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SYNTHESIS OF *N*-CONTAINING HETEROCYCLES BASED ON α-AMINO ACIDS. 1. 8,9-DIMETHOXY-5,6-DIHYDRO-3-PHENYL-1-ALKYLIMIDAZO[5,1-*a*]ISOQUINOLINES

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Cyclization of α*-benzoylamino-*N*-[2-(3,4-dimethoxyphenyl)ethyl]alkyl amides by $POCl_3$ was studied. Spectral analyses and an X-ray crystal structure analysis found that the synthesized compounds contained 5,6-dihydroimidazo[5,1-a]isoquinoline cores.*

Keywords: α-amino acids, 3,4-dimethoxyphenethylamine, *N*-benzoyl-α-amino acid amides, cyclization, 5,6-dihydroimidazo[5,1-*a*]isoquinolines.

The synthesis of multifunctional drug conjugates containing in one molecule several pharmacophores capable of interacting with various biological targets is a current thrust of medicinal chemistry.

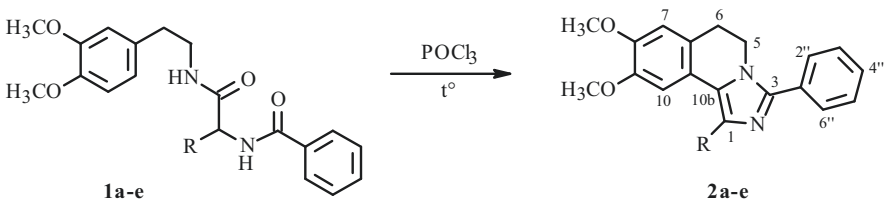
The significance of imidazole derivatives in medicine can hardly be overestimated. Medicines used to treat fungal, viral, oncological, and other diseases are based on them owing to their broad spectra of biological and pharmacological activities [1, 2]. The imidazole core appears in vitamins, enzymes, and amino acids. Tricyclic imidazole derivatives containing a bridgehead N atom, e.g., imidazo[1,2-*a*]pyrimidines, imidazo[1,2-*b*]quinolines and -isoquinolines are especially interesting to researchers. Imidazo[1,2-*a*]pyrimidines exhibited antimicrobial [3]; imidazoquinazolines, antitumor [4] and antihypertensive[5]; and imidazo[1,2-*a*]quinoline, antibacterial activity [6].

Pettit et al. isolated from a blue marine sponge *Cribrochalina* sp. cribrostatin 6 with anticancer and antibacterial activity and a structure based on the imidazo[5,1-*a*]isoquinoline skeleton [7–9]. Recently, total syntheses of cribrostatin 6 and its biologically active analogs were developed [10–12].

Imidazo-*N*-heterocycles were synthesized in several studies from azanaphthalene [13, 14] or aminomethylisoquinoline derivatives [15]. Several approaches to the synthesis of imidazoisoquinolines using amino acids were developed [16]. For example, imidazo[1,5-*a*]isoquinolines with anti-inflammatory activity [17] were prepared from *N*-Boc-protected amino acids [18] or glycine [19].

Considering the inexhaustible possibilities of α-amino acids for constructing heterocyclic compounds, we used α-amino acids and homoveratrylamine as important building blocks to synthesize imidazo[1,5-*a*]isoquinolines.

Previously, the synthesis of *N*-benzoyl-α-amino acid amides from 3,4-dimethoxyphenethylamine was reported by us [20]. Herein, cyclization of amides **1a–e** and preparation of 5,6-dihydroimidazo[1,5-*a*]isoquinoline derivatives (**2a–e**) are reported.



1a-e **2a-e**

R = H (**a**); CH_2CH_3 (**b**); $CH_2CH_2CH_3$ (**c**); $CH(CH_3)CH_3$ (**d**); $CH_2CH(CH_3)CH_3$ (**e**)

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TABLE 1. Intermolecular H-bonds in the Crystal (*d*, distance; D, donor; A, acceptor)

D–H...A	*d*(D…A), Å	*d*(H…A), Å	∠(DHA), deg	Symmetry
O1w–H1…Cl1	3.114	2.22	168	*x,y,z*
O2w–H1…Cl1	3.190	2.30	170	*x,y,z*
O3w–H1…Cl1	3.180	2.23	177	*-x,-y,-z*
O1w–H2…O2w	2.815	1.94	161	*x,y,z*
O2w–H2…O3w	2.763	1.81	154	*x,y,z*
N1–H…O1w	2.724	1.88	165	*0.5+x,0.5-y,0.5+z*

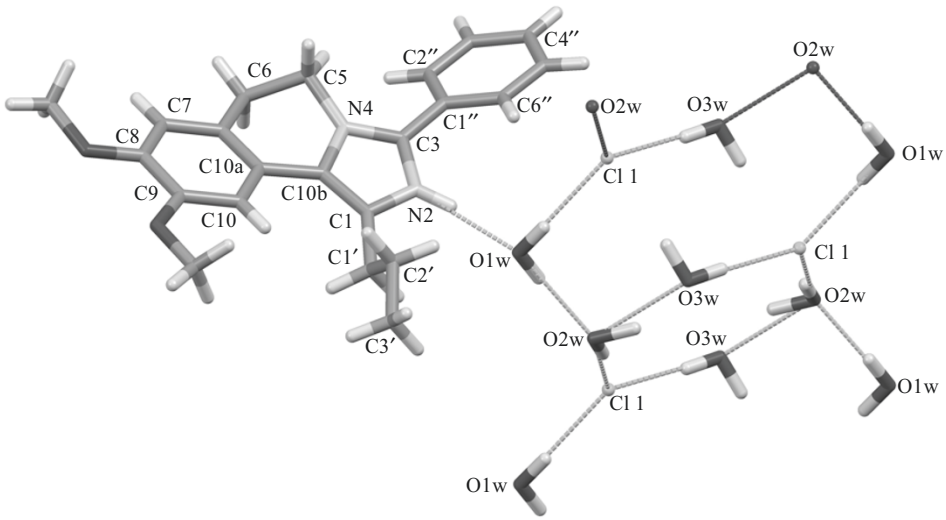

Fig. 1. Molecular structure of **2c**·HCl·3H_2O (H-bonds in the crystal are shown).

The presence of two carbamides in the prepared amides opened the possibility of forming in one step a mutually condensed tricyclic system containing a bridgehead N atom and imidazole and isoquinoline moieties.

Amides **1a–e** were cyclized using Bischler–Napieralski reactions with $POCl_3$, using it as a reagent and solvent. Heating for 4–6 h on a boiling-water bath produced imidazo[1,5-*a*]isoquinolines **2a–e** in 61–82% yields.

The structures of the synthesized compounds were confirmed using IR and PMR spectroscopy. IR spectra of **2a–e**, in contrast to **1a–e**, lacked bands for amide carbonyls. PMR spectra of **2a–e** contained resonances for aromatic isoquinoline protons H-7 and H-10 as two singlets at δ 6.70–6.97 and 7.10–7.18 ppm whereas those of **1a–e** had three resonances for aromatic protons that were characteristic of a 1,3,4-substituted aromatic ring.

Compound **2c** was used as an example to prove its structure by an X-ray crystal structure analysis (XSA). The hydrochloride salt of **2c** crystallized as a trihydrate. Figure 1 shows the molecular structure of **2c**·HCl·3H_2O. Atom N1 was protonated in the crystal of the **2c** salt. The six-membered heterocycle in cationic **2c** adopted a distorted boat conformation (with symmetry passing through the centers of the C10b–C10a and C5–C6 bonds). The other aromatic rings were strictly planar. The benzene ring on C3 was rotated relative to the plane of the imidazole ring by 40°. The bond lengths in the protonated aromatic five-membered heterocycle were C10b–N4 [1.401(5) Å], C10b–C1 [1.361(6)], C1–N2 [1.380(5)], N2–C3 [1.351(6)], and C3–N [1.345(5)] and were characteristic of imidazole [21].

The asymmetric unit in the crystal included protonated cationic **2c**, Cl^-, and three waters of crystallization (Ow). H-bonds Cl…H–O, N–H…O, and O–H…O were observed in the crystal. H atoms of three water molecules surrounded Cl^-. The N1 proton approached an unshared electron pair of O1w. The other H atoms of water molecules and Cl^- formed a six-membered ring because of symmetry elements (Fig. 1). Table 1 lists the parameters of these H-bonds.

EXPERIMENTAL

IR spectra were recorded from KBr pellets on an FTIR System 2000 instrument (PerkinElmer). PMR spectra were taken in $CDCl_3$ with HMDS internal standard on a Unity-400+ spectrometer (400 MHz, Varian). R_f values were determined

on LSL_{254} (5/40 μm) silica gel plates using $CHCl_3$–MeOH (12:1, 1), C_6H_6–MeOH (10:1, 2), and $CHCl_3$–MeOH (8:1, 3). Melting points of all synthesized compounds were determined on a Stuart SMP20 Melting Point Apparatus.

General Method for Synthesizing Dihydroimidazo[5,1-*a*]isoquinolines 2a–e. A mixture of amide **1a–e** (1.1 mmol) and $POCl_3$ (5.5 mmol) was refluxed on a water bath for 4–6 h. The course of the reaction was monitored by TLC. The reaction mixture was poured into ice, made basic with NH_4OH solution (25%) to pH 9, and extracted with $CHCl_3$. The extracts were evaporated. The solid was either triturated with Me_2CO or dissolved in MeOH before producing the hydrochloride. The MeOH was evaporated. The solids (**2b–e**) were crystallized from Me_2CO.

8,9-Dimethoxy-3-phenyl-5,6-dihydroimidazo[5,1-*a*]isoquinoline (2a), $C_{19}H_{18}N_2O_2$, was prepared from **1a** (0.4 g, 1.17 mmol) and $POCl_3$ (0.6 mL). Yield 74% (0.265 g), mp of base 172–174°C (Me_2CO), R_f 0.81 (system 3). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.92 (2H, t, J = 6.6, H-6), 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.18 (2H, t, J = 6.8, H-5), 6.70 (1H, s, H-10), 7.01 (1H, s, H-7), 7.33 (1H, s, H-1), 7.36 (1H, dt, J = 2.6, 7.3, H-4″), 7.41 (2H, dt, J = 2.3, 7.4, H-3″, 5″), 7.59 (1H, dt, J = 2, 6.9, H-2″, 6″).

8,9-Dimethoxy-3-phenyl-1-ethyl-5,6-dihydroimidazo[5,1-*a*]isoquinoline (2b), $C_{21}H_{22}N_2O_2$, was prepared from **1b** (0.4 g, 1.08 mmol) and $POCl_3$ (0.5 mL). Yield 61% (0.22 g), mp of hydrochloride 244–245°C (Me_2CO), R_f 0.34 (system 2). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.38 (3H, t, J = 7.5, CH_3), 2.91 (2H, t, J = 6.4, H-6), 2.97 (2H, q, J = 7.5, CH_2), 3.86 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.16 (2H, t, J = 6.4, H-5), 6.75 (1H, s, H-10), 7.07 (1H, s, H-7), 7.39 (1H, dt, J = 2.7, 7.7, H-4″), 7.44 (2H, dt, J = 2.1, 7.4, H-3″, 5″), 7.60 (2H, dt, J = 2.4, 8.6, H-2″, 6″).

8,9-Dimethoxy-3-phenyl-1-propyl-5,6-dihydroimidazo[5,1-*a*]isoquinoline (2c), $C_{22}H_{24}N_2O_2$, was prepared from **1c** (0.5 g, 1.3 mmol) and $POCl_3$ (0.6 mL). Yield 76% (0.34 g), mp of hydrochloride 219–221°C (Me_2CO), R_f 0.77 (system 1). IR spectrum (ν, cm^{-1}): 3393, 3053, 2961, 2868, 1635, 1544, 1512, 1464. ^{1}H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 1.01 (3H, t, J = 7.3, H-4′), 1.79 (2H, q, J = 7.6, H-3′), 2.95 (2H, t, J = 7.8, H-2′), 2.99 (2H, t, J = 7.7, H-6), 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.26 (2H, t, J = 7, H-5), 6.95 (1H, s, H-10), 7.10 (1H, s, H-7), 7.59 (1H, dt, J = 1.8, 6, H-4″), 7.62 (2H, dt, J = 2, 6.1, H-3″, 5″), 7.69 (2H, dt, J = 2.2, 8, H-2″, 6″). ^{13}C NMR spectrum (100 MHz, CD_3OD, δ, ppm): 14.23 (C-5′), 23.58 (C-4′), 28.14 (C-6), 29.19 (C-3′), 44.9 (C-5), 56.74 (OCH_3), 56.96 (OCH_3), 109.41 (C-10), 113.32 (C-7), 118.17 (C-10a), 123.88 (C-6a), 127.94 (C-2″), 128.17 (C-6″), 129.28 (C-1″), 130.76 (C-3″), 130.85 (C-5″), 133.58 (C-4″), 143.38 (3), 150.27 (C-9), 151.68 (C-8).

8,9-Dimethoxy-3-phenyl-1-isopropyl-5,6-dihydroimidazo[5,1-*a*]isoquinoline (2d), $C_{22}H_{24}N_2O_2$, was prepared from **1d** (0.4 g, 1.04 mmol) and $POCl_3$ (0.5 mL). Yield 70% (0.25 g), mp of hydrochloride 253–255°C (Me_2CO), R_f 0.79 (system 1). IR spectrum (ν, cm^{-1}): 3627, 3394, 2551, 1631, 1514, 1489. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.40 (6H, d, J = 6.8, $2CH_3$), 2.86 (2H, t, J = 6.3, H-6), 3.31 (1H, q, J = 6.8, H-2′), 3.85 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.09 (2H, t, J = 6.9, H-5), 6.74 (1H, s, H-10), 7.10 (1H, s, H-7), 7.32 (1H, dt, J = 2.2, 7.2, H-4″), 7.39 (2H, dt, J = 1.6, 7.6, H-3″, 5″), 7.57 (2H, dt, J = 1.5, 6.9, H-2″, 6″). ^{13}C NMR spectrum (100 MHz, CD_3OD, δ, ppm): 22.03 (C-3′, 2a), 26.75 (C-6), 29.30 (C-2′), 44.35 (C-5), 56.73 (OCH_3), 57.02 (OCH_3), 109.98 (C-10), 113.36 (C-7), 118.19 (C-10a), 124.25 (C-6a), 126.72 (C-1), 128.59 (C-1″), 130.73 (C-2″, 6″), 131.08 (C-3″, 5″), 133.65 (C-4″), 134.72 (C-10b), 144.14 (C-3), 150.27 (C-9), 151.74 (C-8).

8,9-Dimethoxy-3-phenyl-1-isobutyl-5,6-dihydroimidazo[5,1-*a*]isoquinoline (2e), $C_{23}H_{26}N_2O_2$, was prepared from **1e** (0.5 g, 1.25 mmol) and $POCl_3$ (0.7 mL). Yield 82% (0.37 g), mp 202–204°C (Me_2CO), R_f 0.44 (system 2). IR spectrum (ν, cm^{-1}): 3447, 2958, 1629, 1547, 1512, 1465. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.02 (6H, d, J = 6.6, $2CH_3$), 2.09 (1H, q, J = 6.8, H-3′), 2.86 (2H, d, J = 7.3, H-2′), 3.01 (2H, t, J = 6.4, H-6), 3.83 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.26 (2H, t, J = 6.4, H-5), 6.97 (1H, s, H-10), 7.18 (1H, s, H-7), 7.60 (1H, dt, J = 1.4, 6, H-4″), 7.62 (2H, dd, J = 1.7, 6.6, H-3″, 5″), 7.69 (2H, dt, J = 1.9, 6, H-2″, 6″). ^{13}C NMR spectrum (100 MHz, CD_3OCD_3, δ, ppm): 23.02 (C-4′, 3a), 29.62 (C-3′), 30.61 (C-4), 36.02 (C-2′), 44.52 (C-5), 57.05 (OCH_3), 57.27 (OCH_3), 109.98 (C-10), 113.96 (C-7), 119.63 (C-10a), 125.95 (C-6a, 1), 128.73 (C-2″, 6″), 131.06 (C-3″), 131.42 (C-5″), 133.72 (C-10b), 144.77 (C-3), 150.99 (C-9), 152.16 (C-8). ESI-MS (+ESI TIC Scan Frag=125.0 V) *m/z* 363 $[M+H]^+$.

XSA Experiment. Unit-cell constants of **2c**·HCl·$3H_2O$ were determined and refined on a CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using Cu Kα-radiation (T = 288 K). The crystals were monoclinic, space group $P2_1/n$, Z = 4 ($C_{22}H_{31}N_2O_2$·Cl). The unit-cell constants were a = 13.310(1), b = 7.3861(8), c = 23.443(2) Å , β = 100.19(1)°. A three-dimensional dataset of reflections was collected on the diffractometer. Absorption corrections were applied using the SADABS program [22]. The structure was solved by direct methods using the SHELXS-97 program suite [23] and refined using SHELXL-2014/7 software [24]. All nonhydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F^2). H atoms on C atoms were positioned geometrically and refined using a rider model with fixed isotropic shift parameters U_{iso} = nU_{eq}, where n = 1.5 for methyls and 1.2 for others (U_{eq} is the equivalent isotropic shift parameter

of the corresponding C atoms). H atoms of water molecules and NH groups were found in difference electron-density syntheses and refined isotropically using the DFIX instruction. The final agreement factor over all 4571 reflections was 16.3%; over 2026 reflections with $I > 2\sigma(I)$, 8.7%. Data from the XSA analysis were deposited as a CIF file in the Cambridge Crystallographic Data Centre (CCDC 1948404).

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