Polycyclic *N*-Hetero Compounds. XXXIV. Syntheses and Evaluation of Antidepressive Activity of Benzofuro[2,3-*e*]imidazo[1,2-*c*]pyrimidines and Their Precursors

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Syntheses of 2,3-dihydrobenzofuro[2,3-*e*]imidazo[1,2-*c*]pyrimidine and its 5-substituted derivatives, corresponding to B-nor-6-oxa-11,13,15-triazasteroids, are described. These products and their precursors were screened to evaluate the antidepressive activity.

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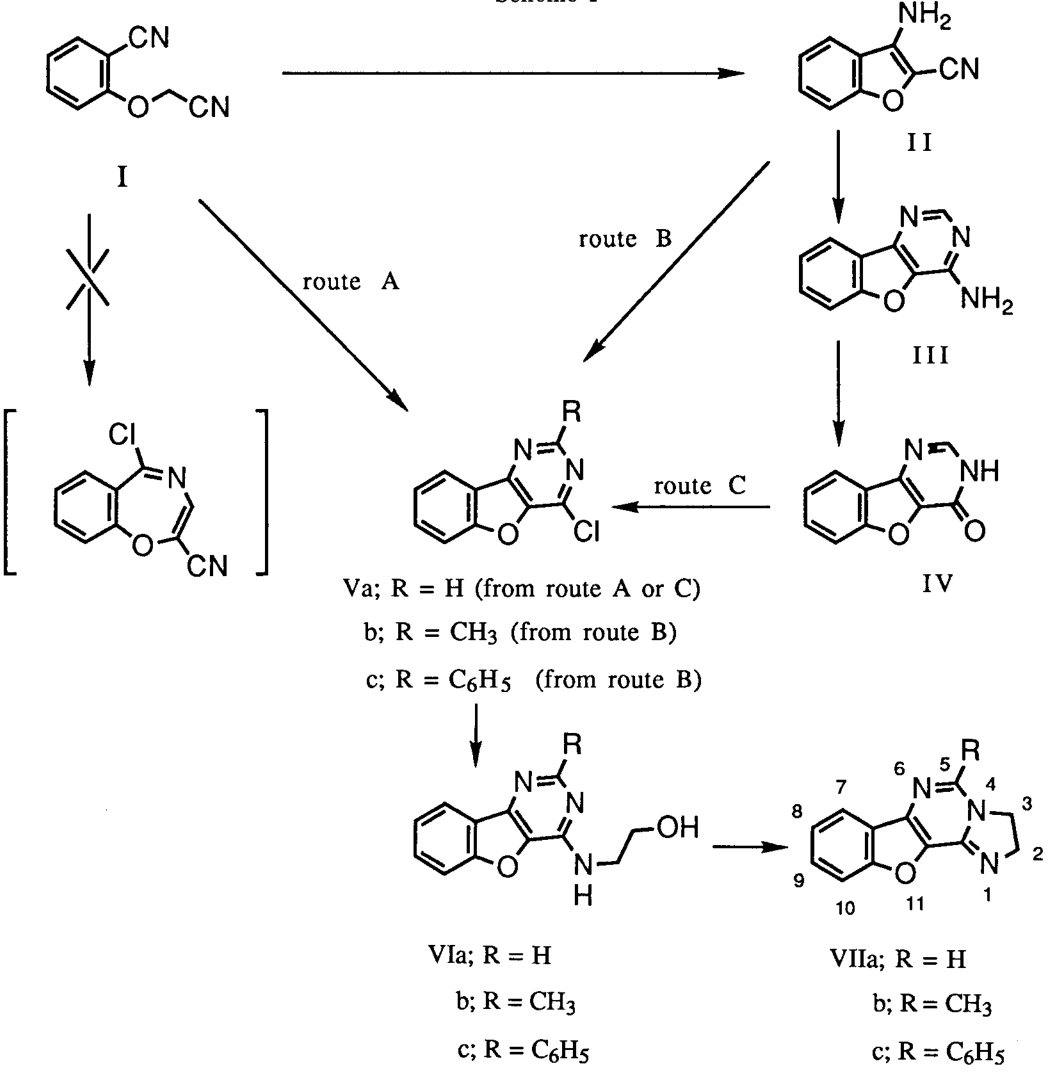
In the previous paper, we have reported a novel synthesis of benzofuran by the Vilsmeier reaction of phenoxyacetonitriles [1]. As an application of this ring-closure reaction, the formation of 2-cyano-1,4-benzoxazepine skeleton was expected when 2-cyanophenoxyacetonitrile (**I**) was used as a starting material instead of phenoxyacetonitrile. Therefore, the Vilsmeier reaction of compound **I** was carried out under similar conditions described previously. However, the obtained product was not the desired 1,4-benzoxazepine derivative but unexpected 4-chlorobenzofuro[3,2-*d*]pyrimidine (**Va**).

Some 4-substituted and 2,4-disubstituted benzofuro-

Scheme 1



[3,2-*d*]pyrimidines were already reported by Angelis and Hess [2] as inhibitors of platelet aggregation. Agasimundin *et al.* [3,4] reported a series of the similar derivatives, and other several investigators [5-7] also reported the similar compounds. However, all of these methods need functional groups at 2- and 3-positions of benzofuran to synthesize the desired 4-substituted or 2,4-disubstituted benzofuro[3,2-*d*]pyrimidines. Among these derivatives, compound **Va** had been synthesized in a similar manner by Angelis and Hess [2] and Sangapure and Agasimundin [3], and they obtained it from ethyl 2-cyanophenoxyacetate, 2-cyanophenoxyacetamide, or 2-cyanophenoxyacetonitrile in 3 steps. In our case, compound **Va** could be directly obtained from compound **I** in one step.

On the other hand, we have also reported the syntheses of 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazolines, corresponding to 11,13,15-triazasteroid derivatives and evaluation of their antidepressive activity [8]. In view of this structure-activity relationship, we are interesting in studying the influence of the change of the ring system of above benzimidazoquinazoline to 2,3-dihydrobenzofuro[2,3-*e*]imidazo[1,2-*c*]pyrimidine (**VIIa**). This change of the ring system is also corresponding to the modification of B-ring of 11,13,15-triazasteroid, and compound **Va** was thought as a useful intermediate.

This paper deals with the syntheses of some 2,3-dihydrobenzofuro[2,3-*e*]imidazo[1,2-*c*]pyrimidine derivatives, corresponding to B-nor-6-oxa-11,13,15-triazasteroids, and evaluation of antidepressive activity for those compounds, including their precursors, using a inhibitory activity test on reserpine-induced hypothermia in mice.

As shown in Scheme 1, compound **Va** was formed from compound **I** under the Vilsmeier reaction in one step (route A). As described above, Angelis and Hess [2] and Sangapure and Agasimundin [3] have already reported about this 4-chloro derivative, but instrumental data of this compound are not described except for its melting point and elemental analytical data in their reports. Compound synthesized by us agreed with Sangapure's compound in respect of its melting point, but disagreed with Angelis' compound. Therefore, alternative synthesis of compound **Va** was planned for the confirmation of the structure of our obtained compound.

As shown in Scheme 1, 4-aminobenzofuro[3,2-*d*]pyrimidine (**III**) was prepared from compound **I** by the method of Sangapure and Agasimundin [3]. Hydrolysis of compound **III** with hydrochloric acid gave 4-oxo-3,4-dihy drobenzofuro[3,2-*d*]pyrimidine (**IV**), which was converted to compound **Va** by refluxing with excess phosphoryl chloride (route C). Instrumental data of thus obtained 4-chloro derivative entirely agreed to those of the compound which was obtained by the Vilsmeier reaction of compound **I**.

Next, the Vilsmeier reaction of the compound **I** with *N,N*-dimethylacetamide or *N,N*-dimethylbenzamide instead of *N,N*-dimethylformamide was carried out for introduction of methyl or phenyl group to the 2-position of benzofuro[3,2-*d*]pyrimidine. However, the desired 2-substituted 4-chlorobenzofuro[3,2-*d*]pyrimidine (**V**) could not be obtained in these reactions under similar conditions and even under severer conditions, and only starting material could be discovered. Earlier workers [2,3] have reported

Table I Effect of Compounds III and VIIa,b on Reserpine-Induced Hypothermia in Mice

Compound	Body temperature (°C), mean value ± SE Before administration	Time after administration 30 minutes	1 hour	2 hours	4 hours
saline	22.9 ± 0.2	24.2 ± 0.6	24.7 ± 0.9	24.8 ± 0.9	25.9 ± 1.3
imipramine	22.8 ± 0.2	25.1 ± 1.1	28.6 ± 2.0	31.8 ± 1.2 [a]	32.9 ± 0.6 [a]
III	23.1 ± 0.3	25.2 ± 0.8	27.1 ± 2.2	29.4 ± 0.8 [a]	32.5 ± 0.7 [a]
VIIa	23.5 ± 0.5	28.0 ± 0.2 [a]	29.7 ± 0.4 [a]	30.0 ± 0.2 [a]	29.7 ± 0.2 [b]
VIIb	22.9 ± 0.3	27.7 ± 0.4 [a]	30.8 ± 0.5 [a]	31.6 ± 0.7 [a]	30.4 ± 1.0 [b]

Five male ICR-JCL mice weighing 22 to 29 g were used in all experiments and test compounds (10 mg/kg, i.p.) were injected at 18 hours after reserpine (2 mg/kg, *i.p.*) was administered to mice. [a] Significantly different from the control (saline) at p<0.01. [b] Significantly different from the control (saline) at p<0.05.

that 2-substituted 4-chlorobenzofuro[3,2-*d*]pyrimidines could be obtained by acylation of 3-amino-2-ethoxycarbonyl (or carbamoyl)benzofuran followed by cyclization with phosphoryl chloride. Therefore, in view of the brief syntheses of 2-substituted 4-chlorobenzofuro[3,2-*d*]pyrimidines, we planned to carry out the direct cyclization of 3-amino-2-benzofurancarbonitrile (**II**) with *N,N*-dimethylacetamide or *N,N*-dimethylbenzamide under the Vilsmeier conditions, and desired 4-chloro-2-methyl- or 4-chloro-2-phenylbenzofuro[3,2-*d*]pyrimidines **Vb,c** could be obtained without necessity of acylation and other treatments (route B).

As the next step, reaction of compound **Va** with ethanolamine gave 4-(2-hydroxyethylamino)benzofuro[3,2-*d*]pyrimidine (**VIa**). This product was easily cyclized with phosphoryl chloride to afford the final desired 2,3-dihydrobenzofuro[2,3-*e*]imidazo[1,2-*c*]pyrimidine (**VIIa**). 2-Methyl- and 2-phenylbenzofuro[3,2-*d*]pyrimidines **Vb,c** were also converted to the desired 5-methyl- and 5-phenyl-2,3-dihydrobenzofuro[2,3-*e*]imidazo[1,2-*c*]pyrimidines **VIIb,c**, respectively, *via* 4-(2-hydroxyethylamino) derivatives **VIb,c** in a similar manner.

Evaluation of the antidepressive activity of thus obtained 2,3-dihydrobenzofuro[2,3-*e*]imidazo[1,2-*c*]pyrimidines (**VII**) and their precursors **I-VI** was screened by the method of Askew [9] which including inhibitory activity against reserpine-induced hypothermia in mice and those data were compared with those of control (saline) and imipramine. When the body temperature of mice administered with a test compound was significantly different from that of mice administered with saline at $p < 0.05$ on the statistical analysis using Student's *t*-test, the test compound was estimated as a potential one. As shown in Table I, compounds **VIIa,b** exhibited the anti-reserpine activity among tetracyclic compounds. Especially, potencies of these compounds at 30 minutes and 1 hour after administration were respectively stronger than that of imipramine. Among precursors **I-VI**, 4-amino derivative **III** was only potential one, and potency of this compound at 4 hours after administration was almost as same as that of imipramine.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were obtained with a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. The pmr spectra were measured with a Hitachi R-22 FTS FT-NMR spectrometer (90 MHz). The chemical shifts (δ) in ppm are measured relative to tetramethylsilane as an internal standard, and the signals are designated as follows; s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br, broad. The EI ms spectra were taken with a Shimadzu LKB-9000 instrument at 70 eV. IUPAC numbering were used in the experimental.

4-Chlorobenzofuro[3,2-*d*]pyrimidine (**Va**).

From 2-Cyanophenoxyacetonitrile (**I**).

The Vilsmeier reagent was prepared by stirring of 0.9 ml (12 mmoles) of *N,N*-dimethylformamide and 2.8 ml (30 mmoles) of phosphoryl chloride for 30 minutes under cooling in an ice bath. To this reagent, was added 1.58 g (10 mmoles) of compound **I** and the mixture was stirred at 70-80° for 3.5 hours. After evaporation of the solvent, the residue was hydrolyzed with small amount of ice water, and the resulting suspension was extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated. The resulting residue was triturated with hot cyclohexane, and hot cyclohexane soluble fraction was chromatographed on silica gel. Benzene eluate was recrystallized from cyclohexane to give 97 mg (5%) of the titled compound as colorless needles, mp 135-138° (lit 142-143° [2], 136° [3]); ms: m/z 204 (M^+); pmr (deuteriochloroform): 7.40-7.90 (3H, m, 6-, 7-, and 8-H), 8.22 (1H, d, J=7.5 Hz, 9-H), 8.96 (1H, s, 2-H).

Anal. Calcd. for $C_{10}H_5ClN_2O$: C, 58.70; H, 2.46; N, 13.69. Found: C, 58.81; H, 2.50; N, 13.91.

From 4-Oxo-3,4-dihydrobenzofuro[3,4-*d*]pyrimidine (**IV**).

The titled compound was prepared by the method of Sangapure and Agasimundin [3], mp 135-138°.

3-Amino-2-benzofurancarbonitrile (**II**).

The titled compound was prepared by the method of Sangapure and Agasimundin [3], mp 154-155° (lit 149° [3]); ms: m/z 158 (M^+); ir (potassium bromide): cm^{-1} 3440, 3350 (N-H), 2200 ($C \equiv N$); pmr (deuteriochloroform): 4.30 (2H, br s, exchangeable with deuterium oxide, NH_2), 7.20-7.70 (4H, m, 4-, 5-, 6-, and 7-H).

Anal. Calcd. for $C_9H_6N_2O$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.08; H, 3.62; N, 17.53.

4-Aminobenzofuro[3,2-*d*]pyrimidine (**III**).

The titled compound was prepared by the method of Sangapure and Agasimundin [3], mp 268-269° (lit. 258° [3]); ms: m/z 185 (M^+); ir (potassium bromide): cm^{-1} 3320, 3145 (N-H); pmr (DMSO-d_6): 7.40-7.80 (5H, m, changed to three protons after addition of deuterium oxide, 6-, 7-, and 8-H, and NH_2), 8.13 (1H, dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 9-H), 8.47 (1H, s, 2-H).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.98; H, 3.66; N, 22.50.

4-Oxo-3,4-dihydrobenzofuro[3,2-*d*]pyrimidine (**IV**).

A solution of 5.05 g (27 mmoles) of compound **III** in 200 ml of 6*N* hydrochloric acid was refluxed for 30 hours. After evaporation of the solvent, saturated sodium hydrogen carbonate solution was added to the residue, and the mixture was extracted with chloroform. The organic layer was worked up usually and the resulting residue was recrystallized from benzene-ethanol to give 2.66 g (52%) of the titled compound as colorless needles, mp 271-273° (lit 277° [3]); ms: m/z 186 (M^+); ir (potassium bromide): cm^{-1} 3100 (N-H), 1705 (C=O); pmr (DMSO-d_6): 7.40-8.10 (4H, m, 6-, 7-, 8-, and 9-H), 8.26 (1H, s, 2-H), 12.9 (1H, br, exchangeable with deuterium oxide, NH).

Anal. Calcd. for $C_{10}H_6N_2O_2$: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.71; H, 3.11; N, 14.81.

4-Chloro-2-methylbenzofuro[3,2-*d*]pyrimidine (**Vb**).

The Vilsmeier reagent was prepared by stirring of 1.1 ml (12 mmoles) of *N*,*N*-dimethylacetamide and 2.8 ml (30 mmoles) of phosphoryl chloride under cooling in an ice bath for 30 minutes. To this reagent, was added 1.58 g (10 mmoles) of compound **II** and the mixture was stirred at 50° for 2 hours. After evaporation of the solvent, small amount of water was added to the residue. The resulting mixture was basified with sodium hydrogen carbonate and the mixture was extracted with chloroform. The organic layer was worked up usually and the resulting residue was recrystallized from benzene to give 1.14 g (52%) of the titled compound as colorless powder, mp 116-118° (lit 114-115° [3]); ms: m/z 218 (M^+); pmr (deuteriochloroform): 2.86 (3H, s, CH_3), 7.40-7.70 (3H, m, 6-, 7-, and 8-H), 8.21 (1H, d, J = 7.5 Hz, 9-H).

Anal. Calcd. for $C_{11}H_7ClN_2O$: C, 60.43; H, 3.23; N, 12.81. Found: C, 60.66; H, 3.38; N, 12.59.

4-Chloro-2-phenylbenzofuro[3,2-*d*]pyrimidine (**Vc**).

The Vilsmeier reagent was prepared by stirring of 1.79 g (12 mmoles) of *N*,*N*-dimethylbenzamide and 1.12 ml (12 mmoles) of phosphoryl chloride under cooling in an ice bath for 30 minutes. To this reagent, was added 1.58 g (10 mmoles) of compound **II** and the mixture was stirred at 70-80° for 3 hours. To the reaction mixture, was added 12 ml of dry chloroform and the mixture was refluxed for further 3 hours. After evaporation of the solvent, the resulting residue was treated in a similar manner described in the synthesis of compound **Vb**, and the residue from the organic layer was recrystallized from benzene-dioxane to give 0.85 g (30%) of the titled compound as colorless powder, mp 160-164°; ms: m/z 280 (M^+); pmr (deuteriochloroform): 7.40-7.80 (6H, m, 6-, 7-, and 8-H and phenyl-3′-, 4′-, and 5′-H), 8.30 (1H, d, J = 7.5 Hz, 9-H), 8.66 (2H, m, phenyl-2′- and 6′-H).

Anal. Calcd. for $C_{16}H_9ClN_2O$: C, 68.45; H, 3.21; N, 9.98. Found: C, 68.42; H, 3.08; N, 9.95.

4-(2-Hydroxyethylamino)benzofuro[3,2-*d*]pyrimidine (**VIa**).

A mixture of 1.02 g (5 mmoles) of compound **Va** and 3.0 g (50 mmoles) of ethanolamine was stirred at 90° for 2.5 hours. After addition of water to the reaction mixture, the precipitated crystalline solid was collected *in vacuo* and washed with water. This solid was recrystallized from benzene-cyclohexane to give 0.52 g (45%) of the titled compound as pale yellow powder, mp 158-160°; ms: m/z 229 (M^+); ir (potassium bromide): cm^{-1} 3375, 3175 (N-H and O-H); pmr (DMSO-d_6): 3.63 (4H, br s, CH_2CH_2), 4.80 and 7.97 (each 1H, each br s, exchangeable with deuterium oxide, NH and OH), 7.40-7.80 (3H, m, 6-, 7-, and 8-H), 8.10 (1H, d, J = 7.5 Hz, 9-H), 8.50 (1H, s, 2-H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.84; N, 18.32. Found: C, 62.68; H, 4.69; N, 18.11.

4-(2-Hydroxyethylamino)-2-methylbenzofuro[3,2-*d*]pyrimidine (**VIb**).

A mixture of 542 mg (2.48 mmoles) of compound **Vb** and 0.74 ml (12.4 mmoles) of ethanolamine was stirred at 70° for 15 minutes. After addition of water to the reaction mixture, the precipitated crystalline solid was collected *in vacuo* and washed with water. This solid was recrystallized from benzene-ethanol to give 591 mg (98%) of the titled compound as colorless powder, mp 189-190°; ms: m/z 243 (M^+); ir (potassium bromide): cm^{-1} 3300, 3170 (N-H and O-H); pmr (DMSO-d_6): 2.55 (3H, s, CH_3), 3.64 (4H, br s, CH_2CH_2), 4.79 (1H, br s, exchangeable with deuterium oxide, NH or OH), 7.30-7.90 (4H, m, changed to three protons after addition of deuterium oxide, 6-, 7-, and 8-H and NH or OH), 8.06 (1H, d, J = 7.5 Hz, 9-H).

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.41; H, 5.20; N, 17.42.

4-(2-Hydroxyethylamino)-2-phenylbenzofuro[3,2-*d*]pyrimidine (**VIc**).

A mixture of 680 mg (2.43 mmoles) of compound **Vc** and 0.74 ml (12.4 mmoles) of ethanolamine was stirred at 100° for 2 hours. After further addition of 0.74 ml of ethanolamine, the mixture was stirred at 130-150° for 1 hour, and water was added to the reaction mixture. The precipitated crystalline solid was collected *in vacuo* and recrystallized from benzene-ethanol to give 480 mg (65%) of the titled compound as colorless powder, mp 177-180°; ms: m/z 305 (M^+); ir (potassium bromide): cm^{-1} 3250, 3200 (N-H and O-H); pmr (DMSO-d_6): 3.80 (4H, br s, CH_2CH_2), 4.83 (1H, br, exchangeable with deuterium oxide, NH or OH), 7.40-7.80 (7H, m, changed to six protons after addition of deuterium oxide, 6-, 7-, and 8-H, phenyl-3′-, 4′-, and 5′-H, and NH or OH), 8.20 (1H, d, J = 7.5 Hz, 9-H), 8.40-8.60 (2H, m, phenyl-2′- and 6′-H).

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.82; H, 4.92; N, 13.77. Found: C, 70.65; H, 4.82; N, 13.52.

2,3-Dihydrobenzofuro[2,3-*e*]imidazo[1,2-*c*]pyrimidine (**VIIa**).

A mixture of 377 mg (1.65 mmoles) of compound **VIa**, 0.77 ml (8.25 mmoles) of phosphoryl chloride, and 2 ml of dry chloroform was refluxed for 50 minutes. After evaporation of the solvent, the residue was basified with saturated sodium hydrogen carbonate solution and the mixture was further evaporated to dryness. The resulting residue was triturated with hot cyclohexane and the hot cyclohexane-insoluble fraction was recrystallized from benzene-cyclohexane to give 116 mg (33%) of the titled compound as colorless powder, mp 242-244°; ms: m/z 211 (M^+); pmr (DMSO-d_6): 4.00-4.40 (4H, m, 2- and 3-H), 7.30-8.00 (4H, m, 7-, 8-, 9-, and 10-H), 8.25 (1H, s, 5-H).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.98. Found: C, 67.99; H, 4.10; N, 19.86.

5-Methyl-2,3-dihydrobenzofuro[2,3-*e*]imidazo[1,2-c]pyimidine (**VIIb**).

A mixture of 378 mg (1.55 mmoles) of compound **VIb**, 0.72 ml (7.75 mmoles) of phosphoryl chloride, and 20 ml of dry dichloromethane was refluxed for 3.5 hours. After evaporation of the solvent, the residue was basified with saturated sodium hydrogen carbonate solution and the mixture was extracted with chloroform. The organic layer was worked up usually and the resulting residue was recrystallized from benzene-ethanol to give 140 mg (40%) of the titled compound as colorless powder, mp 236-237°; ms: m/z 225 (M^+); pmr (deuteriochloroform): 2.45 (3H, s, CH_3), 4.20 (4H, s, 2- and 3-H), 7.30-7.60 (3H, m, 8-, 9-, and 10-H), 7.97 (1H, d, J = 7.5 Hz, 7-H).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.61; H, 5.01; N, 18.53.

5-Phenyl-2,3-dihydrobenzofuro[2,3-*e*]imidazo[1,2-c]pyrimidine (**VIIc**).

A mixture of 340 mg (1.1 mmoles) of compound **VIc**, 0.5 ml (5.4 mmoles) of phosphoryl chloride, and 2 ml of dry chloroform was refluxed for 2 hours. After evaporation of the solvent, the residue was basified with aqueous sodium carbonate solution and the mixture was extracted with chloroform. The organic layer was worked up usually, and the resulting residue was recrystallized from aqueous methanol to give 69 mg (21%) of the titled compound as pale yellow powder, mp 158-160°; ms: m/z 287 (M^+); pmr (deuteriochloroform): 4.16 (4H, s, 2- and 3-H), 7.30-7.50 (8H, m, 8-, 9-, and 10-H and phenyl-H), 8.03 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz, 7-H).

Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.26; H, 4.53; N, 14.63. Found: C, 75.50; H, 4.38; N, 14.58.

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