), 3.15 (t, 2H, J = 6 Hz, $-CH_2-$) and 2.97 (s, 3H, $-CH_3$); ms: m/z 290 (30) and 219 (100).

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.1; H, 6.3; N, 9.7. Found: C, 61.7; H, 6.2; N, 9.7.

8,10-Dihydroxy-2,3-dihydro-7-methyl-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-1,5-dione (**9**).

Compound **6** (0.5 g, 1.84 mmol) and 49 % hydrobromic acid (15 mL) were heated under reflux (oil-bath) overnight. The mixture was allowed to cool to room temperature and then cooled in ice. The purple solid was collected, washed with a little 49 % hydrobromic acid and then water and dried under vacuum over phosphorous pentoxide giving compound **9** (0.41 g, 91 %) as a pale red solid, mp >300°. Compound **9** had: ir (potassium bromide) 3100 and 1660-1560 (broad) cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 7.22 (s, 1H, Ar-H), 6.83 (s, 1H, Ar-H), 4.96 (t, 2H, J = 6 Hz, $-CH_2-$), 3.30 (t, 2H, J = 6 Hz, $-CH_2-$) and 3.06 (s, 3H, $-CH_3$); ms: m/z calc. for $C_{13}H_{11}NO_4$: 245.0688. Found: 245.0678. Compound **9** gave a dibenzoate, mp 237° (with decomposition) (from acetone).

Anal. Calcd. for $C_{27}H_{19}NO_6$: C, 71.5; H, 4.2; N, 3.1. Found: C, 71.6; H, 4.4; N, 3.2.

1,2-Dihydro-7,9-dimethoxy-6-methylpyimido[1,2-*a*]quinolin-3-one (**11**).

A mixture of amide **8** (0.3 g, 1.0 mmol) and phosphorous pentoxide (0.4 g) in dry toluene was heated under reflux (oil-bath) overnight protected from moisture (calcium chloride guard tube). The mixture was allowed to cool to room temperature and was diluted with chloroform. The organic solution was decanted from the red residue and evaporated giving compound **11** (0.1 g, 36 %) as a cream solid, mp 188-189° (from toluene). Compound **11** had: ir: (chloroform) 1650 and 1610 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.54 (s, 1H, Ar-H), 6.32 (s, 1H, Ar-H), 6.27 (s, 1H, Ar-H), 4.54 (t, 2H, J = 6 Hz, $-CH_2-$), 3.94 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-OCH_3$), 2.80 (t, 2H, J = 6 Hz, $-CH_2-$) and 2.58 (s, 3H, $-CH_3$); ms: m/z 272 (80) and 219 (100).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.1; H, 5.9; N, 10.3. Found: C, 65.8; H, 5.8; N, 10.0.

REFERENCES AND NOTES

[1] W. D. Ollis, S. P. Stanforth and B. J. Price, *J. Chem. Soc., Perkin Trans 1*, 1501 (1992).

[2] G. F. Katekar, *Aust. J. Chem*., **25**, 1283 (1972).

[3] B. Joseph, F. Darro, A. Béhard, B. Lesur, F. Collignon, C. Decaestecker, A. Frydman, G. Guillaumet and R. Kiss, *J. Med. Chem*., **45**, 2543 (2002).

[4] W. M. F. Fabian, K. S. Niederreiter, G. Uray and W. Stadlbauer, *J. Mol. Struct*., **477**, 209 (1999).