Angular to Linear Rearrangement of an Isoindolo[2,1-*a*]quinazoline Skeleton

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Received April 28, 1994

Demethylation of the angular 3-methoxyisoindolo[2,1-*a*]quinazolin-11(5*H*)-one by pyridinium chloride led to the rearranged linear 8-hydroxyisoindolo[1,2-*b*]quinazolin-12(10*H*)-one.

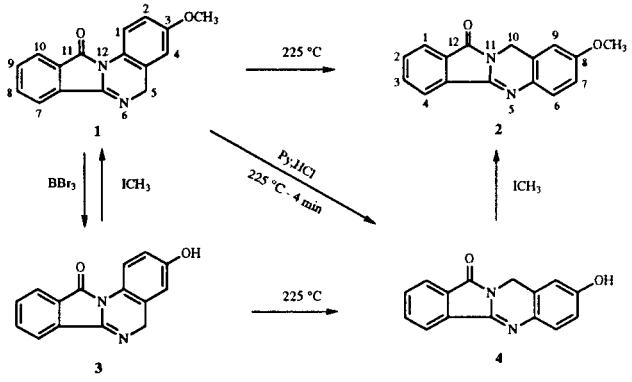
J. Heterocyclic Chem., **31**, 1297 (1994).

In the context of our work concerning isoindoloquinazoline derivatives of biological interest, we recently needed to prepare some novel hydroxyisoindolo[2,1-*a*]-quinazolin-11(5*H*)-ones starting from their methoxy precursors.

We observed that demethylation of the angular compound **1**, in refluxing anhydrous pyridinium chloride, exclusively furnished the linear rearranged hydroxyisoindoloquinazolinone **4**. However, the expected angular hydroxy compound **3** was conveniently synthesized in good yields by use of boron tribromide as the dealkylating agent (Scheme 1).

In fact, the rearrangement of the angular isoindolo[2,1-*a*]quinazoline structure was of thermal origin. We have checked that both methoxy and hydroxy compounds **1** and **3** respectively, underwent a transformation to their linear isomers **2** and **4** respectively at 225°, near from the temperature of boiling pyridinium chloride. At this temperature, the angular hydroxy compounds were transformed twice as quick as their methoxy analogs.

Scheme 1

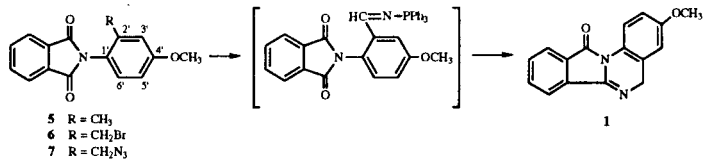


A similar thermal rearrangement has already been observed by Kurihara [1] in the case of an isoindolo[2,1-*a*]quinazoline-5,11-dione, but at a higher temperature (270°) than that required in the case of the monooxo compounds described here.

The structures of the angular and linear isomers were easily differentiated by comparison of the nmr chemical shifts of H_1 (angular) and H_6 (linear) protons [1].

Starting from the 3-methoxyisoindolo[2,1-*a*]quinazoline **1**, easily accessible through an intramolecular aza-Wittig reaction [2,3] (Scheme 2), it is therefore possible to obtain, in good yields, either the angular or the linear hydroxy compounds **3** or **4** by selecting the appropriate dealkylating agent.

Scheme 2



5 R = CH_3
6 R = CH_2Br
7 R = CH_2N_3

EXPERIMENTAL

Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. The nmr spectra were recorded at 90 MHz (Varian EM 390) and tetramethylsilane was used as internal reference. The ir spectra were recorded on a Perkin Elmer 1720 spectrometer. The mass spectra were determined on a Ribermag R10-10C apparatus either under 70 eV electron impact (EI) or chemical ionization (CI) techniques. Commercially available reagents and solvents were used without further purification. The yields indicated are the average of at least two experiments.

2-(4-Methoxy-2-methylphenyl)-1*H*-isoindole-1,3(2*H*)-dione (**5**).

A mixture of phthalic anhydride (7.4 g, 50 mmoles) and commercial 4-methoxy-2-methylaniline (7.2 g, 52 mmoles) in acetic anhydride (50 ml) was refluxed for five hours. The mixture was then poured into water and the resulting precipitate was filtered off, carefully washed with water, dried, and recrystallized from ethanol. Compound **5** (12 g, 90%), white bright needles, had mp 146-147° (lit. [4] mp 158-159°); ^1H nmr (deuteriochloroform): δ 2.16 (s, CH_3), 3.83 (s, OCH_3), 6.83-6.86 (m, $H_{3'}$ and $H_{5'}$), 7.10 (d, $H_{6'}$, J_o = 9 Hz), 7.66-8.00 (m, 4H arom); ir (deuteriochloroform): ν 1724 (C=O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.74; H, 5.09; N, 5.15.

2-[(2-Bromomethyl)-4-methoxyphenyl]-1*H*-isoindole-1,3(2*H*)-dione (**6**).

A suspension of the isoindole-1,3-dione **5** (5.35 g, 20 mmoles), *N*-bromosuccinimide (3.9 g, 22 mmoles) and benzoyl

peroxide (25 mg, 0.1 mmole) in dry carbon tetrachloride (70 ml) was refluxed, with stirring, under exposure of a 150 W tungsten lamp, for eight hours. After cooling, the reaction mixture was poured into water and extracted with dichloromethane. The organic phase was washed with water, dried (magnesium sulfate), and the solvent eliminated under reduced pressure. The crude product was purified by three successive crystallizations from ethanol to give **6** (2.8 g, 40%), cream-coloured crystals, mp 182-183°; ^{1}H nmr (deuteriochloroform): δ 3.86 (s, OCH_3), 4.36 (s, CH_2Br), 6.88-7.33 (m, 3H arom), 7.73-8.06 (m, 4H arom); ir (deuteriochloroform): ν 1726 (C=O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; Br, 23.08; N, 4.05. Found: C, 55.60; H, 3.46; Br, 22.79; N, 4.03.

2-(2-Azidomethyl-4-methoxyphenyl)-1*H*-isoindole-1,3(2*H*)-dione (**7**).

A mixture of the bromomethylated compound **6** (1 g, 2.9 mmoles), sodium azide (0.47 g, 7.25 mmoles), Adogen 464 (0.15 g), toluene (20 ml) and water (10 ml) was refluxed with stirring, for six hours. The organic phase was separated, washed with water, dried (magnesium sulfate), and the solvent evaporated under reduced pressure. The crude product was purified through column chromatography (30 g of 230-400 mesh silica gel, elution with toluene-dichloromethane 1:1) followed by recrystallization from cyclohexane-toluene (9:1). Compound **7** (0.7 g, 80%), cream coloured crystals, had mp 132-133°; ^{1}H nmr (deuteriochloroform): δ 3.85 (s, OCH_3), 4.26 (s, CH_2), 6.86-7.13 (m, H_3, and $H_{5'}$), 7.20 (d, $H_{6'}$, J_o = 8.7 Hz), 7.70-8.01 (m, 4H arom); ir (deuteriochloroform): ν 2105 (N_3), 1729 (C=O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_4O_3$: C, 62.34; H, 3.92; N, 18.17. Found: C, 62.03; H, 3.95; N, 17.93.

3-Methoxyisoindolo[2,1-*a*]quinazolin-11(5*H*)-one (**1**).

Method A. By Intramolecular Aza-Wittig Reaction.

A solution of the azide **7** (5 g, 16 mmoles) and triphenylphosphine (4.2 g, 16 mmoles) in dry toluene (50 ml) was refluxed with stirring for four hours. After cooling, the crude solid was separated by filtration and purified by recrystallization from toluene. The isoindoloquinazoline **1** (3 g, 71%), pale yellow needles, had mp 205-206°; ^{1}H nmr (deuteriochloroform): δ 3.81 (s, OCH_3), 5.06 (s, CH_2), 6.66 (d, H_4, J_m = 3 Hz), 6.85 (dd, H_2, J_o = 9 Hz), 7.61-8.06 (m, H_7, H_8, H_9, H_{10}), 8.60 (d, H_1); ir (deuteriochloroform): ν 1729 (C=O), 1686 (C=N) cm^{-1}; ms: (EI) m/z (%) 264 (M^+, 80), 220 (40), 192 (40), 130 (30), 102 (100).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.49; H, 4.62; N, 10.53.

Method B. By Methylation of **3**.

To a solution of hydroxyquinazolinone **3** (0.25 g, 1 mmole) in butanone (10 ml) are successively added methyl iodide (0.2 g, 1.5 mmoles) and potassium carbonate (0.21 g, 1.5 mmoles). After refluxing for eight hours, the usual work-up furnished 0.2 g (75%) of **1**.

Demethylation of **1** with Pyridinium Chloride.

A mixture of methoxy compound **1** (4.7 g, 18 mmoles) and anhydrous pyridinium chloride (24 g, 207 mmoles) was refluxed for four minutes, then immediately poured into ice-water (200 ml). The precipitate was separated by filtration, carefully washed with cold water, dried, and chromatographed (100 g of 70-200 mesh silica gel, elution with dichloromethane-methanol 99.5:0.5) furnishing the rearranged hydroxy compound **4** (2.8 g, 63%), as yellow crystals (chlorobenzene-dimethylformamide 9:1), mp (projection) 295-296° ; ^{1}H nmr (DMSO-d_6) : δ 4.86 (s, CH_2), 6.63-6.83 (m, H_7 and H_9), 7.26 (d, H_6, J_o = 9 Hz), 7.65-8.06 (m, 4H arom), 9.80 (bs, OH); ir (potassium bromide): ν 3449 (OH), 1733 (C=O), 1642 (C=N) cm^{-1}; ms: (CI) m/z (%) 251 ([M + H]$^+$, 100).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 71.77; H, 4.11; N, 11.20.

Demethylation of **1** with Boron Tribromide.

To a stirred and cooled (-70°) solution of methoxy compound **1** (1.5 g, 5.7 mmoles) in dichloromethane (75 ml), was added, under an argon atmosphere, a commercial 1*M* boron tribromide solution in dichloromethane (38 ml, 28.4 mmoles) *via* a syringe. After one hour at -70°, the mixture was stirred at room temperature during five hours. The reaction mixture was then quenched by addition of water (100 ml) and the solid formed was separated by filtration, washed with water, dried, and recrystallised from chlorobenzene-dimethylformamide (9:1). The angular hydroxy compound **3** (1.2 g, 85%), fine yellow needles, had mp (projection) 290-291°; ^{1}H nmr (DMSO-d_6) : δ 4.96 (s, CH_2), 6.63 (d, H_4, J_m = 2.4 Hz), 6.70 (dd, H_2), 7.63-8.00 (m, H_7, H_8, H_9, H_{10}), 8.36 (d, H_1, J_o = 9 Hz), 9.50 (bs, OH); ir (potassium bromide): ν 3249 (OH), 1736 and 1713 (C=O), 1677 (C=N) cm^{-1}; ms: (CI) m/z (%) 251 ([M + H]$^+$, 100).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 71.69; H, 3.95; N, 10.91.

8-Methoxyisoindolo[1,2-*b*]quinazoline-12(10*H*)-one **2**.

This compound was prepared by methylation of crude **4** (0.25 g, 1 mmole) according to method B reported for synthesis of compound **1** using methyl iodide (0.21 g, 1.5 mmoles), and potassium carbonate (0.207 g, 1.5 mmoles) in butanone (10 ml). The crude product was chromatographed on silica gel (230-400 mesh, elution with dichloromethane), to give **2** (49%) which was further recrystallized from toluene (yellow needles), mp 203-204°; ^{1}H nmr (deuteriochloroform): δ 3.86 (s, OCH_3), 4.98 (s, CH_2), 6.73 (d, H_9, J_m = 2,4 Hz), 6.86 (dd, H_7, J_o = 9 Hz), 7.46 (d, H_6), 7.63-8.20 (m, H_1, H_2 , H_3, H_4); ir (deuteriochloroform): ν 1724 (C=O), 1650 (C=N) cm^{-1}; ms: (CI) m/z (%) 265 ([M + H]$^+$, 100).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.75; H, 4.68; N, 10.50.

Thermal Rearrangements of Compounds **1** and **3**.

Compounds **1** or **3** (50 mg), placed in a test tube, was immersed in an oil bath regulated at 225°, during four minutes. The ^{1}H nmr analysis of the crude products indicated a total rearrangement of the hydroxy compound **3** into its linear isomer **4**. On the other hand, in the case of the methoxy derivative **1**, only 50% of the starting material was rearranged to **2**, in a similar manner.

REFERENCES AND NOTES

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