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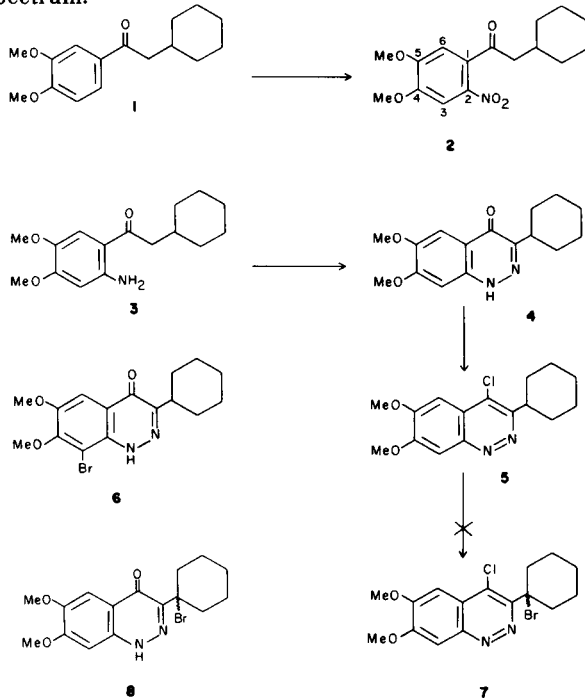
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The synthesis of 3-cyclohexyl-6,7-dimethoxy-1*H*-4-cinnolone (4), 4-chloro-3-cyclohexyl-6,7-dimethoxycinnoline (5) and 8-bromo-3-cyclohexyl-6,7-dimethoxy-1*H*-4-cinnolone (6) are reported.

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We have been interested in the chemistry of cinnolines from a number of points of view (1,4-15) for a number of years. In connection with a program to use cinnolines in the synthesis of other heterocycles, a need for 3-cyclohexylcinnolines arose.

The starting compound, α -cyclohexyl-3,4-dimethoxyacetophenone (1) has been described by Barrio, *et al* (16). Compound 1 was smoothly nitrated to give α -cyclohexyl-4,5-dimethoxy-2-nitroacetophenone (2) which was readily hydrogenated over palladium-carbon at atmospheric pressure and room temperature to give 2-amino- α -cyclohexyl-4,5-dimethoxyacetophenone (3). Compound 3 was diazotized and cyclized into 3-cyclohexyl-6,7-dimethoxy-1*H*-4-cinnolone (4) which was converted into 4-chloro-3-cyclohexyl-6,7-dimethoxycinnoline (5) with phosphorus oxychloride. Attempts to convert 4 into 7 were unsuccessful. Attempts to convert 4 into 8 *via* NBS bromination gave only 8-bromo-3-cyclohexyl-6,7-dimethoxy-1*H*-4-cinnolone (6). This was established by the disappearance of the proton signal at $\delta \sim 7.16$ at C-8 and the continued presence of the cyclohexyl CH signal at $\delta 3.25$ in the pmr spectrum.



EXPERIMENTAL

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The pmr spectra were recorded on a Varian EM-390 90 MHz spectrometer in the solvent indicated using TMS as the internal standard.

α -Cyclohexyl-4,5-dimethoxy-2-nitroacetophenone (2).

To a solution of 2.0 g. of 1 (16) in 15 ml. of acetic anhydride was slowly added 0.7 g. of 70% nitric acid in 5 ml. of acetic anhydride at 0° for one hour. The reaction mixture was poured on ice-water and extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate, the drying agent removed by filtration and the filtrate was evaporated under reduced pressure. The solid obtained was recrystallized from methanol to give 1.3 g. of 2 as yellow prisms, m.p. 134-135°; ms: m/e 307; ir (potassium bromide): 1675 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.0-2.0 (m, cyclohexyl methylene protons), 2.64 (d, 2H, J = 8 Hz, -CH₂-), 4.00 (s, 6H, -OCH₃), 6.72 (s, 1H, H at C-6), 7.62 (s, 1H, H at C-3).

Anal. Calcd. for C₁₆H₂₁NO₅: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.30; H, 6.93; N, 4.54.

2-Amino- α -cyclohexyl-4,5-dimethoxyacetophenone (3).

To a suspension of 300 mg. of 5% palladium-carbon in 50 ml. of methanol was added a solution of 5.1 g. of 2 in 200 ml. of methanol and the mixture was stirred under hydrogen at atmospheric pressure and at room temperature for three hours. After the catalyst was removed by filtration, the solvent was evaporated under reduced pressure. The residual solid was recrystallized from methanol to give 4.3 g. of 3 as colorless needles, m.p. 127-128°; ms: m/e 267; ir (potassium bromide): 3420, 3300 (NH₂), 1600 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.0-2.0 (m, cyclohexyl methylene protons), 2.72 (d, 2H, J = 8 Hz, -CH₂-), 3.83 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 6.11 (s, 1H, H at C-3), 6.35 (br. s, 2H, NH₂, exchangeable), 7.17 (s, 1H, H at C-6).

Anal. Calcd. for C₁₆H₂₃NO₃: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.17; H, 8.50; N, 4.95.

3-Cyclohexyl-6,7-dimethoxy-1*H*-4-cinnolone (4).

To a stirred solution of 3.8 g. of 3 in 150 ml. of concentrated hydrochloric acid and 30 ml. of water at -5° was added 2.0 g. of sodium nitrite in 10 ml. of water over a 30 minute period. The mixture was stirred for an additional hour at 0° and then heated at 60-75° for four hours to effect ring closure. Crystals of the product separated during the heating and additional crystals were formed upon cooling the reaction mixture. Pale yellow crystals were collected and dissolved in 10% sodium hydroxide solution and filtered. The filtrate was neutralized with acetic acid to give the crystalline product which was recrystallized from ethyl acetate to give 2.3 g. of 4 as colorless needles, m.p. 222-223°; ms: m/e 288; ir (potassium bromide): 3230 (NH), 1620 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.0-2.0 (m, cyclohexyl methylene protons); 3.42 (broad, 1H, cyclohexyl CH), 4.00 (s, 6H, OCH₃), 7.16 (s, 1H, H at C-8), 7.66 (s, 1H, H at C-5), 12.26 (broad, 1H, NH, exchangeable).

Anal. Calcd. for C₁₆H₂₀N₂O₃: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.28; H, 7.09; N, 9.44.

4-Chloro-3-cyclohexyl-6,7-dimethoxycinnoline (5).

A mixture of 300 mg. of **4** and 5 ml. of phosphorus oxychloride was heated for 30 minutes at 120°. The reaction mixture was poured into ice-water and extracted with three 10 ml. portions of chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate, the drying agent removed by filtration and the filtrate evaporated under reduced pressure. Recrystallization of the residue from 90% methanol gave 180 mg. of colorless needles of **5**, m.p. 184-185°; ms: m/e 306; nmr (deuteriochloroform): δ 1.0-2.0 (m, cyclohexyl methylene protons), 3.46 (broad, 1H, cyclohexyl CH), 4.20 (s, 3H, OCH₃), 4.27 (s, 3H, OCH₃), 7.41 (s, 1H, H at C-8), 8.26 (s, 1H, H at C-5).

Anal. Calcd. for C₁₆H₁₉ClN₂O₂: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.39; H, 6.11; N, 9.35.

8-Bromo-3-cyclohexyl-6,7-dimethoxy-1H-4-cinnolone (6).

A mixture of 300 mg. of **4**, 500 mg. of *N*-bromosuccinimide, 50 mg. of benzoyl peroxide and 10 ml. of chloroform was refluxed for five hours. After evaporation of the chloroform under reduced pressure, the products were isolated by column chromatography on silica-gel with chloroform as the eluent and successively recrystallized from ether to give 110 mg. of **6** as colorless needles, m.p. 153-155°; ms: m/e 366; ir (potassium bromide): 3220 (NH), 1580 cm⁻¹ (C=O); nmr (deuteriochloroform): δ 1.0-2.0 (m, cyclohexyl methylene protons), 3.25 (broad, 1H, cyclohexyl CH), 3.96 (s, 3H, OCH₃), 4.00 (s, 3H, OCH₃), 7.63 (s, 1H, H at C-5), 10.25 (broad, 1H, NH, exchangeable).

Anal. Calcd. for C₂₀H₁₉BrN₂O₂: C, 52.33; H, 5.21; N, 7.63. Found: C, 52.47; H, 5.19; N, 7.86.

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