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A one step synthesis of 2-phenyl-5*H*-imidazo[2,1-*a*][2,4]benzodiazepines (**4**) from 2-(2-imidazolyl)benzophenones (**3**) is reported. Oxiamation and reduction of the benzophenone, **3a** led to the benzhydrylamine derivative **7** which was cyclized to differently substituted 6,7-dihydroimidazo[2,1-*a*][2,4]benzodiazepines depending on the reactant chosen.

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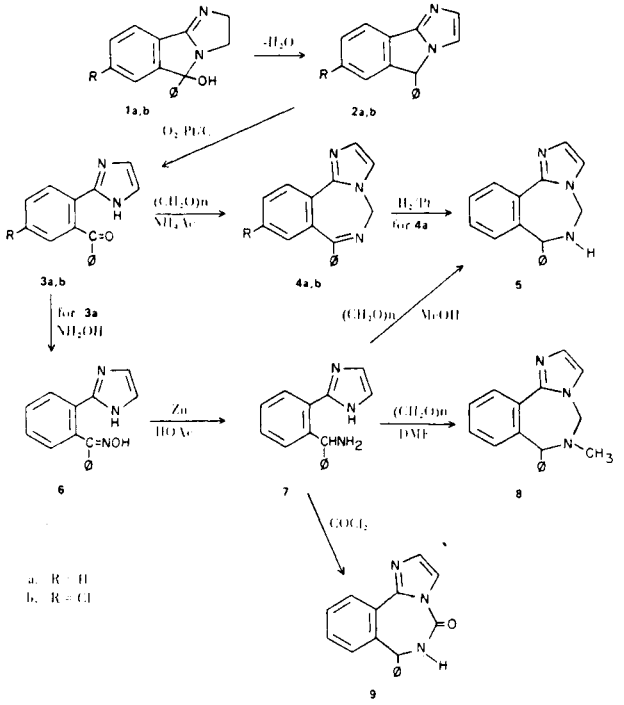
Current research on CNS active benzodiazepines has been centered largely on various triazolo and imidazo derivatives (1). We have extended this line of investigation into the recently described 2,4-benzodiazepines (2) and wish to report a facile synthesis of 5*H*-imidazo[2,1-*a*]-[2,4]benzodiazepines. Attempts to synthesize the analogous triazolo compounds were reported as unsuccessful (3).



Rather than the conventional approach in which an additional heterocyclic ring is fused to an existing benzodiazepine, we chose to prepare imidazolylbenzophenones first and complete the ring system with construction of the seven-membered ring.

2-(2-Imidazolyl)benzophenone **3a** (4) and the corresponding 5-chloro derivative **3b** were prepared from their respective 2-(2-imidazolin-2-yl)benzophenone precursors **1a** and **1b** respectively (5a,b) using our previously described procedure (4). Treatment of **3a** and **3b** with paraformaldehyde in the presence of ammonium acetate afforded the desired imidazo-2,4-benzodiazepines **4a, b** in greater than 85% isolated yields.

Another useful intermediate for the preparation of imidazo-2,4-benzodiazepines was the benzhydrylamine **7**, which was obtained by oxiamation of **3a** to **6** followed by reduction with zinc and acetic acid. Treatment of **7** with phosgene, using 1,2-epoxy-3-phenoxypropane as a hydrogen chloride scavenger, led to the 5-one derivative, compound **9**. Treatment of **7** with paraformaldehyde yielded the 6,7-dihydroimidazo-2,4-benzodiazepine **5** when methanol was used as solvent and to the 6-methyl analog **8** when *N,N*-dimethylformamide was used as solvent. Compound **5** was also obtained directly from **4a** by catalytic reduction over platinum.

EXPERIMENTAL

Melting points were taken microscopically on a hot stage and are corrected. Spectra of all compounds were taken and compared in order to confirm or exclude structural changes. Only significant spectral data are reported. The uv spectra were taken on a Cary Model 14 spectrophotometer, nmr spectra with a Varian A-60 instrument; ir spectra on a Beckman IR-9 spectrophotometer and mass spectra using a CEC-21-110B instrument at 70 eV by direct insertion.

7-Chloro-5-phenyl-5*H*-imidazo[2,1-*a*]isoindole (**2b**).

A solution of 1.6 g. (5.61 mmoles) of 2-[4′-chloro-2′-benzoylphenyl]-2-imidazoline (**1b**) (5b) in 40 ml. of xylene was treated with 0.1 g. (0.53 mmole) of *p*-toluene sulfonic acid monohydrate, and heated under reflux for 1 hour using a Dean Stark trap. The reaction mixture was evaporated and the residue was dissolved in 50 ml. of dichloromethane. The solution was washed with 25 ml. of 0.5 *N* sodium hydroxide, dried, and filtered through 50 g. of Florisil, using 400 ml. of ether as eluent. The combined filtrates were concentrated and the product was filtered and then recrystallized twice from a mixture of dichloromethane and ether to give 0.8 g. (53%) of **2b** as white needles, m.p. 174-179°.

Anal. Calcd. for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.32; H, 4.10; N, 10.47.

5-Chloro-2-(2-imidazolyl)benzophenone (**3b**).

A mixture of 0.5 g. (1.87 mmoles) of **2b**, 0.2 g. of 10% platinum on carbon and 100 ml. of ethanol was stirred and heated under reflux for 15 hours while bubbling in a slow stream of air. The reaction mixture was filtered, evaporated and the residue was crystallized from ether. Recrystallization from a mixture of dichloromethane and ether gave 0.3 g. (57%) of **3b** as white rods, m.p. 192-200°; ir (chloroform): 3375 (NH), 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.90. Found: C, 67.90; H, 3.71; N, 9.80.

7-Phenyl-5*H*-imidazo[2,1-*a*][2,4]benzodiazepine (**4a**).

A mixture of 12 g. (0.0484 mole) of 2-(2-imidazolyl)benzophenone (**3a**) (4), 6 g. (0.2 mole) of paraformaldehyde, 15 g.

(0.195 mole) of ammonium acetate, and 500 ml. of ethanol was heated under reflux for 8 hours, and then evaporated to dryness. The oil was dissolved in 150 ml. of dichloromethane, washed with 100 ml. of 0.5 *N* sodium hydroxide, dried and evaporated. The residue was crystallized from a mixture of dichloromethane and ethyl acetate to give 9.0 g. of product, and a second crop of 2.1 g. (89%). A sample was recrystallized from the same solvents to give the analytical product as off-white rods, m.p. 187-191°; nmr (deuteriochloroform): δ 5.39 (s, 2H, CH_2).

Anal. Calcd. for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.63; H, 4.72; N, 16.21.

9-Chloro-7-phenyl-5*H*-imidazo[2,1-*a*][2,4]benzodiazepine (**4b**).

A solution of 9 g. (0.0318 mole) of **3b**, 4.5 g. (0.15 mole) of paraformaldehyde and 12 g. (0.156 mole) of ammonium acetate in 250 ml. of ethanol was heated under reflux for 9 hours, and then evaporated to dryness. The resulting oil was partitioned between 150 ml. of dichloromethane and 100 ml. of cold 0.5 *N* sodium hydroxide, and the organic layer was separated, dried and filtered through 200 g. of silica gel using ether followed by ethyl acetate as eluents. The combined filtrates were evaporated to dryness and the residual oil was crystallized from ether, recrystallization of the product from a mixture of dichloromethane and ether gave 8 g. (86%) of **4b** as pale yellow prisms, m.p. 116-124°; ir (chloroform): 1613 cm^{-1} (C=N).

Anal. Calcd. for $C_{17}H_{12}ClN_3$: C, 69.51; H, 4.12; N, 14.30. Found: C, 69.61; H, 4.11; N, 14.20.

2-(2-Imidazolyl)benzophenone Oxime (**6**).

A solution of 15.6 g. (0.0629 mole) of **3a** in 400 ml. of ethanol was treated with 5.2 g. (0.0743 mole) of hydroxylamine hydrochloride and 100 ml. of water. The reaction mixture was treated with 11 g. (0.275 mole) of sodium hydroxide added in portions, and then heated under reflux for 6 hours. The ethanol was evaporated and the residual mixture was treated with 100 ml. of dichloromethane, acidified with acetic acid and then made slightly basic with ammonium hydroxide. After standing for a few minutes the precipitate was removed by filtration and was heated under reflux for 5 minutes in 75 ml. of methanol. The solution was cooled and filtered to give 14 g. (85%) of product. A sample was recrystallized from ethanol to give analytically pure **6** as white rods, m.p. 249-252°; ir (potassium bromide): 3310 (NH), (2660-2520), 1900 cm^{-1} (OH, NH).

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.98; N, 15.96. Found: C, 73.29; H, 4.90; N, 15.95.

2-[2-(α-Aminobenzyl)phenyl]imidazole (**7**).

A mixture of 4.5 g. (0.0171 mole) of **6**, 4.5 g. (0.0692 mole) of zinc dust and 30 ml. of glacial acetic acid was treated with 2.7 ml. of concentrated hydrochloric acid. The reaction mixture was stirred at 70° for 1 hour, filtered, made basic with ammonium hydroxide, and extracted with 100 ml. of dichloromethane. The organic layers were combined dried and evaporated. The residue was crystallized first from ether, then dissolved in dichloromethane. Ether was added and an amorphous material was filtered off. The filtrates were evaporated and the residue was crystallized from ethyl acetate to give 3.4 g. (79%) of **7** as off-white prisms, m.p. 144-147°; ir (chloroform): 3385, 3310 cm^{-1} (NH, NH_2).

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 76.81; H, 6.09; N, 16.80.

6,7-Dihydro-7-phenyl-5*H*-imidazo[2,1-*a*][2,4]benzodiazepine (**5**).

A. From Compound **7**.

Hydrogen chloride was bubbled into a mixture of 0.3 g. (1.2 mmoles) of **7**, 0.4 g. (13.3 mmoles) of paraformaldehyde and 5 ml. of methanol for 2 minutes. After 3 hours at room temperature the reaction mixture was made basic with dilute sodium hydroxide solution. The precipitate was removed by filtration, dissolved in 50 ml. of dichloromethane and washed with 20 ml. of 0.5 *N* sodium hydroxide. The organic layer was dried, evaporated and the residue was crystallized from ether. Recrystallization from a mixture of dichloromethane and ether gave 0.1 g. (32%) of **5** as off-white prisms, m.p. 127-130°; ir (chloroform): 3350 cm^{-1} (NH); nmr (deuteriochloroform): δ 2.83 (s, 1H, NH), 4.72, 5.02 (AB, 2H, J = 14 Hz, NCH_2N), 5.33 (s, 1H, CHPh).

Anal. Calcd. for $C_{17}H_{15}N_3$: C, 78.14; H, 5.79; N, 16.08. Found: C, 78.12; H, 5.81; N, 15.91.

B. From Compound **4a**.

A solution of 1.3 g. (5.02 mmoles) of **4a** in 75 ml. of methanol was treated with 0.1 g. of platinum oxide, and the reaction mixture was hydrogenated to completion. The solution was filtered, evaporated and the product was crystallized from a mixture of dichloromethane and ether to give 1.1 g. (85%) of **5** as off-white prisms, m.p. and m.m.p. with a sample obtained from Method A above, 125-129°.

6,7-Dihydro-6-methyl-7-phenyl-5*H*-imidazo[2,1-*a*][2,4]benzodiazepine (**8**).

Hydrogen chloride was bubbled into a solution of 1 g. (4.02 mmoles) of **7**, and 0.5 g. (16.7 mmoles) of paraformaldehyde in 5 ml. of *N*,*N*-dimethylformamide for 6 minutes. The reaction mixture was heated for 2 hours on the steam bath, and hydrogen chloride was bubbled in for one minute during each hour. The mixture was poured into 40 ml. of ice water, extracted with 50 ml. of dichloromethane. The organic layer was washed with 0.5 *N* sodium hydroxide solution (2 x 15 ml.), dried and filtered through 40 g. of Florisil using ether as the eluent. The combined filtrates were concentrated and petroleum ether was added. The precipitate was filtered and recrystallized from a mixture of ether and petroleum ether to give 0.6 g. (55%) of **8** as white prisms, m.p. 134-140°; nmr (deuteriochloroform): δ 2.47 (s, 3H, NCH_3), 4.64 (s, 1H, CHPh), 4.68. 4.84 (AB, 2H, J = 14 Hz, NCH_2N).

Anal. Calcd. for $C_{18}H_{17}N_3$: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.63; H, 6.13; N, 15.08.

6,7-Dihydro-7-phenyl-5*H*-imidazo[2,1-*a*][2,4]benzodiazepin-5-one (**9**).

A solution of 0.5 g. (2.01 mmoles) of **7**, in 25 ml. of dichloromethane was treated with 0.5 g. (3.33 mmoles) of 1,2-epoxy-3-phenoxypropane. The reaction was cooled to 0°, and phosgene was bubbled in for 3 minutes. After 18 hours at room temperature the reaction mixture was evaporated and the residue was triturated with ether. The solution was decanted and the solid was partitioned between 25 ml. of dichloromethane and 10 ml. of dilute ammonium hydroxide, the layers were separated and the organic layer was dried and evaporated. Crystallization of the residue from ether and recrystallization from a mixture of methanol and ether gave 0.25 g. (45%) of **9** as white rods, m.p. 225-229°; ir (chloroform): 3430 (NH), 1725 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.83 (s, 1H, NH), 5.33 (s, 1H, CHPh).

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.15; H, 4.86; N, 15.24.

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