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SYNTHESIS OF 3,4-DIHYDROBENZO-[*h*]ISOQUINOLINE DERIVATIVES

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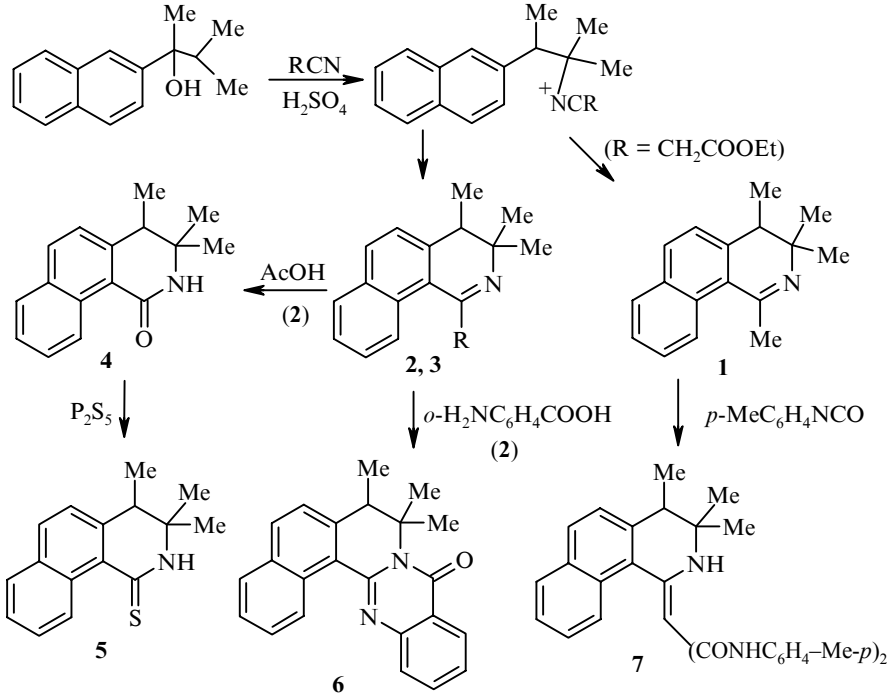
1-Substituted 3,3,4-trimethyl-3,4-dihydrobenzo[h]isoquinolines have been obtained by the reaction of 1,2-dimethyl-1-(2-naphthyl)-1-propanol with nitriles in conc. H_2SO_4. It was shown that the presence of a benzene ring annelated at positions 7 and 8 of the isoquinoline does not influence reaction of the 1-methyl derivative with isocyanate, however reactions of the 1-methylthio derivative with C and N nucleophiles are affected significantly.

Keywords: 3,4-dihydrobenzo[*h*]isoquinolines, 1,2-dimethyl-1-(2-naphthyl)-1-propanol, nitriles, Ritter reaction.

Derivatives of benzo[*f*]isoquinoline are readily formed by the Ritter reaction from the corresponding carbinol and nitrile [1], and cyclization proceeds exclusively at the β-position of the naphthalene ring. It seemed of interest to study the analogous reaction for naphthalenes containing a carbinol substituent at the β-position of the naphthalene ring.



2 R = SMe, **3** R = CH_2CONH_2

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It is not difficult to see that in this case reaction may proceed at positions 1 and 3 of the naphthalene nucleus with the formation of the corresponding benzo[*h*]- and benzo[*g*]isoquinolines.

The investigation showed that the sole reaction products were the 3,4-dihydrobenzo[*h*]isoquinoline derivatives **1-3**, i.e. the carbimmonium ion attacks the most electron-saturated α-position of the naphthalene nucleus.

The 1-methyl derivative **1** obtained possesses mainly the same chemical properties as the 1,3,3-trimethyl-3,4-dihydroisoquinolines. It gives a salt **1a** with salicylic acid and reacts with *p*-tolyl isocyanate with the formation of the biscarbamoyl derivative **7**.

At the same time the influence of the annelated benzene ring was fairly noticeable for reactions of the thiolactim ether **2** in which the isoquinoline fragment acts as an electrophilic reactant. The reaction of compound **2** with morpholine did not proceed in practice at the boiling point of the latter. Only the initial thiolactim ether was isolated after heating for 24 h. The influence of the benzene ring is also displayed in the greater ease of substitution of the methylthio group on carrying out reactions with reactive CH compounds in acetic acid, which is not characteristic of 3,3-dimethyl-1-methylthio-3,4-dihydroisoquinoline and its analogs unsubstituted at position 8. Evidently the electron-donating character of the naphthalene nucleus also contributes to the result observed. As a result of this the charge δ^+ on the carbon atom in position 1 is reduced and in its turn increases the basicity of the ring nitrogen atom. This leads to the formation of the 1-acetoxy-1-methylthio derivative, hydrolysis of which under the reaction conditions leads to the dihydroisocarbostyryl **4**, analogous to that described previously in [2].

On heating thiolactim ether **2** with anthranilic acid in the absence of solvent the corresponding quinazoline derivative **6** is readily formed.

In the ^{1}H NMR spectra of compounds **1a-7** a quartet of signals was observed for the proton at position 4 and a doublet for the protons of the methyl group at position 4, but for compounds **2**, **3**, and **6** there were two singlets for the protons of the *gem*-dimethyl groups, which indicates their nonequivalence. It was established by computer analysis of compound **1** that the methyl group at position 1 and the hydrogen atom at position 10 of the aromatic nucleus overlap in coplanar disposition which causes a mutual repulsion of the substituents and as a result emergence of this methyl group from the plane of the ring by an angle of ~22°. This leads to the dihydropyridine nucleus taking the half-boat conformation. The *gem*-dimethyl groups occupy pseudoaxial and pseudoequatorial positions, which is also reflected in the ^{1}H NMR spectra.

In favor of the benzo[*h*]isoquinoline structure for compound **1** there is the presence at 7.41 and 7.93 ppm of two doublets of signals for the protons at positions 5 and 6, which is not possible for the benzo[*g*]isoquinoline structure. In addition, as in the case of 3,4-dihydroisoquinolines with an *exo* double bond at position 1 [2], significant deshielding of the proton at position 10 was observed for the synthesized compounds. This causes significant displacement of its signal towards low field and the size of the displacement depends on the character of the substituent at position 1. For compound **1a** the 10-H signal is found at 8.30 and for compound **2** at 8.86 ppm, but when it is deshielded by an azomethine double bond (compound **6**) the doublet is observed at 9.25 ppm, possibly due to the participation of the unshared electron pair on nitrogen in the deshielding.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrophotometer in Nujol. The ^{1}H NMR spectra were taken on a Bruker AM 300 (300 MHz) spectrometer in DMSO-d_6 with TMS as internal standard. The progress of reactions and the purity of the compounds obtained were checked by TLC (Silufol UV 254, chloroform–acetone, 9:1, visualization was with 0.5% chloranil solution in toluene).

1,3,3,4-Tetramethyl-3,4-dihydrobenzo[*h*]isoquinoline (1). A mixture of 1,2-dimethyl-1-(2-naphthyl)-1-propanol (21.4 g, 0.1 mol) and cyanoacetic ester (11.3 g, 0.1 mol) in benzene (20 ml) was added dropwise with stirring and cooling to conc. H_2SO_4 (50 ml). The reaction mixture was stirred for 30 min, diluted with water (200 ml), and the organic layer separated. The acid aqueous layer was washed with benzene (50 ml), the benzene separated, and the aqueous phase heated at 100°C for 2 h. After cooling, the reaction mixture was neutralized with aqueous ammonia to pH 9. The product was extracted with benzene, the extract dried over anhydrous Na_2SO_4, evaporated on a water bath, and compound **1** was obtained in 20% yield. The product was characterized as the salicylate.

Salicylate 1a. A solution of salicylic acid (1.38 g, 0.01 mol) in dry diethyl ether (20 ml) was added in one portion to a solution of compound **1** (2.37 g, 0.1 mol) in dry diethyl ether (10 ml). The mixture was stirred for 1 min, and left for 30 min. The precipitated solid was filtered off, washed on the filter with ether (20 ml), and recrystallized from ethanol. A product (3.6 g, 95%) of mp 122-123°C was obtained. ^{1}H NMR spectrum, δ, ppm: 1.21 (3H, d, $C_{(4)}CH_3$); 1.38 (6H, s, $C_{(3)}(CH_3)_2$); 2.40 (3H, s, $C_{(1)}CH_3$); 2.92 (1H, q, 4-H); 6.74-8.14 (9H, m, H arom.); 8.30 (1H, d, 10-H); 12.14 (1H, br. s, OH phenol).

3,3,4-Trimethyl-1-methylthio-3,4-dihydrobenzo[*h*]isoquinoline (2) was obtained analogously to compound **1** from 1,2-dimethyl-1-(2-naphthyl)-1-propanol and methyl thiocyanate. Yield 38%; mp 49-50°C (ethanol). IR spectrum, ν, cm^{-1}: 1620 (C=N), 1320 (MeS). ^{1}H NMR spectrum, δ, ppm: 1.08 (3H, s, $C_{(3)}CH_3$ pseudoax.); 1.15 (3H, d, $C_{(4)}CH_3$); 1.28 (3H, s, $C_{(3)}CH_3$ pseudoeq.); 2.33 (3H, s, SCH_3); 2.76 (1H, q, 4-H); 7.45-7.95 (5H, m, H arom.); 8.86 (1H, d, 10-H). Found, %: C 75.90; H 7.10; N 5.12; S 11.80. $C_{17}H_{19}NS$. Calculated, %: C 75.84; H 7.60; N 5.20; S 11.90.

(3,3,4-Trimethyl-3,4-dihydrobenzo[*h*]isoquinolin-1-yl)acetamide (3). Cyanoacetamide (1.68 g, 0.02 mol) was dissolved with stirring in cold conc. H_2SO_4 (10 ml) and 1,2-dimethyl-1-(2-naphthyl)-1-propanol (4.28 g, 0.02 mol) was added rapidly in one portion. The mixture was stirred for 15 min, diluted with water (100 ml), and extracted with benzene (20 ml). The organic layer was discarded, and the aqueous made alkaline to pH 8-9. The precipitated solid was separated, washed with water, dried in the air, and recrystallized from hexane. A product (3.08 g, 55%) of mp 166-167°C was obtained. IR spectrum, ν, cm^{-1}: 3200, 3150, 1630 (CONH). ^{1}H NMR spectrum, δ, ppm: 1.07 (3H, s, $C_{(3)}CH_3$ pseudoax.); 1.20 (3H, d, $C_{(4)}CH_3$); 1.28 (3H, s, $C_{(3)}CH_3$ pseudoeq.); 2.82 (1H, q, 4-H); 5.00 (1H, s, $C_{(1)}CH$); 6.25 (2H, s, NH_2); 7.35-7.90 (5H, m, H arom.); 8.53 (1H, d, 10-H); 9.65 (1H, br. s, NH isoquin.). Found, %: C 77.03; H 7.19; N 9.92. $C_{18}H_{20}N_2O$. Calculated, %: C 77.14; H 7.14; N 10.00.

3,3,4-Trimethyl-3,4-dihydrobenzo[*h*]isocarbostyryl (4). A solution of compound **2** (1.35 g, 5 mmol) in CH_3COOH (20 ml) was heated for 2 h, diluted with water (200 ml), and made alkaline to pH 7-8. The precipitated solid was filtered off, dried in the air, and recrystallized from a mixture of benzene–hexane, 1:1. A product (1.08 g, 91%) of mp 181-182°C was obtained. IR spectrum, ν, cm^{-1}: 3170 (N-H), 1660 (C=O), 1595 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.18 (6H, s, $C_{(3)}(CH_3)_2$); 1.27 (3H, d, $C_{(4)}CH_3$); 2.88 (1H, q, 4-H); 7.40-7.58 (5H, m, H arom.); 7.67 (1H, br. s, NH isoquin.); 9.48 (1H, d, 10-H). Found, %: C 80.44; H 7.19; N 5.73. $C_{16}H_{17}NO$. Calculated, %: C 80.33; H 7.11; N 5.86.

3,3,4-Trimethyl-3,4-dihydrobenzo[*h*]thioisocarbostyryl (5). A mixture of compound **4** (2.38 g, 10 mmol) and P_2S_5 (3.33 g, 15 mmol) in dry pyridine (30 ml) was heated for 2 h and then poured into water (150 ml). The solid was separated, dried in the air, and recrystallized from ethanol. A product (2.25 g, 88%) of mp 164-165°C was obtained. IR spectrum, ν, cm^{-1}: 3180 (N-H), 1645 (C=S); 1595 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.29 (3H, d, $C_{(4)}CH_3$); 1.36 (6H, s, $C_{(3)}(CH_3)_2$); 2.88 (1H, q, 4-H); 7.24 (1H, br. s, NH isoquin.); 7.50-7.87 (5H, m, H arom.); 9.55 (1H, d, 10-H). Found, %: C 75.39; H 6.59; N 5.41; S 12.61. $C_{16}H_{17}NS$. Calculated, %: C 75.29; H 6.67; N 5.49; S 12.55.

3,3,4-Trimethyl-3,4-dihydro-1*H*-benzo[*h*]isoquino[1,2-*b*]quinazolin-11-one (6). A mixture of compound **2** (2.56 g, 0.01 mol) and anthranilic acid (1.37 g, 0.01 mol) was heated in a metal bath at 170°C until the disappearance of the spot for the initial compound **2** by TLC. The melt was poured into a mixture of hexane–ethyl

acetate, 3:1. The separated crystals were filtered off, and recrystallized from ethanol. A product (2.0 g, 59%) of mp 189-190°C was obtained. IR spectrum, ν, cm^{-1}: 1658 (C=O), 1587 (C=N). ^1H NMR spectrum, δ, ppm: 1.22 (3H, d, $C_{(4)}CH_3$); 1.43 (3H, s, $C_{(3)}CH_3$ pseudoax.); 1.90 (3H, s, $C_{(3)}CH_3$ pseudoeq.); 3.04 (1H, q, 4-H); 7.40-8.18 (9H, m, H arom.); 9.25 (1H, d, 10-H). Found, %: C 81.29; H 5.76; N 8.36. $C_{23}H_{20}N_2O$. Calculated, %: C 81.18; H 5.88; N 8.24.

3,3,4-Trimethyl-1-[(bis-*p*-tolylcarbamoyl)methylene]-3,4-dihydrobenzo[*h*]isoquinoline (7). A mixture of compound **1** (1.2 g, 5 mmol) and *p*-tolyl isocyanate (1.33 g, 10 mmol) was heated in benzene (50 ml) for 4 h. The benzene was evaporated. The residue was recrystallized from ethanol. A product (1.6 g, 64%) of mp 229-231°C was obtained. IR spectrum, ν, cm^{-1}: 3308, 3212 br, 1636 (CONH). ^1H NMR spectrum, δ, ppm: 1.39 (3H, d, $C_{(4)}CH_3$); 1.56 (6H, s, $C_{(3)}(CH_3)_2$); 2.28 (6H, s, $2CH_3$ tolyl); 3.45 (1H, q, 4-H); 6.70-8.05 (14H, m, H arom.); 10.70 (2H, br. s, NHCO); 11.48 (1H, br. s, NH isoquin.). Found, %: C 78.66; H 6.67; N 8.24. $C_{33}H_{33}N_3O_2$. Calculated, %: C 78.73; H 6.56; N 8.37.

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