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2-CHLORO-3-QUINOLINECARBOXALDEHYDE IN THE SYNTHESIS OF CONDENSED QUINOLINE SYSTEMS. 1. SYNTHESIS OF DERIVATIVES OF 3,4-DIHYDRO-2H-[1,3]THIAZINO[6,5-*b*]QUINOLINES

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A method for the synthesis of derivatives of previously unknown heterocyclic systems – 3,4-dihydro-2H-[1,3]thiazino[6,5-b]quinolines – has been developed based on 7,8-dimethyl-2-chloro-3-quinolinecarboxaldehyde via the consecutive steps of conversion into its Schiff's base with a primary amine, reduction to the corresponding aminomethyl derivative, conversion to the thiourea with isothiocyanates, and heterocyclization by intramolecular substitution of the chlorine atom.

Keywords: 3,4-dihydro-2H-[1,3]thiazino[6,5-*b*]quinolines, 2-methoxyethylamine, Schiff's base, thiourea, intramolecular nucleophilic cyclization.

Systems based on the quinoline unit annelated to partially substituted heterocycle are of considerable interest to study for possible biological activity. We have shown previously that the synthesis of one such system – 4,5-dihydro[1,4]oxazepino[7,6-*b*]quinolines-3 – is readily achieved based on 3-aminomethyl-quinolones-2 [1].

The objective of the present study is the development of a method for the synthesis of the previously unknown dihydrothiazinoquinoline system. Our proposed synthesis is based on a method used for the preparation of pyridothiazines, in which the key step is the heterocyclization of the isothiuronium salt under the influence of sodium ethoxide with the intramolecular nucleophilic substitution of the mobile chlorine atom in position 2 of the pyridine ring [2]. However there is no information in the literature of the use of quinoline structures in similar syntheses. We have used substituted 2-chloro-3-quinolinecarboxaldehydes [3], which are suitable universal synthons for the construction of condensed heterocycles [4, 5], as the initial quinoline structure for the synthesis of dihydrothiazinoquinolines. We have proposed the following sequence of reactions for the synthesis of derivatives dihydrothiazinoquinoline systems (Scheme 1).

This sequence includes the formation of the Schiff's base of aldehyde **1** with a primary amine, its reduction to the corresponding aminomethyl derivative **2**, which is converted to the thioureas **3** by reaction with isothiocyanates. Cyclization of these thioureas in the presence of KOH in ethanol leads to the formation of the desired derivatives of dihydrothiazinoquinoline **4**. Since the objective of the study is not strictly the synthesis of new heterocyclic systems, but the most promising materials with respect to biological activity, we used 2-methoxyethylamine as the primary amine. The choice of this model was determined by calculation of molecular parameters satisfying the Lipinski parameters [6, 7] for compounds possessing biological activity (log P, the number of freely rotating bonds, the type and bonding of heteroatoms in the molecule, etc.) The best results were obtained for the amine $NH_2(CH_2)_2OMe$.

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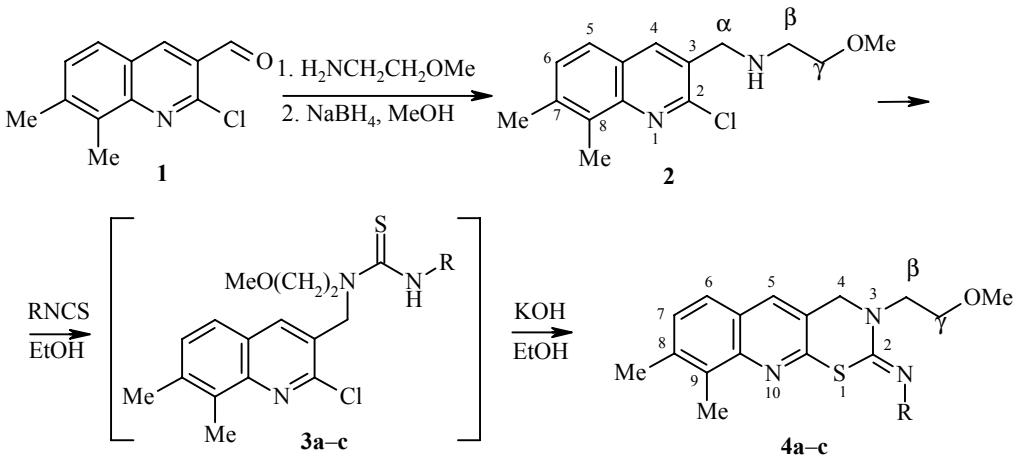
Scheme 1



3, **4 a** R = Me, **b** R = CH_2Ph, **c** R = 4-MeC_6H_4

The synthesis of amines **2** needed to be carried out under mild conditions because reaction of the 2-chloro-3-quinolinecarboxaldehyde **1** with a primary amine could give not only the Schiff's base which we required but also the undesirable substitution of the labile chlorine atom at position of the quinoline substrate. Best results were obtained by carrying out the reaction in ethanol with an equivalent amount of triethyl orthoformate as dehydrating agent. The Schiff 's bases obtained in this way were readily reduced by $NaBH_4$ in methanol to the corresponding amines, which are of interest in their own right both from the point of view of biological activity and from the point of view of their use for the synthesis of combinatorial libraries of derivatives.

It is evident that the interaction of the amine with isothiocyanates initially forms the thioureas **3** which we isolated and characterised. However our choice of reaction conditions led to cyclization in the presence of KOH without isolation which improved the synthetic method. The rate and completion of the reaction depended little on the structure of the isothiocyanates, which shows that this method is universal for the synthesis of a variety of derivatives in which R may be a substituents of alkyl, benzyl, or phenyl type. Formation of the cyclic structure **4** is indicated by elemental analysis of the products (Table 1) and the ^{1}H NMR spectra (Table 2). When the cyclic structures are formed the ^{1}H NMR spectra of compounds **4** show shifts of the protons of the 4-, β-, and γ-methylene groups to weaker fields in comparison with spectra of the alicyclic starting materials **2**. The largest shifts are observed for protons 4-H (α-H of structures **2**) and γ-H, by 0.85 and 0.95 ppm respectively, while the signals of the β-protons are shifted by approximately 0.65 ppm. These changes can serve as spectral criteria for the formation of a cyclic structure.

TABLE 1. Characteristics of Compounds **2**, **4a-c**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent)	Yield, %
		C	H	N		
2	$C_{15}H_{19}ClN_2O$	64.87 / 64.63	7.04 / 6.87	10.15 / 10.05	58-61 (aq. ethanol)	94
4a	$C_{17}H_{21}N_3OS$	65.30 / 64.73	6.76 / 6.71	13.70 / 13.32	105 (subl.) 127-129 (ethanol)	65
4b	$C_{23}H_{25}N_3OS$	70.77 / 70.56	6.47 / 6.44	10.77 / 10.73	120-122 (ethanol)	89
4c	$C_{23}H_{25}N_3OS$	70.98 / 70.56	6.77 / 6.44	11.07 / 10.73	136-138 (ethanol)	92

TABLE 2. ^{1}H NMR Spectra of Compounds **2**, **4a-c**

Com-pound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
2	2.25 (1H, br. s, NH); 2.45 and 2.61 (2×3H, 2 s, 7- and 8-Me); 2.75 (2H, t, β-H); 3.25 (3H, s, OMe); 3.44 (2H, t, γ-H); 3.92 (2H, s, α-H); 7.45 (1H, d, J_{56} = 10, 5-H); 7.73 (1H, d, J_{65} = 10, 6-H); 8.34 (1H, s, 4-H)
4a	2.43 and 2.62 (2×3H, 2 s, 8- and 9-Me); 3.28 (3H, s, OMe); 3.70 (2H, t, β-H); 3.86 (3H, s, =N–Me); 4.18 (2H, t, γ-H); 4.78 (2H, s, 4-H); 7.30 (1H, d, J_{76} = 10, 7-H); 7.61 (1H, d, J_{67} = 10, 6-H); 8.05 (1H, s, 5-H)
4b	2.38 and 2.42 (2×3H, 2 s, 8- and 9-Me); 3.32 (3H, s, OMe); 3.75 (2H, t, β-H); 4.25 (2H, t, γ-H); 4.87 (2H, s, 4-H); 6.12 (2H, s, $\underline{CH_2}$Ph); 7.13-7.29 (5H, m, Ph); 7.34 (1H, d, J_{76} = 10, 7-H); 7.58 (1H, d, J_{67} = 10, 6-H); 8.05 (1H, s, 5-H)
4c	2.30, 2.44 and 2.53 (2×3H, 3 s, 8-, 9-Me and $\underline{Me}C_6H_4$); 3.28 (3H, s, OMe); 3.65 (2H, t, β-H); 3.87 (2H, t, γ-H); 4.65 (2H, s, 4-H); 6.71 (2H, d, *J* = 10, 3'-, 5'-H), 7.12 (2H, d, *J* = 10, 2'-, 6'-H); 7.40 (1H, d, J_{76} = 10, 7-H); 7.68 (1H, d, J_{67} = 10, 6-H); 8.18 (1H, s, 5-H)

For isothiocyanates which do not contain halogen, the Beilstein test for halogens is a simple and reliable for monitoring the purity of products **4**. It is positive for the amine starting material but negative for the cyclization products.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker AM-400 (400 MHz) instrument. Purity of the products was controlled by TLC on Sorbfil strips with 20:1 chloroform–methanol as eluent.

Synthesis of starting **2-chloro-7,8-dimethyl-3-quinolinecarboxaldehyde** (**1**) was carried out by a method analogous to that reported in [3].

N-[(2-Chloro-7,8-dimethylquinolin-3-yl)methyl]-2-methoxyethylamine (2). Triethyl orthoformate (1.6 ml, 15.0 mmol) and 2-methoxyethylamine (0.75 ml, 14.0 mmol) were added to a suspension of aldehyde **1** (3 g, 13.6 mmol) in ethanol (30 ml) – the aldehyde dissolved. The reaction mixture was stirred for 2 h at 50°C. The precipitate which deposited on cooling was filtered off and washed with ethanol (2 × 10 ml). The Schiff's base obtained in this way was reduced without further purification by sodium borohydride (0.76 g, 20 mmol) in methanol (50 ml). The solvent was removed in vacuum and the residue was treated with water (50 ml). The crystals which separated were filtered off, washed with water (2 × 15 ml), and air dried to give amine **2** (3.67 g) which was used in further synthesis without further purification. An analytical sample was obtained by recrystallization from 90% aqueous ethanol.

2-Imino-3-(2-methoxyethyl)-8,9-dimethyl-3,4-dihydro-2H-[1,3]thiazino[6,5-*b*]quinolines (4a-c). The corresponding isothiocyanate (1 mmol) was added to a solution of amine **2** (0.278 g, 1 mmol) in ethanol (3-4 ml). The reaction mixture was boiled for 30 min (controlled by TLC). Potassium hydroxide (0.062 g, 1.1 mmol) was then added and the mixture was boiled for a further 20 min (TLC monitoring). The crystals which separated after cooling were filtered off, washed with water (2 × 5 ml), and recrystallized from ethanol.

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