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NOVEL SYNTHESIS OF BENZO[*a*]QUINOLIZINES (PYRIDO[2,1-*a*]ISOQUINOLINES) BY [3+3]-CYCLOCONDENSATION OF 1-ALKYL-3,4-DIHYDROISOQUINOLINES WITH β-KETOESTERS

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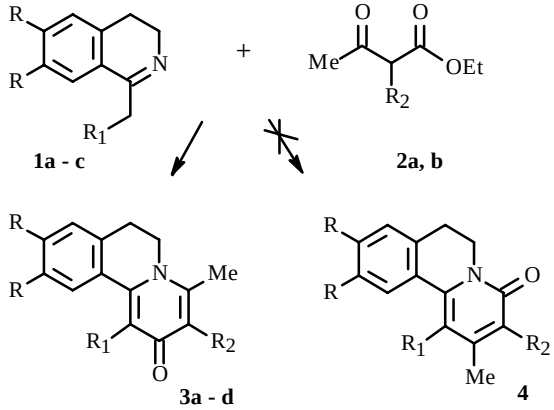
Benzo[a]quinolizines (pyrido[2,1-a]isoquinolines) were synthesized via heterocyclization of 1-alkyldihydroisoquinoline Schiff bases with β*-ketoesters.*

Key words: synthesis, 1-alkyl-3,4-dihydroisoquinoline, acetoacetic and 2-benzylacetoacetic esters, benzo[*a*]quinolizine (pyrido[2,1-*a*]isoquinoline).

The tricyclic molecular fragment benzo[*a*]quinolizine (pyrido[2,1-*a*]isoquinoline) is a key part of the structures of several important natural [1, 2] and synthetic [3] bioregulators. Thus, the development of synthetic methods and the study of the physicochemical, medical, biological, and other properties of this molecular structure are of interest. Progress in research on benzo[*a*]quinolizines is determined to a large extent by success in developing new effective methods of synthesizing and transforming them. At present several dozens of methods for constructing the tricyclic molecular framework of benzo[*a*]quinolizine have been developed [4-7]. Nevertheless, research in this direction is proceeding.

We studied the reaction of 1-alkyl-3,4-dihydroisoquinolines **1a-c** with β-ketoesters **2a** and **2b** within a program on the synthesis of condensed N-containing heterocycles (azines), in particular, containing the benzo[*a*]quinolizine tricyclic fragment. The synthesis is based on heterocyclization of cyclic Schiff bases with carbonyl compounds, their enols, and α,β-unsaturated derivatives.



R = H (**1a**, **3a**), OMe (**1b**, **c**, **3b-d**)

R_1 = H (**1b**, **3b**, **c**), Me (**1a**, **c**, **3a**, **d**)

R_2 = H (**2a**, **3a**, **b**, **d**), CH_2Ph (**2b**, **3c**)

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Condensation of azomethines **1a-c** (**1b** is dehydrosalsolidine) with acetoacetic (**2a**) and 2-benzylacetoacetic (**2b**) esters was performed by heating equimolar mixtures of the reagents under N_2 atmosphere at 160-180°C for 1.5-6 h. The yields of benzo[*a*]quinolizinones **3a-e** reached 66-99.5% calculated for isolated and purified product. This indicates that the reactions are preparative. It is important to note that the reaction of **1a-c** with β-ketoesters **2a** and **2b** can be expected to form **3a-e** and the isomeric derivatives **4**. However, the latter were not observed in the reaction mixtures, indicating that the reaction is specific.

The reaction represented by the four examples is obviously general in nature for other cyclic azomethines (e.g., 1-alkyl-3,4-dihydro-β-carbolines, 1-alkyl-3,4-dihydropyrrolo[1,2-*a*]pyrimidines, and β-ketoesters, in particular, alicyclic and heterocyclic) and presents a simple one-step approach to condensed N-containing heterocycles with a N atom in fused rings.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates. Melting points were determined on a Boetius micro-heating block. IR spectra were obtained on a UR-20 instrument. UV spectra were recorded on a Specord M-400 spectrophotometer; PMR spectra, on a Bruker AC-200 (200 MHz) instrument in $CDCl_3$ with TMS internal standard. Mass spectra were measured in a HP 5972 MS mass spectrometer with direct sample introduction and 70 eV ionizing electron energy. Elemental analyses of all compounds agreed with those calculated.

1,4-Dimethyl-6,7-dihydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (3a). A mixture of **1a** (1.59 g, 10 mmole) and acetoacetic ester (**2a**, 3 mL, 23.5 mmole) was heated for 1.5 h at 150-160°C under N_2. The reaction mixture was left in the cold overnight. The separated compound was collected and recyrstallized twice from alcohol. Yield 2.03 g (83.4%) of **3a** as a crystal solvate with 1 mole of H_2O, mp 75-77°C.

$C_{15}H_{15}NO \cdot H_2O$, M.W. 243.30.

IR spectrum (KBr, ν_{max}, cm^{-1}): 3550-3200, 3100-2830, 1628, 1585, 1565-1520, 1493, 1444, 1386, 1349, 1311, 1270, 1252, 1228, 1192, 1180, 1093, 940, 864, 852, 773, 755-740. UV spectrum (EtOH, λ_{max}, nm, ε): 269.1 (36550), 280.9 (17055); (EtOH, λ_{min}, nm, ε): 229.4 (9570), 269.1 (15645). PMR spectrum (δ, ppm, J/Hz): 2.22 (2H, br.s, H_2O), 2.33 (3H, s, C^1Me), 2.40 (3H, s, C^4Me), 2.97 (2H, t, J = 6.0, C^7H_2), 3.96 (2H, t, J = 6.0, C^6H_2), 6.32 (1H, s, C^3H), 7.29 (1H, d, J = 7.0, C^8H), 7.28 (2H, t, J = 7.0, C^9H, $C^{10}H$), 7.65 (1H, d, J = 7.0, $C^{11}H$). Mass spectrum, *m*/*z* (I_{rel}, %): 226.15 $[M + 1]^+$ (5.00), 225.15 $[M]^+$, (37.03), 224.25 $[M - 1]^+$ (100), 197.15 (12.68), 196.16 (21.94), 182.15 (4.71), 181.15 (7.03), 180.15 (6.76), 167.10 (3.82), 154.05 (3.29), 128 (5.48), 127 (3.55), 115 (6.21), 111.50 (3.24), 98.55 (6.86), 90.25 (3.35), 83.50 (4.25), 77 (5.25), 62.95 (3.16), 50.95 (3.15).

9,10-Dimethoxy-4-methyl-6,7-dihydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (3b). Prepared analogously as above from **1b** (1.03 g, 5 mmole) and **2a** (1.2 mL, 9.4 mmole) after heating for 2 h at 150-160°C and crystallization of the dry product from absolute alcohol. Yield of **3b**, 1.35 g (99.5%), mp 254-256°C (alcohol—ether).

$C_{16}H_{17}NO_3$, M.W. 271.32.

IR spectrum (KBr, ν_{max}, cm^{-1}): 3280, 3100-2820, 1637, 1614, 1593, 1565-1535, 1520, 1480-1445, 1388, 1365-1345, 1330, 1296, 1274, 1248, 1217, 1186, 1158, 1076, 1040, 1008, 978, 868, 782. UV spectrum (EtOH, λ_{max}, nm, ε): 203.6 (11680), 218.9 (16390), 239.2 (21480), 258.5 (20725), 317.1 (15450); (EtOH, λ_{min}, nm, ε): 242 (15450), 250 (17710), 273 (9985). PMR spectrum (δ, ppm, J/Hz): 2.40 (3H, s, C^4Me), 2.98 (2H, t, J = 6.0, C^7H_2), 3.90 (3H, s, OMe), 3.94 (3H, s, OMe), 4.00 (2H, t, J = 6.0, C^6H_2), 6.28 (1H, d, J = 3.0, C^3H), 6.72 (1H, s, C^8H), 6.78 (1H, d, J = 3.0, C^1H), 7.18 (1H, s, $C^{11}H$). Mass spectrum, *m*/*z* (I_{rel}, %): 272.15 $[M + 1]^+$ (16.48), 271.25 $[M]^+$ (84.93), 244.15 (14.45), 243.15 (87.01), 242.05 (3.26), 229.15 (14.64), 228.15 (100), 227.05 (6.04), 226.15 (6.32), 213 (4.24), 212 (3.19), 209 (3.93), 208 (5.87), 207 (31.88), 200.10 (24.01), 199.05 (26.57), 198.05 (21.67), 196.05 (3.83), 190.95 (4.03), 185.95 (5.65), 185.05 (43.60), 184.05 (14.04), 183.05 (4.98), 182.05 (6.98). 181.15 (4.21), 180.15 (3.87), 170.10 (4.01), 169 (6.67), 168.10 (11.49), 167.10 (7.88), 157.10 (8.93), 156 (18.45), 155.10 (8.30), 154.05 (12.64), 142.05 (5.75), 141.05 (6.12), 133.05 (3.02), 132.75 (3.10), 130.90 (4.10), 129.90 (6.13), 128 (7.37), 126.90 (5.21), 121.50 (26.88), 118 (3.48), 116.90 (3.87), 116 (3.06), 115 (7.70), 113.80 (5.49), 113.10 (6.03), 104.05 (3.68), 103.05 (3.67), 101.95 (4.61), 98.45 (5.71), 95.85 (5.03), 90.75 (4.89), 90.15 (3.75), 88.95 (5.42), 83.40 (8.32), 77.90 (5.21), 77.10 (11.44), 75.90 (4.36), 74.90 (4.88), 73 (6.21), 67 (4.34), 65 (4.36), 63.95 (3.55), 62.95 (8.65), 61.85 (3.79), 54.95 (3.88), 53.05 (3.51), 52.05 (4.11), 50.95 (7.67).

9,10-Dimethoxy-1,4-dimethyl-6,7-dihydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (3c). Prepared analogously as above from **1a** (1.1 g, 5 mmole) and **2a** (1.6 mL, 12.6 mmole) by heating for 2.5 h at 160°C and crystallization of the dry product from a mixture of alcohol and ether. Yield of **3a**, 1.12 g (78.7%), mp 284-285.5°C.

$C_{17}H_{19}NO_3$, M.W. 285.34.

IR spectrum (KBr, ν_{max}, cm^{-1}): 3100-2830, 1635-1605, 1592, 1563, 1544, 1511, 1485, 1473, 1445, 1423, 1393, 1346, 1290, 1279, 1250, 1225, 1216, 1203, 1170, 1132, 1083, 1038, 1017, 1005, 881, 861, 852, 778. UV spectrum (EtOH, λ_{max}, nm, ε): 203.8 (14520), 217.8 (18090), 239.6 (25480), 257.9 (20635), 311.1 (17325); (EtOH, λ_{min}, nm, ε): 224 (17325), 250 (18600), 279 (10700). PMR spectrum (δ, ppm, J/Hz): 2.36 (3H, s, C^1Me), 2.40 (3H, s, C^4Me), 2.98 (2H, t, J = 6.0, C^7H_2), 3.90 (3H, s, OMe), 3.94 (2H, t, J = 6.0, C^6H_2), 3.96 (3H, s, OMe), 6.28 (1H, s, C^3H), 6.78 (1H, s, C^8H), 7.18 (1H, s, C^{11}H). Mass spectrum, *m*/*z* (I_{rel}, %): 286.25 $[M + 1]^+$ (11.79), 285.35 $[M]^+$ (68.63), 284.25 $[M - 1]^+$ (100), 271.25 (7.74), 270.25 (42.86), 269.25 (6.80), 268.15 (17.88), 257.20 (6.76), 254.20 (7.43), 243.15 (7.98), 242.15 (47.26), 241.15 (4.55), 240.15 (16.03), 239.15 (19.06), 238.15 (4.88), 227.15 (6.43), 224,15 (3.81), 214.10 (6.36), 213.10 (11.06), 212.10 (11.81), 211.10 (6.81), 210.10 (12.18), 200.10 (3.78), 199.05 (23.78), 198.05 (16.14), 197.05 (5.12), 196.15 (3.72), 184.05 (8.61), 183.15 (4.27), 182.15 (6.35), 181.15 (3.50), 180.05 (3.31), 171.10 (9.80), 170.10 (15.68), 169.10 (4.16), 168.10 (8.26), 167.10 (4.87), 156.10 (4.18), 155.10 (4.03), 154.05 (8.21), 147.05 (4.85), 144.05 (3.50), 142.95 (3.39), 142.05 (4.53), 141.05 (3.42), 130 (4.81), 128.50 (28.54), 127 (7.32), 117 (3.23), 116 (3.78), 115 (11.19), 113.50 (14.20), 103.05 (4.20), 102.05 (4.50), 98.55 (12.86), 91.75 (3.07), 90.75 (5.45), 89.05 (5.12). 86.60 (3.35), 83.50 (6.84), 77.80 (3.72), 77 (9.63), 76 (3.65), 67 (4.80), 65 (4.66), 62.95 (5.77), 54.95 (3.81), 52.95 (3.18), 50.95 (5.37).

3-Benzyl-4-methyl-9,10-dimethoxy-6,7-dihydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (3d). Prepared from **1c** (1.54 g, 7.5 mmole) and **2b** (1.78 g, 8.1 mmole) after heating for 6 h at 150-160°C, filtration of the dry product through silica gel, and crystallization from alcohol—ether. Yield of **3c**, 1.8 g (66.4%) of pale pink crystals, mp 243-246°C (alcohol—ether).

$C_{23}H_{23}NO_3$, M.W. 361.44.

IR spectrum (KBr, ν_{max}, cm^{-1}): 3100-2820, 1620, 1605, 1590, 1558, 1520-1500, 1495, 1467, 1450, 1385, 1357, 1344, 1319, 1280-1260, 1227, 1189, 1181, 1160, 1121, 1044, 899, 870, 859, 830, 780, 750, 705. UV spectrum (EtOH, λ_{max}, nm, ε): 240 (26230), 263.6 (27555), 313.8 (20170); (EtOH, λ_{min}, nm, ε): 229.4 (20800), 250 (19490), 293.6 (14745). PMR spectrum (δ, ppm, J/Hz): 2.36 (3H, s, C^4Me), 2.98 (2H, t, J = 6.0, C^7H_2), 3.94 (6H, s, 2OMe), 4.00 (2H, t, J = 6.0, C^6H_2), 4.11 (2H, s, $C^{14}H_2$), 6.71 (1H, s, C^1H), 6.90 (1H, m, C^8H), 6.22 (1H, s, C^{11}H), 7.08 (5H, m, $C^{2'}$H, $C^{3'}$H, $C^{4'}$H, $C^{5'}$H, $C^{6'}$H). Mass spectrum *m*/*z* (I_{rel}, %): 362.25 $[M + 1]^+$ (18.80), 361.25 $[M]^+$ (85.04), 360.35 $[M - 1]^+$ (100), 347.20 (4.82), 346.20 (19.47), 345.20 (7.90), 344.30 (22.56), 330.25 (6.123), 318.25 (3.27), 316.25 (7;04), 302.10 (4.84), 300.20 (3.15), 288.15 (3.72), 287.15 (3.07), 286.15 (4.38), 285.15 (8.01), 284.15 (35.76), 274.15 (5.20), 272.25 (4.06), 271.15 (4.12), 270.15 (18.46), 268.15 (3.84), 258.10 (3.15), 240.15 (3.91), 226.05 (3.07), 210.20 (3.07), 209.10 (3.67), 208 (5.19), 207.10 (19.12), 199.05 (3.58), 198.05 (6.78), 196.05 (3.51), 194.15 (3.06), 190.95 (3.30), 181.95 (3.53), 180.65 (29.81), 172.90 (9.33), 171.20 (3.06), 168 (4.64), 167 (3.79), 165.20 (5.62), 157.50 (10.43), 156.80 (4.75), 156.20 (3.67), 155.10 (3.29), 154.05 (4.25), 151.75 (7.90), 150.75 (5.85), 149.75 (7.32), 143.85 (7.26), 142.55 (13.96), 141.75 (9.43), 141.35 (9.14), 139.05 (4.24), 136.45 (7.30), 135.65 (10.02), 133.75 (4.64), 133.15 (5.08), 131 (4.42), 129.90 (6.61), 128.90 (11.76), 128.10 (23.43), 127.10 (17.26), 123.50 (4.79), 122.40 (3.86), 120.70 (6.12), 120.40 (5.99), 117.10 (5.19), 115.90 (5.61), 115 (15.74), 114.10 (5.72), 108.35 (3.07), 103.05 (6.60), 102.05 (10.10), 100.95 (4.85), 96.05 (3.73), 95.75 (3.74), 91.05 (16.63), 90.05 (3.25), 89.05 (5.70), 78 (8.49), 77 (14.99), 75.90 (3.05), 75 (3.78), 73 (5.10), 65 (6.01), 62.95 (5.40), 52.95 (5.54), 50.95 (9.46).

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