Monatshefte für Chemie 121, 1017–1021 (1990)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Some Fused Quinoline Derivatives

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Summary. Preparations of the novel fused dimethoxyquinoline derivatives of furo[2,3-b]quinoline (**5**), *s*-triazolo[4,3-a]quinoline (**8**) and tetrazolo[1,5-a]quinoline (**10**) from 6,7-dimethoxy-3-carboxyquinoline-1-oxide (**1**) are reported.

Keywords. O-alkylation; Furoquinoline; Nucleophilic displacement; *s*-Triazoloquinoline; Tetrazoloquinoline.

Synthese kondensierter Chinolinderivate

Zusammenfassung. Die Synthese der neuen kondensierten Dimethoxy-Chinolinderivate Furo[2,3-b]chinolin (**5**), *s*-Triazolo[4,3-a]chinolin (**8**) und Tetrazolo[1,5-a]chinolin (**10**) aus 6,7-Dimethoxy-3-carboxychinolin-1-oxid (**1**) wird beschrieben.

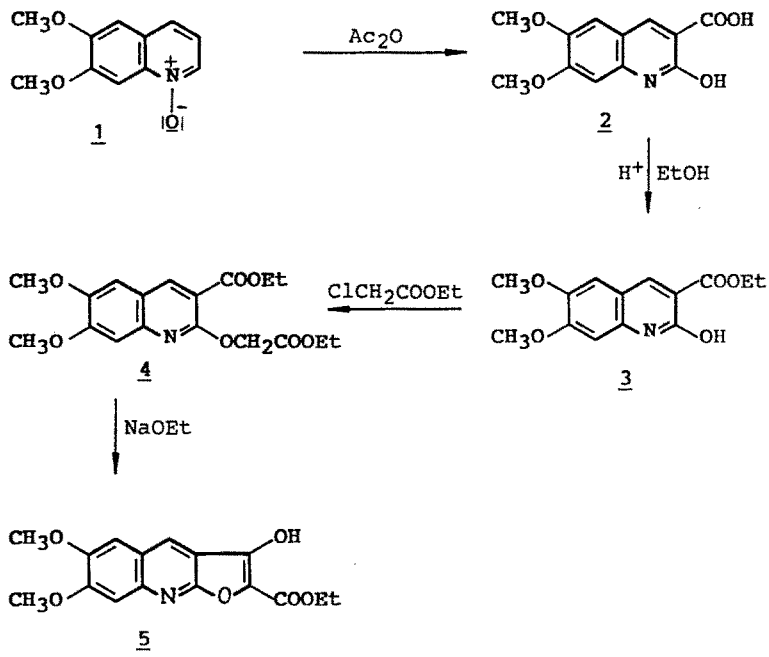
Introduction

Quinolines represent important building moieties in a variety of valuable drugs [1–4]. Moreover, efforts involving the syntheses and investigations of the biological activity of fused quinoline derivatives have been undertaken [5–7]. As part of a continuing interest in the chemistry of alkoxyquinolines [8], the present paper deals with the syntheses of several fused quinoline derivatives as possible chemotherapeutic agents.

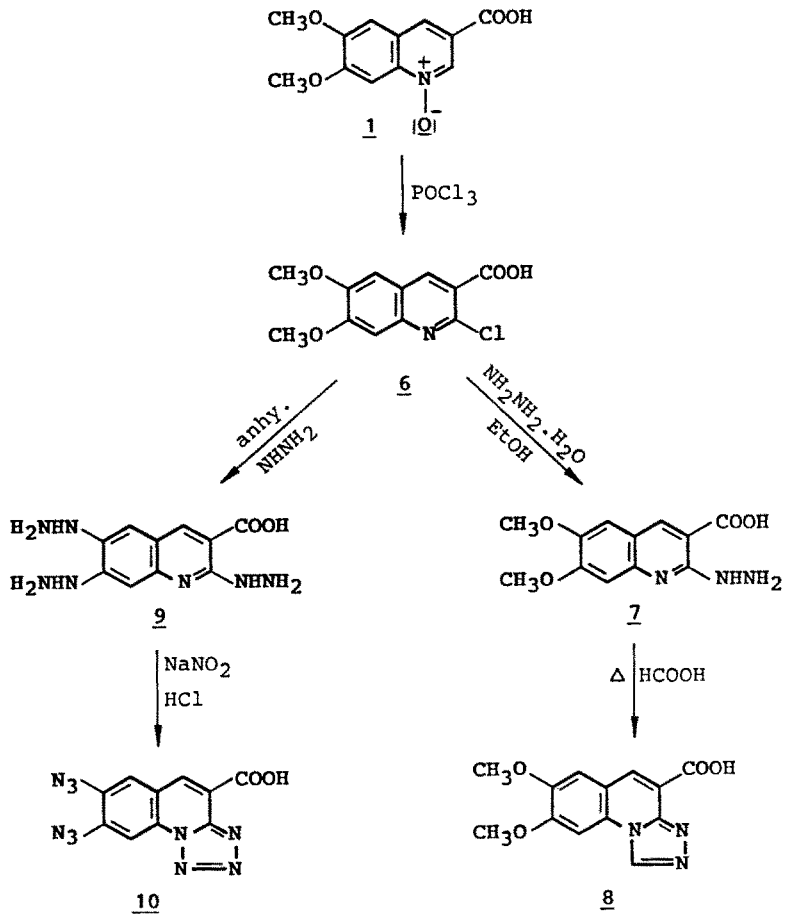
Results and Discussion

In order to prepare the desired fused quinolines **5**, **8**, and **10**, the parent compound 6,7-dimethoxy-3-carboxyquinoline-1-oxide (**1**) had to be synthesized from veratraldehyde by means of Stobbe condensation [9, 10], nitration [11], and cyclization [12]. The hydroxy acid **2** was prepared according to [12] by heating **1** with acetic anhydride. Esterification of the acid **2** with ethanol in presence of 3% sulphuric acid [12] gave 6,7-dimethoxy-3-ethoxycarbonyl-2-hydroxyquinoline (**3**).

A useful approach to the synthesis of the desired furo[2,3-b]quinoline **5** is shown in Scheme 1. The ester **3** was O-alkylated with ethyl chloroacetate in refluxing acetone in presence of potassium carbonate to give the diester **4**. Compound **4** was then treated with sodium ethoxide in refluxing toluene to afford **5**.



Scheme 1



Scheme 2

The preparation of 7,8-dimethoxy-*s*-triazolo[4,3-a]quinoline-4-carboxylic acid (**9**) required the formation of the 2-chloro-derivative **6** which was obtained from **1** with phosphorus oxychloride (Scheme 2). Similar chloro-derivatives, e.g. 2-chloropyridines [13] and 3-chloropyridazine [14], have been reported to undergo nucleophilic displacement of the Cl-atom by hydrazine. Consequently the 2-chloro derivative **6** was allowed to react with hydrazine hydrate in ethanol for 3 h. The expected hydrazide **7** was obtained in good yield. The desired triazoloquinoline **8** was obtained by heating **7** with formic acid by a method similar to that described in Ref. [15] for the preparation of *s*-triazolo[1,5-c]benzothienopyridine.

Interestingly, it was reported by Eisa et al. [16] that the 4-methoxy group in pyrido[3,2-d]pyrimidines is readily susceptible to nucleophilic displacement by hydrazine. Thus, it seemed to be interesting to study the effect of anhydrous hydrazine on 2-chloro-6,7-dimethoxyquinoline-3-carboxylic acid (**6**). Heating **6** with excess anhydrous hydrazine afforded an orange product in good yield. This product was assigned to structure **9** (Scheme 2) by means of elemental analysis and its ^{1}H-nmr spectrum which confirmed the disappearance of the two methoxy signals. Treatment of **9** with nitrous acid resulted in the formation of the tetrazoloquinoline **10** in a similar procedure as that reported earlier [16] for the synthesis of tetrazolo[1,5-c]pyridopyrimidine carbonylazides.

Experimental

Melting points (uncorrected) were determined using a Fisher Johns melting point apparatus. ^{1}H-nmr spectra were determined using a JEOL FX 90 Q Spectrometer using *DMSO-d_6* as a solvent and *TMS* as internal standard (chemical shift in δ, ppm). Analytical data (C, H, N) were within ± 0.4% of the theoretical values.

Ethyl 2-(6,7-dimethoxy-3-ethoxycarbonyl-2-quinolinyloxy)acetate (**4**)

A mixture of compound **1** [12] (2.65 g, 0.01 mol), ethylchloroacetate (1.2 g, 0.01 mol) and anhydrous potassium carbonate (2 g) in dry acetone (20 ml) was refluxed with stirring for 15 h. After cooling the inorganic materials were filtered and the filtrate was dissolved in chloroform (20 ml) washed with water and dried ($MgSO_4$). Chloroform was removed under reduced pressure to give a creamy powder. Recrystallization from ethanol/chloroform. Yield: 1.8 g (47%); m.p. 235–237°; ^{1}H-nmr: 1.20 (t, 3 H, CH_3), 1.40 (t, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.20 (q, 2 H, CH_2CH_3), 4.40 (q, 2 H, CH_2CH_3), 4.60 (s, 2 H, OCH_2–), 7.2–8.1 (m, 3 H, H-4, H-5, H-8). $C_{18}H_{21}NO_7$ (363.37).

Ethyl 6,7-dimethoxy-3-hydroxyfuro[2,3-b]quinoline-2-carboxylate (**5**)

A mixture of compound **4** (0.5 g, 0.001 mol), sodium ethoxide (0.13 g, 0.002 mol) in toluene (30 ml) was refluxed with stirring for 18 h. After cooling the crystalline precipitate was filtered, dried, then dissolved in water (20 ml) and acidified with acetic acid. The product formed was filtered, dried, and crystallized from ethanol to give a yellow powder. Yield: 0.12 g (28%); m.p. >290°; ^{1}H-nmr: 1.40 (t, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.40 (q, 2 H, CH_2), 7.2–8.3 (m, 3 H, H-4, H-5, H-8), 13.00 (br.s, 1 H, OH). $C_{16}H_{15}NO_6$ (317.30).

2-Chloro-6,7-dimethoxyquinoline-3-carboxylic acid (**6**)

A mixture of compound **1** (3.0 g, 0.011 mol) and phosphorus oxychloride (20 ml) was heated on a steam bath for 18 h. The reaction mixture was then concentrated under reduced pressure and ice-

cold water (300 ml) was added. The precipitate formed was filtered, washed thoroughly with water and dried to give a yellowish green powder of crude **5** which was then used without further purification. Yield: 2.0 g (63%); m.p. 245–247°.

6,7-Dimethoxy-2-hydrazidoquinoline-3-carboxylic acid (**7**)

Hydrazine hydrate (0.5 g, 0.01 mol) was added to a warm solution of crude **6** (2.6 g, 0.01 mol) in ethanol (20 ml) and the reaction mixture was left at room temperature for 3 h. The separated product was filtered, dried, and recrystallized from aqueous ethanol to afford a yellowish white powder. Yield: 2.0 g (85%); m.p. >290°; ^{1}H-nmr: 3.9 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 4.80 (s, 2 H, NH_2), 7.5–8.2 (m, 3 H, H-4, H-5, H-8), 9.0 (s, 1 H, NH), 9.3 (s, 1 H, COOH). $C_{12}H_{13}N_3O_4$ (263.25).

7,8-Dimethoxy-s-triazolo[4,3-a]quinoline-4-carboxylic acid (**8**)

A mixture of the hydrazide **7** (1.0 g, 0.003 mol) and formic acid (25 ml) was heated for 3 h. The reaction mixture was cooled and poured into water (60 ml). The solid obtained was filtered, dried, and crystallized from aqueous ethanol to give a creamy powder. Yield: 0.7 g (67%); m.p. >290°; ^{1}H-nmr: 3.90 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 7.5–8.2 (m, 3 H, H-5, H-6, H-9), 8.9 (s, 1 H, H-1), 9.3 (s, 1 H, COOH). $C_{13}H_{11}N_3O_4$ (273.25).

2,6,7-Trihydrazidoquinoline-3-carboxylic acid (**9**)

A mixture of (1.5 g, 0.006 mol) of crude **6** and anhydrous hydrazine (10 ml) was refluxed for 6 h and excess hydrazine was removed in vacuo. After cooling, the residue was triturated with ethanol, filtered, and crystallized from ethanol to give an orange powder. Yield: 1.5 g (93%); m.p. >290°: ^{1}H-nmr: 4.8–5.1 (br.s, 6 H, NH_2), 7.6–8.1 (m, 3 H, H-5, H-9), 9.0–9.5 (br.s, 4 H, 3 (NH), COOH). $C_{10}H_{13}N_7O_2$ (263.26).

7,8-Diazidotetrazolo[1,5-a]quinoline-4-carboxylic acid (**10**)

Compound **9** (0.5 g, 0.002 mol) was dissolved in conc. hydrochloric acid (5 ml) and then a solution of sodium nitrite (0.69 g, 0.01 mol) in water (3 ml) was added dropwise over a period 1 h with stirring. The precipitated solid product was filtered, washed with ice-cooled water (10 ml), dried and then washed thoroughly with ether to give a brownish powder. Yield: 0.32 g (57%), m.p. >290°. $C_{10}H_4N_{10}O_2$ (296.21).

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Received March 17, 1990. Accepted June 22, 1990