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SYNTHESIS OF DERIVATIVES OF PYRIDO-[1,2-*c*][1,3,2]OXAZABORININE AND PYRIDO-[2,1,6-*f,g*][1,3,7,2]DIOXAZAPHOSPHACYCLO-DECANE

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The condensation of 2,6-di(o-hydroxyphenyl)-3,5-diphenyl-γ-piperidone with boric and boronic acids gave a series of 1,3,4,11b-tetrahydro-2H-benzo[e]pyrido[1,2-c][1,3,2]oxazaborinin-2-ones. The action of phosphorus oxytrichloride on this piperidone gave a derivative of 8,10-dioxa-21-aza-9-phospha-pentacyclohenicosahexaene.

Keywords: boronic acids, 2,6-di(2-hydroxyphenyl)-3,5-diphenyl-4-piperidone, 8,10-dioxa-21-aza-9-phosphapentacyclohenicosahexaene, 1,3,4,11b-tetrahydro-2H-benzo[*e*]pyrido[1,2-*c*][1,3,2]oxaza-2-borininones, phosphorus oxytrichloride.

In previous work [1-4], we reported the synthesis of representatives of a new class of dioxaborininopiperidines by the condensation of arylboronic acids or triisopropyl borate with 4-hydroxy-3-hydroxymethylpiperidines (heterocyclic 1,3-diols) and the molecular structure of these compounds. Similar compounds with four cyclic heteroatoms hold interest in light of their potential biological activity predicted with high probability by the InterPASS program [5] (for example, spasmolytic activity similar to the action of the alkaloid, papaverine). In the present work, we developed a synthesis of another new group of compounds also containing a cyclic boron atom derived from 2,6-di(*o*-hydroxyphenyl)-3,5-diphenyl-4-piperidone (**1**), which is formally a heterocyclic 1,7-diol. Piperidone **1** was prepared in our laboratory in 74% yield by the Petrenko-Kritchenko condensation of 1,3-diphenylacetone with salicylaldehyde and ammonium acetate. We should note that a similar method of synthesis of 2,6-di(hydroxyphenyl)piperidones was found successful only using methyl benzyl ketone [6]; in other cases, complex mixtures of compounds with fundamentally different structures were formed instead of the expected products [7-9].

Piperidone **1** in deuterochloroform solution is a 1,4-zwitter-ion. The ^{1}H NMR spectrum of this compound shows a narrow singlet at 2.10 ppm (with integral intensity 2H) for the $^+NH_2$ protons and a narrow singlet at 7.76 ppm (1H) assigned to the phenol hydroxyl group. Exhaustive acetylation of **1** gives triacetate **2**. The ^{1}H NMR spectrum of **2** lacks the abovementioned signals but has four singlets at 1.47-2.33 ppm (the integral intensity of each signal corresponds to 3H) for the four methyl group protons, which is additional evidence for the structure of starting piperidone **1**.

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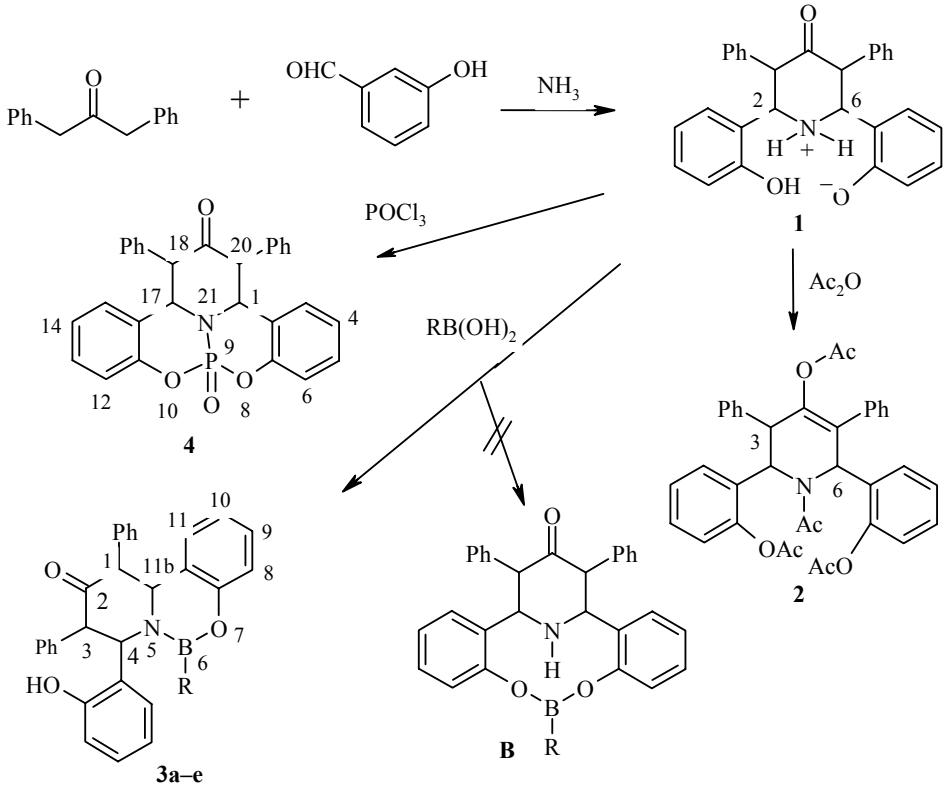
The condensation of piperidone **1** with arylboronic and alkylboronic acids R-B(OH)$_2$ and boric acid upon heating in acetic acid at reflux leads not to boronates **B**, but rather to benzopyridooxazaborinine derivatives **3a-e**. The formation of these borinine derivatives indicates initial selective attack by boronic acid (a soft reagent) at the most reactive nitrogen atom with subsequent tandem cyclization of the intermediate amide NB(R)OH at one of the hydroxyl groups of the two phenol substituents. An attempt to form a type-**B** system using boric acid was unsuccessful, probably since the *o*-C_6H_4OH substituent at C(4) and the OH substituent at B(6) in resultant cyclic amide **3c** are in 1,3-*pseudotrans* arrangement relative to each other. The use of phosphorus oxytrichloride permitted the participation of all three potentially active groups in the cascade condensation to give piperidodioxazaphosphacyclodecane derivative **4**.



3a R = C_6H_4OMe-*m*, **b** R = C_6H_4COOH-*p*, **c** R = OH,
d R = $OCHMe_2$, **e** R = pyrimidin-5-yl

The structure of products **3a-e** was supported by spectral data. Thus, the ^{1}H NMR spectra show the piperidone ring protons as doublets at 2.25-5.15 ppm with a large vicinal coupling constants (from 10.3 to 18.0 Hz). The phenolic OH proton gives a singlet at 8.55-8.68 ppm. The empirical formulas of **3a-e** were supported by finding molecular ion peaks in their mass spectra. The ^{1}H NMR spectrum of phosphorus-containing compound **4** is highly symmetrical and lacks the signal for the phenolic hydroxyl proton. The ^{31}P NMR spectrum has a signal at 4.39 ppm, characteristic for amidophosphates (NPO_3).

The InterPASS program predicts cutinase inhibitor activity (83% probability) and spasmolytic activity (73 and 69% probability) for **3b** and **3c**, respectively, as well as cardiotonic action (71 and 75% probability) for **3b** and **3e**, respectively. Starting piperidone **1** may prove interesting as a topoisomerase I inhibitor (75%) and cell membrane integrity agonist (72%) and its enol acetate **2** may manifest activity as an aminocarboxymuconatesemialdehyde carboxylase inhibitor (90%) and arylacetylamidase inhibitor (76%). The latter should also be tested as an antiseborrheic agent.

EXPERIMENTAL

The IR spectra were obtained on an IR-75 spectrometer in KBr pellets. The ^{1}H NMR spectra were taken on a Bruker WM-400 spectrometer at 400 MHz in $CDCl_3$ with TMS as the internal standard. The ^{31}P NMR spectra were taken on a Bruker WM-80 spectrometer at 34 MHz with 85% H_3PO_4 as the external standard. The solvents are indicated below. The mass spectra were taken on a Finnigan MAT Incos 50 mass spectrometer with direct sample inlet and ionizing electron energy 70 eV. The LCMS spectra were obtained on a system containing a Shimadzu Analytical HPLC SCL10Avp, Gilson 215 autosampler, Sedex 75 (55) ELSD (evaporative light scattering detector), and PE SCIEX API 165 (150) mass spectrometer. L-60 (40/100) silica gel was used for the column chromatography. Silufol UV-254 plates with iodine vapor development were used for thin-layer chromatography.

2,6-Di(2-hydroxyphenyl)-3,5-diphenyl-4-piperidone (1). A solution of diphenylacetone (1.05 g, 5 mmol), salicylaldehyde (1.22 g, 10 mmol), and ammonium acetate (0.72 g, 10 mmol) in a mixture of ethanol (30 ml) and acetic acid (1 ml) was maintained for 72 h at 20°C. The precipitate formed was separated, washed with ether, and crystallized from ethanol to give 1.6 g (74%) product **1**, mp 180-182°C. IR spectrum, ν, cm^{-1}: 3441 (OH); 3283 (NH); 1702 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (2H, s, $^+NH_2$); 3.82 (1H, d, *J* = 11.6, H-3); 4.13 (1H, d, *J* = 1.4, H-5); 4.28 (1H, d, *J* = 11.6, H-2); 4.61 (1H, d, *J* = 1.4, H-6); 6.17 (1H, d, *J* = 7.2, H Ar); 6.33 (1H, t, *J* = 7.2, H Ar); 6.67 (1H, t, *J* = 7.7, H Ar); 6.83 (2H, dd, J_1 = 7.55, J_2 = 6.7, H Ar); 7.00-7.52 (13H, m, H Ar); 7.76 (1H, s, OH). Mass spectrum, *m/z* (I_{rel}, %): 435 $[M]^+$ (4), 226 (100), 196 (14), 181 (5), 167 (10), 122 (20), 107 (9), 91 (32), 77 (12). Found, %: C 79.87; H 5.85; N 3.31. $C_{29}H_{25}NO_3$. Calculated, %: C 79.98; H 5.79; N 3.22.

4-Acetoxy-1-acetyl-2,6-di(2-acetoxyphenyl)-3,5-diphenyl-1,2,3,6-tetrahydropiperidine (2). A solution of piperidone **1** (1 g, 2.3 mmol) in acetic anhydride (10 ml, 110 mmol) was heated at reflux for 5 h. The mixture was treated with saturated aqueous sodium carbonate and extracted with chloroform. The dried extract was subjected to column chromatography using 3:1 ethyl acetate–hexane as the eluent to give 1.09 g (78.3%) product **2** as colorless crystals, mp 98-100°C. IR spectrum, ν, cm^{-1}: 1650 (NC=O, br. s); 1765 (OC=O, br. s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (3H, s, $OCOCH_3$); 1.95 (3H, s, $NCOCH_3$); 2.16 and 2.33 (3H and 3H, two s, $OCOCH_3$); 4.77 (1H, d, *J* = 1.0, H-3); 5.31 (1H, d, *J* = 1.0, H-2); 6.12 (1H, br. s, H-6); 6.44-7.61 (18H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 603 $[M]^+$ (12), 561 (3), 518 (13), 502 (3), 476 (5), 460 (4), 356 (7), 310 (2), 280 (4), 248 (11), 223 (10), 196 (15), 165 (12), 146 (7), 122 (15), 105 (10). Found, %: C 73.70; H 5.44; N 2.25. $C_{37}H_{33}NO_7$. Calculated , %: C 73.62; H 5.51; N 2.32.

6-(3-Methoxyphenyl)- (3a), 6-(Hydroxycarbonylphenyl)- (3b), 6-Hydroxy- (3c), 6-(2-Propoxy) (3d), and 6-(5-Pyrimidinyl)-4-(2-hydroxyphenyl-1,3-diphenyl-1,3,4,11b-tetrahydro-2H-benzo[*e*]pyrido[1,2-*c*]-[1,3,2]oxaza-2-borinone (3e) (General Method). A solution of piperidone **1** (0.87 g, 2 mmol) and boric or corresponding boronic acid (2.1 mmol) in glacial acetic acid (20 ml) was heated at reflux for 3-7 h, then cooled, poured into 50 ml water, neutralized by adding 20% aqueous sodium carbonate, and extracted with ethyl acetate. The dried extract was subjected to column chromatography using chloroform as the eluent to give product **3a-e** as yellowish crystals.

Borinone 3a was obtained in 54% yield, mp 210-212°C. IR spectrum, ν, cm^{-1}: 1634 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (1H, d, *J* = 18.0, H-1); 3.15 (1H, d, *J* = 18.0, H-11*b*); 3.78 (3H, s, OCH_3); 4.44 (1H, d, *J* = 10.8, H-3); 5.15 (1H, d, *J* = 10.8, H-4); 5.96 (1H, d, *J* = 7.5, H-8); 6.42 (1H, t, *J* = 6.9, H-10); 6.65-7.50 (20H, m, 18H Ar, H-9, H-11); 8.68 (1H, s, OH). Mass spectrum, *m/z* (I_{rel}, %): 551 $[M]^+$ (4), 444 (47), 443 (21), 342 (12), 235 (100), 234 (38), 91 (32), 77 (7). Found, %: C 78.35; H 5.54; N 2.47. $C_{36}H_{30}BNO_4$. Calculated, %: C 78.41; H 5.48; N 2.54.

Borinone 3b was obtained in 38% yield, mp 239-241°C. IR spectrum, ν, cm^{-1}: 1628 (C=O), 1698 (OC=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.06 (1H, d, *J* = 18.0, H-1); 3.09 (1H, d, *J* = 18.0, H-11*b*); 4.25 (1H, d, *J* = 10.8, H-3); 5.14 (1H, d, *J* = 10.8, H-4); 5.95 (1H, d, *J* = 7.2, H-8); 6.41 (1H, m, H-10); 6.70-7.50

(16H, m, 14H Ar, H-9, H-11); 7.76 and 8.10 (2H and 2H, two d, $J_1 = J_2 = 8.0$, 6-Ar); 8.66 (1H, s, OH); 9.90 (1H, s, CO_2H). Mass spectrum, *m/z* (I_{rel}, %): 565 $[M]^+$. Found, %: C 76.36; H 5.09; N 2.37. $C_{36}H_{28}BNO_5$. Calculated, %: C 76.47; H 4.99; N 2.48.

Borinone 3c was obtained in 52% yield, mp 200-202°C. IR spectrum, ν, cm^{-1}: 1714 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (1H, br. s, BOH); 3.73 (1H, d, $J = 17.3$, H-1); 3.86 (1H, d, $J = 17.3$, H-11*b*); 5.07 (1H, d, $J = 10.3$, H-3); 5.20 (1H, d, $J = 10.3$, H-4); 6.01 (1H, d, $J = 7.5$, H-8); 6.43 (1H, t, $J = 7.2$, H-10); 6.90-7.55 (16H, m, 14H Ar, H-9, H-11); 8.56 (1H, s, OH). Mass spectrum, *m/z* (I_{rel}, %): 461 $[M]^+$ (2), 443 (2), 324 (3), 252 (100), 251 (28), 235 (20), 165 (13), 132 (38), 91 (26), 77 (11). Found, %: C 75.45; H 5.32; N 2.98. $C_{29}H_{24}BNO_4$. Calculated, %: C 75.50; H 5.24; N 3.04.

Borinone 3c was also obtained in 18% yield as a sideproduct in the condensation of piperidone **2** with triisopropyl borate.

Borinone 3d was obtained in 35% yield, mp 140-142°C. IR spectrum, ν, cm^{-1}: 1637 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.21 and 1.26 (3H and 3H, two d, $J_1 = J_2 = 6.0$; CH_3); 2.09 (1H, d, $J = 18.6$, H-1); 3.48 (1H, m, OCH); 3.71 (1H, d, $J = 18.6$, H-11*b*); 4.72 (1H, d, $J = 11.0$, H-3); 5.03 (1H, d, $J = 11.0$, H-4); 5.93 (1H, br. s, H-8); 6.41 (1H, br. s, H-10); 6.89-7.59 (16H, m, 14H Ar, H-9, H-11); 8.66 (1H, s, OH). Mass spectrum, *m/z* (I_{rel}, %): 503 $[M]^+$ (5), 461 (2), 443 (11), 352 (7), 324 (6), 322 (8), 309 (2), 294 (25), 252 (32), 235 (100), 234 (40), 206 (5), 178 (10), 165 (11), 132 (20), 118 (18), 91 (46), 77 (10). Found, %: C 76.43; H 5.92; N 2.84. $C_{32}H_{30}BNO_4$. Calculated, %: C 76.35; H 6.01; N 2.78. (After storage in the air for 30 days, borinone **3d** is completely converted to borinone **3c**).

Borinone 3e was obtained in 32.4% yield, mp 208-210°C. IR spectrum, ν, cm^{-1}: 1632 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (1H, d, $J = 17.8$, H-1); 3.25 (1H, d, $J = 17.8$, H-11*b*); 4.23 (1H, d, $J = 10.8$, H-3); 5.17 (1H, d, $J = 10.8$, H-4); 6.00 (1H, d, $J = 7.3$, H-8); 6.46 (1H, m, H-10); 6.70-7.55 (16H, m, 14H Ar, H-9, H-11); 8.70 (1H, s, OH); 8.92 (2H, s, H Het); 9.20 (1H, s, H Het). Mass spectrum, *m/z* (I_{rel}, %): 523 $[M]^+$ (2), 444 (16), 392 (2), 352 (2), 314 (15), 272 (2), 248 (3), 235 (100), 210 (10), 165 (12), 148 (7), 128 (15), 91 (100), 77 (10). Found, %: C 75.83; H 5.10; N 7.93. $C_{33}H_{26}BN_3O_3$. Calculated, %: C 75.73; H 5.01; N 8.03.

9,19-Dioxo-18,20-diphenyl-8,10-dioxa-21-aza-9-phosphapentacyclo[15.3.1.$0^{2,7}$.$0^{9,21}$.$0^{11,16}$]henicosa-2,4,6,11,13,15-hexaene (4). Phosphorus oxytrichloride 1.5 ml (0.99 g, 6.44 mmol) was added with stirring to a solution of piperidone **1** (2 g, 4.6 mmol) in dichloromethane (20 ml) and then a solution of triethylamine (1.2 g, 11.9 mmol) was added at a rate such that the mixture was at low reflux. The solution was then stirred for an additional 1 h at room temperature, washed with two 10-ml water portions, dried over $MgSO_4$, and evaporated to dryness. The residue was subjected to column chromatography using 3:1 ethyl acetate–hexane as the eluent to give 0.86 (39%) product **4**, as white crystals with mp 262-264°C, R_f 0.7 (ethyl acetate). IR spectrum, ν, cm^{-1}: 1720 (C=O), 1275 (P=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.13 (2H, d, $J = 8.8$, H-18, H-20); 5.01 (1H, d, $J = 8.8$, H-1); 5.04 (1H, d, $J = 8.8$, H-17); 6.29 (2H, d, $J = 7.6$, H-6, H-12); 6.77 (2H, dd, $J_1 = J_2 = 7.0$, H-4, H-14); 7.01 (4H, br. s, H-3, H-5, H-13, H-15); 7.21-7.31 (10H, m, H Ph); ^{31}P NMR spectrum (benzene), δ, ppm: 4.39 (NPO_3). Mass spectrum, *m/z* (I_{rel}, %): 479 $[M]^+$. Found, %: C 72.54; H 4.73; N 2.86. $C_{29}H_{22}NO_4P$. Calculated, %: C 72.65; H 4.62; H 2.92.

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