# Polycyclic *N*-Hetero Compounds; XXXIX: A Facile Synthesis of 1,2,4,5-Tetrahydro-[1]benzoxepino[4,5-*e*]imidazo[1,2-*c*]pyrimidines via Ring Closure of 4-(2-Hydroxyalkylamino)-5,6-dihydro-[1]benzoxepino[5,4-*d*]pyrimidines

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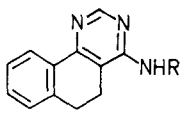
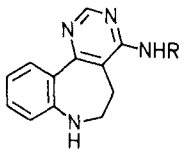
The first example of the unknown [1]benzoxepino[4,5-*e*]imidazo[1,2-*c*]pyrimidine ring system is demonstrated as a new class of potent anit-platelet aggregation agents. That is, the 1,2,4,5-tetrahydro-[1]benzoxepino[4,5-*e*]imidazo[1,2-*c*]pyrimidines **11a–c** were prepared by ring closure of 4-(2-hydroxyalkylamino)-5,6-dihydro-[1]benzoxepino[5,4-*d*]pyrimidines **10a–c** with phosphoryl chloride.

In connection with our a program of preparing polyheterocyclic compounds which might have potential biological activities such as antidepressive activity[1] and anti-platelet aggregation activity,[2] we have designed to prepare such compounds with new ring systems. Indeed, we have discovered that 4-alkylamino-5,6-dihydrobenzo[*h*]quinazolines **1**,[2] 4-alkylamino-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines **2**,[3] and 1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepines **3**[3] had stronger inhibitory activities against collagen-induced aggregation of rabbit blood *in vitro* than that of aspirin which was familiar as an anti-platelet agent.[4]




**1**

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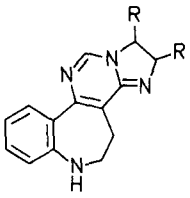
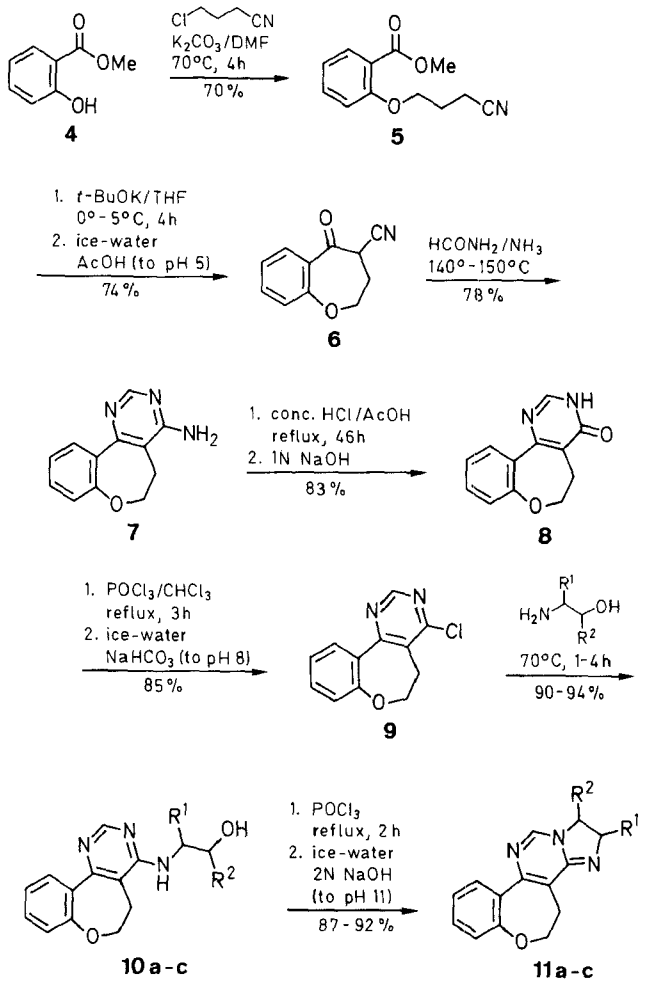



**3**

R = H, alkyl

We report herein an efficient methodology for the preparation of the hitherto unknown ring system 1,2,4,5-tetrahydro-[1]benzoxepino[4,5-*e*]imidazo[1,2-*c*]pyrimidines **11a–c** via 4-(2-hydroxyalkylamino)-5,6-dihydro-[1]benzoxepino[5,4-*d*]pyrimidines **10a–c** in a simple synthetic route. As shown in the Scheme, the key intermediate 5-oxo-2,3,4,5-tetrahydro-[1]benzoxepin-4-carbonitrile **(6)**[5] was prepared by the Dieckmann-type cyclization of methyl *O*-(3-cyanopropyl)salicylate **(5)** with potassium *tert*-butoxide as a condensing agent by application of the method[6] described by Unangst et al. Heating of methyl salicylate **(4)** with 4-chlorobutyronitrile in dry dimethylformamide containing anhydrous potassium carbonate gave the necessary compound **5**. Treatment of **5** with potassium *tert*-butoxide in dry tetrahydrofuran at 0–5°C afforded the desired compound **6** which was identical with the authentic sample[5] prepared from 4,5-dihydro-[1]benzoxepino[4,5-*d*]-isoxazole. The structure of **6** having a 7-membered β-oxo nitrile was verified by the IR spectrum which showed the characteristic C≡N band at $\nu = 2250\ cm^{-1}$ and the C=O band at $\nu = 1681\ cm^{-1}$, and the $^1$H-NMR spectrum indicated the double doublet signal of one proton at $\delta = 4.22$ which was attributable to the presence of a proton at the 4-position. The β-oxo nitrile **6** obtained was then successfully cyclized in good yield by the reaction with formamide under ammonia stream at 140–150°C to produce an additional pyrimidine ring on the 1-benzoxepin skeleton. The structure of the tricyclic compound, 4-amino-5,6-dihydro-[1]benzoxepino[5,4-*d*]pyrimidine **(7)**, was supported by satisfactory analytical and spectral data. In particular, the IR spectrum showed the characteristic N-H bands at $\nu_{as} = 3420$, $\nu_s = 3320$ and $\delta = 1650\ cm^{-1}$, and the $^1$H-NMR spectrum demonstrated one proton singlet at $\delta = 8.60$ which was attributable to the proton at 2-position on the newly synthesized pyrimidine ring. Hydrolysis of the 4-amino group of **7** to afford **8** was achieved by heating **7** with a mixture of concentrated hydrochloric acid and glacial acetic acid. Compound **8** exhibited N–H and C=O absorptions in the IR spectrum at $\nu = 3140$ and $1660\ cm^{-1}$, respectively, and demonstrated one proton singlet in the $^1$H-NMR spectrum at $\delta = 8.23$ attributable to the pyrimidine ring proton. Treatment of **8** with phosphoryl chloride gave the corresponding 4-chloro derivative **9** in 85% yield. The precursors 4-(2-hydroxyalkylamino)-5,6-dihydro-[1]benzoxepino[5,4-*d*]pyrimidines **10a–c** of the intended tetracyclic derivatives **11a–c** were prepared by heating **9** with an appropriate 2-hydroxyalkylamines in almost quantitative yield. Finally, the title compounds,

1,2,4,5-tetrahydro-[1]benzoxepino[4,5-*e*]imidazo[1,2-*c*]pyrimidines **11a–c**, were synthesized by the intramolecular dehydrating cyclization of **10a–c** thus obtained with phosphoryl chloride in excellent yields. The structures were verified by elemental analyses, FAB mass spectrometry, and $^1$H-NMR spectroscopy as shown in the experimental part. To our knowledge, the ring system of tetracyclic hetero compounds **11a–c** has not yet been reported, and that of tricyclic hetero compounds **10a–c** only twice.[7,8]




| 10, 11 | $R^1$ | $R^2$ |
|---|---|---|
| **a** | H | H |
| **b** | H | Me |
| **c** | Me | H |

Scheme

The products prepared herein were carried out the screening test for the inhibitory activity against rabbit platelet aggregation by a turbidimetric method reported by Born and Cross[9] using an aggregometer. Among them, the compounds **10a–c** and **11b, c** were found to have stronger inhibitory activities than that of aspirin. Further investigation along this line are now in progress.

All reagents were of commercial quality from freshly opened containers and were used without further purification. Methyl salicylate, ethanolamine, D,L-1-amino-2-propanol, and D,L-2-amino-1-propanol were purchased from Tokyo Kasei Co. 4-Chlorobutyronitrile was purchased from Merck Chemical Co. Reactions were monitored by analytical thin layer chromatography (TLC) performed on Wako 70 FM silica gel plates and products were visualized by UV light. Column chromatography was carried out with Kiesel gel 60 (70–230 mesh ASTM, Merck). Melting points were taken using a Yanagimoto micro melting point apparatus and are uncorrected. Microanalyses were obtained using a Yanagimoto MT-2 CHN Corder element analyser. Mass spectra were obtained using a VG-70SE spectrometer with FAB ionization. IR spectra were obtained using a JASCO IRA-102 spectrophotometer. $^1$H-NMR spectra were obtained using a Varian VXR 200 MHz spectrometer with TMS as the internal standard.

**Methyl *O*-(3-Cyanopropyl)salicylate (5):**
A mixture of methyl salicylate (**4**; 50 g, 329 mmol), 4-chlorobutyronitrile (51 g, 493 mmol), and anhydr. $K_2CO_3$ (125 g, 904 mmol) in dry DMF (250 mL) is heated with stirring at 70°C for 4 h. The solvent is evaporated at reduced pressure and the residual oil is distilled to get pure compound **5** as a colorless oil; yield: 50.5 g (70%); bp 174–175°C/2.5 Torr; $R_f$ 0.11 (benzene).

$C_{12}H_{13}NO_3$ calc. C 65.74 H 5.98 N 6.39
(219.2) found 65.59 6.09 6.43

IR ($CHCl_3$): $\nu$ = 2250 (C≡N), 1720 (C=O), 1250, 1130 cm$^{-1}$ (COC).

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 1.96 (m, 2H, $OCH_2CH_2$), 2.37 (t, 2H, $J$ = 6.20 Hz, $CH_2CN$), 2.96 (s, 3H, $OCH_3$), 3.47 (t, 2H, $J$ = 6.20 Hz, $OCH_2$), 6.80 (m, 2H, H-3, H-5), 7.30 (m, 2H, H-4, H-6).

MS: $m/z$ = 220 ($MH^+$).

**5-Oxo-2,3,4,5-tetrahydro-[1]benzoxepin-4-carbonitrile (6):**
To an ice-cooled suspension of *t*-BuOK (22.1 g, 200 mmol) in dry THF (300 mL) is added **5** (26.5 g, 121 mmol) in dry THF (130 mL) in one portion, and the mixture is stirred at 0–5°C for 4 h. After the reaction, the mixture is taken up in ice-water (900 mL) and acidified (pH 5) with AcOH to obtain a precipitate, which is recrystallized from MeOH/$Et_2O$ to give **6** as colorless prisms; yield: 16.6 g (74%); mp 75–77°C (Lit.[5] mp 78°C); $R_f$ 0.71 (EtOAc/benzene/$CHCl_3$/AcOH, 5:4:3:1).

IR (KBr): $\nu$ = 2250 (C≡N), 1681 cm$^{-1}$ (C=O).

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 2.41 (m, 1H, one of H-3), 2.83 (m, 1H, one of H-3), 4.01 (m, 1H, one of H-2), 4.22 (dd, 1H, $J$ = 6.97, 10.61 Hz, H-4, exchangeable with $D_2O$), 4.58 (m, 1H, one of H-2), 7.11 (m, 1H, H-9), 7.17 (m, 1H, H-8), 7.51 (m, 1H, H-7), 7.83 (dd, 1H, $J$ = 7.80, 1.76 Hz, H-6).

**4-Amino-5,6-dihydro-[1]benzoxepino[5,4-*d*]pyrimidine (7):**
A mixture of **6** (26.7 g, 143 mmol) and formamide (200 mL) is heated at 140–150°C with stirring under $NH_3$ stream until the substrate **6** disappears. The reaction is monitored by TLC using EtOAc/benzene/$CHCl_3$/AcOH (5:4:3:1) as eluent and the product is visualized by UV light. The mixture is allowed to stand overnight in a refrigerator, and the resultant crystals are collected by filtration and recrystallized from EtOH to give **7** as colorless prisms; yield: 23.8 g (78%); mp 135–136°C; $R_f$ 0.26.

$C_{12}H_{11}N_3O$ calc. C 67.59 H 5.20 N 19.71
(213.2) found 67.51 5.12 18.82

IR (KBr): $\nu$ = 3420, 3320 cm$^{-1}$ ($NH_2$), and $\delta$ = 1650 cm$^{-1}$ ($NH_2$).

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 2.74 (t, 2H, $J$ = 5.92 Hz, H-5), 4.55 (t, 2H, $J$ = 5.92 Hz, H-6), 5.02 (br s, 2H, $NH_2$, exchangeable with $D_2O$), 7.10 (dd, 1H, $J_{8-9}$ = 7.97 Hz, $J_{8-10}$ = 1.38 Hz, H-8), 7.24 (dt, 1H, $J_{8-10}$ = 1.38 Hz, $J_{9-10}$ = 7.35 Hz, $J_{10-11}$ = 7.74 Hz, H-10), 7.40 (ddd, 1H, $J_{8-9}$ = 7.97 Hz, $J_{9-10}$ = 7.35 Hz, $J_{9-11}$ = 1.76 Hz, H-9), 8.12 (dd, 1H, $J_{9-11}$ = 1.76 Hz, $J_{10-11}$ = 7.74 Hz, H-11), 8.60 (s, 1H, H-2).

MS: $m/z$ = 214 ($MH^+$).

**5,6-Dihydro-[1]benzoxepino[5,4-*d*]pyrimidin-4(3*H*)-one (8):**
A mixture of **7** (11.2 g, 52.5 mmol) with concentrated HCl (183 mL) and AcOH (83 mL) is heated under reflux for 46 h. In completing the reaction, further addition of conc. HCl (4 × 40 mL) is necessary during the reaction. The resulting solution is concentrated to dryness *in vacuo*, and the residue is dissolved in $H_2O$ and neutralized with 1 N NaOH under cooling. The precipitate formed is filtered by suction, washed with cold $H_2O$, and recrystallized from EtOH to give **8** as colorless prisms; yield: 9.9 g (83%); mp 246–247 °C; $R_f$ 0.83 (MeOH/$CHCl_3$, 2:3).

| $C_{12}H_{10}N_2O_2$ | calc. | C 67.28 | H 4.71 | N 13.08 |
|---|---|---|---|---|
| (214.2) | found | 67.23 | 4.63 | 13.01 |

IR (KBr): $\nu$ = 3140 (NH), 1660 (C=O), 1330 $cm^{-1}$ (C–N).

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 2.97 (t, 2 H, $J$ = 5.86 Hz, H-5), 4.60 (t, 2 H, $J$ = 5.86 Hz, H-6), 7.13 (dd, 1 H, $J_{8-9}$ = 7.90 Hz, $J_{8-10}$ = 1.30 Hz, H-8), 7.23 (dt, 1 H, $J_{8-10}$ = 1.30 Hz, $J_{9-10}$ = 7.57 Hz, $J_{10-11}$ = 7.86 Hz, H-10), 7.42 (ddd, 1 H, $J_{8-9}$ = 7.90 Hz, $J_{9-10}$ = 7.57 Hz, $J_{9-11}$ = 1.76 Hz, H-9), 8.04 (dd, 1 H, $J_{9-11}$ = 1.76 Hz, $J_{10-11}$ = 7.86 Hz, H-11), 8.23 (s, 1 H, H-2), 13.33 (br s, 1 H, NH, exchangeable with $D_2O$).

MS: $m/z$ = 215 ($MH^+$).

**4-Chloro-5,6-dihydro-[1]benzoxepino[5,4-*d*]pyrimidine (9):**
To a stirring mixture of **8** (21.1 g, 98.5 mmol) in ethanol-free dry $CHCl_3$ (53 mL) is added $POCl_3$ (92 mL, 985 mmol), and the solution is heated under reflux for 3 h. The solution is concentrated to dryness *in vacuo* and ice-water (ca. 70 mL) is poured at once to the residue. The resulting solution is basified (pH ca. 8) with sat. aq $NaHCO_3$ to afford the solid, which is filtered by suction, washed with cold $H_2O$, and recrystallized from EtOH to give **9** as colorless needles; yield: 19.6 g (85%); mp 112–113 °C; $R_f$ 0.90 (MeOH/$CHCl_3$, 2:3).

| $C_{12}H_9ClN_2O$ | calc. | C 61.95 | H 3.90 | N 12.04 |
|---|---|---|---|---|
| (232.7) | found | 61.73 | 3.81 | 11.89 |

IR (KBr): $\nu$ = 762 $cm^{-1}$ (C–Cl).

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 3.12 (t, 2 H, $J$ = 6.10 Hz, H-5), 4.63 (t, 2 H, $J$ = 6.10 Hz, H-6), 7.16 (dd, 1 H, $J_{8-9}$ = 8.0 Hz, $J_{8-10}$ = 1.22 Hz, H-8), 7.29 (dt, 1 H, $J_{8-10}$ = 1.22 Hz, $J_{9-10}$ = 7.37 Hz, $J_{10-11}$ = 7.78 Hz, H-10), 7.49 (ddd, 1 H, $J_{8-9}$ = 8.0 Hz, $J_{9-10}$ = 7.37 Hz, $J_{9-11}$ = 1.77 Hz, H-9), 7.98 (dd, 1 H, $J_{9-11}$ = 1.77 Hz, $J_{10-11}$ = 7.78 Hz, H-11), 8.96 (s, 1 H, H-11).

MS: $m/z$ = 233 ($MH^+$).

**4-(2-Hydroxyethylamino)-5,6-dihydro-[1]benzoxepino[5,4-*d*]pyrimidine (10a):**
A mixture of **9** (1 g, 4.3 mmol) and ethanolamine (1.8 g, 30.1 mmol) is heated with stirring at 70 °C for 1.5 h. Evaporation of the excess ethanolamine *in vacuo* and treatment of the residue with $H_2O$ (ca. 20 mL) yields the solid, which is filtered by suction, washed with cold $H_2O$, and recrystallized from benzene to give **10a** as colorless prisms; yield: 1.1 g (94%); mp 145–147 °C; $R_f$ 0.76 (MeOH/$CHCl_3$, 2:3).

| $C_{14}H_{15}N_3O_2$ | calc. | C 65.35 | H 5.88 | N 16.33 |
|---|---|---|---|---|
| (257.3) | found | 65.38 | 5.89 | 16.63 |

IR (KBr): $\nu$ = 3560 (OH), 3320 (NH), 1060 $cm^{-1}$ (COH).

$^1$H-NMR (DMSO-$d_6$/TMS): $\delta$ = 2.72 (t, 2 H, $J$ = 5.95 Hz, H-5), 3.48 (t, 2 H, $J$ = 5.0 Hz, $NHCH_2$), 3.54 (t, 2 H, $J$ = 5.0 Hz, $CH_2OH$), 4.46 (t, 2 H, $J$ = 5.95 Hz, H-6), 4.75 (t, 1 H, $J$ = 5.37 Hz, OH, exchangeable with $D_2O$), 7.07 (dd, 1 H, $J_{8-9}$ = 7.90 Hz, $J_{8-10}$ = 1.28 Hz, H-8), 7.16 (br s, 1 H, NH, exchangeable with $D_2O$), 7.21 (dt, 1 H, $J_{8-10}$ = 1.28 Hz, $J_{9-10}$ = 7.41 Hz, $J_{10-11}$ = 7.78 Hz, H-10), 7.40 (ddd, 1 H, $J_{8-9}$ = 7.90 Hz, $J_{9-10}$ = 7.41 Hz, $J_{9-11}$ = 1.77 Hz, H-9), 7.89 (dd, 1 H, $J_{9-11}$ = 1.77 Hz, $J_{10-11}$ = 7.78 Hz, H-11), 8.44 (s, 1 H, H-2).

MS: $m/z$ = 258 ($MH^+$).

**4-(2-Hydroxypropylamino)-5,6-dihydro-[1]benzoxepino[5,4-*d*]pyrimidine (10b):**
A mixture of **9** (2 g, 8.6 mmol) and 1-amino-2-propanol (2.6 g, 34.6 mmol) is heated with stirring at 70 °C for 1 h. Treatment of the mixture with $H_2O$ (ca. 40 mL) gives the solid, which is filtered by suction, washed with cold $H_2O$, and recrystallized from EtOH/benzene to obtain **10b** as colorless granules; yield: 2.2 g (94%); mp 189–190 °C; $R_f$ 0.81 (MeOH/$CHCl_3$ 2:3).

| $C_{15}H_{17}N_3O_2$ | calc. | C 66.40 | H 6.32 | N 15.49 |
|---|---|---|---|---|
| (271.3) | found | 66.17 | 6.45 | 15.38 |

IR (KBr): $\nu$ = 3320 (OH), 3170 (NH), 1030 $cm^{-1}$ (COH).

$^1$H-NMR (DMSO-$d_6$/TMS): $\delta$ = 1.07 (d, 3 H, $J$ = 6.11 Hz, $CH_3$), 2.73 (t, 2 H, $J$ = 5.98 Hz, H-5), 3.37 (m, 2 H, $NHCH_2$), 3.88 (m, 1 H, $NHCH_2CH$), 4.46 (t, 2 H, $J$ = 5.98 Hz, H-6), 4.79 (d, 1 H, $J$ = 4.58 Hz, OH, exchangeable with $D_2O$), 7.07 (dd, 1 H, $J_{8-9}$ = 7.90 Hz, $J_{8-10}$ = 1.28 Hz, H-8), 7.15 (br s, 1 H, NH, exchangeable with $D_2O$), 7.22 (dt, 1 H, $J_{8-10}$ = 1.28 Hz, $J_{9-10}$ = 7.30 Hz, $J_{10-11}$ = 7.71 Hz, H-10), 7.40 (ddd, 1 H, $J_{8-9}$ = 7.90 Hz, $J_{9-10}$ = 7.30 Hz, $J_{9-11}$ = 1.75 Hz, H-9, 7.88 (dd, 1 H, $J_{9-11}$ = 1.75 Hz ($J_{10-11}$ = 7.71 Hz, H-11), 8.43 (s, 1 H, H-2).

MS: $m/z$ = 272 ($MH^+$).

**4-[(2-Hydroxy-1-methylethyl)amino]-5,6-dihydro-[1]benzoxepino-[5,4-*d*]pyrimidine (10c):**
A mixture of **9** (2 g, 8.6 mmol) and 2-amino-1-propanol (1.9 g, 25.8 mmol) is heated with stirring at 70 °C for 4 h. The mixture is diluted with $H_2O$ (40 mL) and extracted with EtOAc (4 × 15 mL). The organic layer is washed several times with sat. aq NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to yield the solid, which is recrystallized from EtOH/benzene to obtain **10c** as colorless needles; yield: 2.1 g (90%); mp 155–156 °C; $R_f$ 0.77 (MeOH/$CHCl_3$, 2:3).

| $C_{15}H_{17}N_3O_2$ | calc. | H 66.40 | H 6.32 | N 15.49 |
|---|---|---|---|---|
| (271.3) | found | 66.39 | 6.42 | 15.65 |

IR (KBr): $\nu$ = 3330 (OH), 3100 (NH), 1050 $cm^{-1}$ (COH).

$^1$H-NMR (DMSO-$d_6$/TMS): $\delta$ = 1.16 (d, 3 H, $J$ = 6.70 Hz, $CH_3$), 2.73 (t, 2 H, $J$ = 5.86 Hz, H-5), 3.37, 3.49 (each m, 2 H, $CHCH_2OH$), 4.26 (m, 1 H, NHCH), 4.46 (t, 2 H, $J$ = 5.86 Hz, H-6), 4.73 (br, 1 H, OH, exchangeable with $D_2O$), 6.73 (d, 1 H, $J$ = 7.63 Hz, NH, exchangeable with $D_2O$), 7.07 (dd, 1 H, $J_{8-9}$ = 7.94 Hz, $J_{8-10}$ = 1.30 Hz, H-8), 7.22 (dt, 1 H, $J_{8-10}$ = 1.30 Hz, $J_{9-10}$ = 7.38 Hz, $J_{10-11}$ = 7.70 Hz, H-10), 7.41 (dd, 1 H, $J_{8-9}$ = 7.94 Hz, $J_{9-10}$ = 7.38 Hz, $J_{9-11}$ = 1.81 Hz, H-9), 7.86 (dd, 1 H, $J_{9-11}$ = 1.81 Hz, $J_{10-11}$ = 7.70 Hz, H-11), 8.44 (s, 1 H, H-2).

MS: $m/z$ = 272 ($MH^+$).

**1,2,4,5-Tetrahydro-[1]benzoxepino[4,5-*e*]imidazo[1,2-*c*]pyrimidine (11a); Typical Procedure:**
A mixture of **10a** (1 g, 3.9 mmol) and $POCl_3$ (5.6 mL, 60 mmol) is heated under reflux for 3 h. The excess of $POCl_3$ is then removed *in vacuo* and ice-water (ca. 25 mL) is poured at once to the residue. The pH of the resulting solution is adjusted to 11 by adding 2 N NaOH and extracted with EtOAc (4 × 10 mL). The organic layer is washed with sat. aq NaCl, dried ($MgSO_4$), and evaporated *in vacuo*. The residue is recrystallized from EtOAc to afford **11a** as yellow prisms; yield: 0.81 g (87%); mp 104–106 °C; $R_f$ 0.42 (MeOH/$CHCl_3$, 2:3).

| $C_{14}H_{13}N_3O$ | calc. | C 70.27 | H 5.48 | N 17.56 |
|---|---|---|---|---|
| (239.3) | found | 70.23 | 5.60 | 17.27 |

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 2.83 (t, 2 H, $J$ = 5.89 Hz, H-5), 4.10 (m, 4 H, H-1, H-2), 4.53 (t, 2 H, $J$ = 5.89 Hz, H-6), 7.07 (dd, 1 H, $J_{7-8}$ = 7.93 Hz, $J_{7-9}$ = 1.38 Hz, H-7), 7.17 (dt, 1 H, $J_{7-9}$ = 1.38 Hz, $J_{8-9}$ = 7.37 Hz, $J_{9-10}$ = 7.81 Hz, H-9), 7.33 (ddd, 1 H, $J_{7-8}$ = 7.93 Hz, $J_{8-9}$ = 7.37 Hz, $J_{8-10}$ = 1.80 Hz, H-8), 7.84 (s, 1 H, H-12), 7.96 (dd, 1 H, $J_{8-10}$ = 1.80 Hz, $J_{9-10}$ = 7.81 Hz, H-10).

MS: $m/z$ = 240 ($MH^+$).

*1-Methyl-1,2,4,5-tetrahydro-[1]benzoxepino[4,5-e]imidazo[1,2-c]pyrimidine* **(11b)**: The compound **11b** is prepared according to the above procedure by employing **10b** (1 g, 3.7 mmol). The crude compound thus obtained is purified by column chromatography on silica gel (benzene/EtOAc, 4:1) and recrystallized from EtOH/EtOAc to afford **11b** as yellow needles; yield: 0.86 g (92%); mp 256–258 °C; $R_f$ 0.49 (MeOH/$CHCl_3$, 2:3).

| | | | | |
|---|---|---|---|---|
| $C_{15}H_{14}N_3O$ | calc. | C 71.12 | H 5.97 | N 14.59 |
| (253.3) | found | 71.42 | 5.90 | 14.48 |

$^1$H-NMR (DMSO-$d_6$/TMS): $\delta$ = 1.65 (d, 3 H, $J$ = 6.52 Hz, $CH_3$), 2.96 (t, 2 H, $J$ = 5.80 Hz, H-4), 3.63 (dd, 1 H, $J$ = 7.81, 10.98 Hz, one of H-2), 4.19 (t, 1 H, $J$ = 10.72 Hz, one of H-2), 4.54 (t, 2 H, $J$ = 5.80 Hz, H-5), 5.11 (m, 1 H, H-1), 7.17 (dd, 1 H, $J_{7-8}$ = 8.06 Hz, $J_{7-9}$ = 1.25 Hz, H-7), 7.29 (dt, 1 H, $J_{7-9}$ = 1.25 Hz, $J_{8-9}$ = 7.33 Hz, $J_{9-10}$ = 7.83 Hz, H-9), 7.54 (ddd, 1 H, $J_{7-8}$ = 8.06 Hz, $J_{8-9}$ = 7.33 Hz, $J_{8-10}$ = 1.77 Hz, H-8), 8.04 (dd, 1 H, $J_{8-10}$ = 1.77 Hz, $J_{9-10}$ = 7.83 Hz, H-10), 9.00 (s, 1 H, H-12).

MS: $m/z$ = 254 ($MH^+$).

*2-Methyl-1,2,4,5-tetrahydro-[1]benzoxepino[4,5-e]imidazo[1,2-c]-pyrimidine* (**11c**): The compound **11c** is prepared according to the above procedure by employing **10c** (1 g, 3.7 mmol). The crude compound thus obtained is purified by column chromatography on silica gel (benzene/EtOAc, 4:1) and recrystallized from EtOH/EtOAc to afford **11c** as colorless prisms; yield: 0.85 g (91 %); mp 278–280 °C; $R_f$ 0.18 (MeOH/$CHCl_3$, 2:3).

| | | | | |
|---|---|---|---|---|
| $C_{15}H_{14}N_3O$ | calc. | C 71.12 | H 5.97 | N 14.59 |
| (253.3) | found | 71.36 | 6.00 | 14.38 |

$^1$H-NMR (DMSO-$d_6$/TMS): $\delta$ = 1.19 (d, 3 H, $J$ = 6.16 Hz, $CH_3$), 2.69 (t, 2 H, $J$ = 5.79 Hz, H-4), 3.63 (m, 1 H, H-2), 4.19 (m, 2 H, H-1), 4.37 (t, 2 H, $J$ = 5.79 Hz, H-5), 7.02 (dd, 1 H, $J_{7-8}$ = 7.95 Hz, $J_{7-9}$ = 1.36 Hz, H-7), 7.14 (ddd, 1 H, $J_{7-9}$ = 1.36 Hz, $J_{8-9}$ = 7.30 Hz, $J_{9-10}$ = 7.94 Hz, H-9), 7.33 (ddd, 1 H, $J_{7-8}$ = 7.95 Hz, $J_{8-9}$ = 7.30 Hz, $J_{8-10}$ = 1.82 Hz, H-8), 7.99 (dd, 1 H, $J_{8-10}$ = 1.82 Hz, $J_{9-10}$ = 7.94 Hz, H-10), 8.02 (s, 1 H, H-12).

MS: $m/z$ = 254 ($MH^+$).

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