Polycyclic *N*-Hetero Compounds. XXXVII. A Convenient Synthesis and Evaluation of Anti-platelet Aggregation Activity of 1,2,4,5-Tetrahydro[1]-benzothiepino[4,5-*e*]imidazo[1,2-*c*]pyrimidine and Its Related Compounds

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A simple and highly efficient methodology for the synthesis of 1,2,4,5-tetrahydro[1]benzothiepino[4,5-*e*]-imidazo[1,2-*c*]pyrimidine (**XI**) having a novel ring system *via* 4-substituted 5,6-dihydro[1]benzothiepino-[5,4-*d*]pyrimidines **VII-X** is described. The anti-platelet aggregation activity for it and its related compounds against collagen-induced aggregation of rabbit blood platelets *in vitro* was found.

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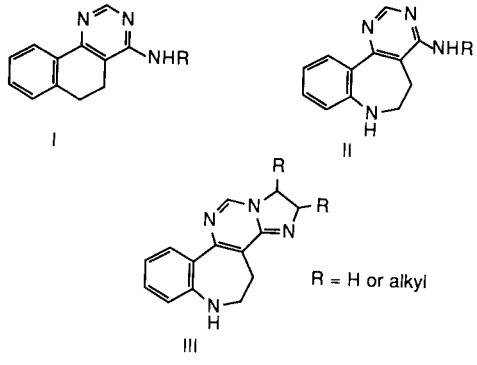
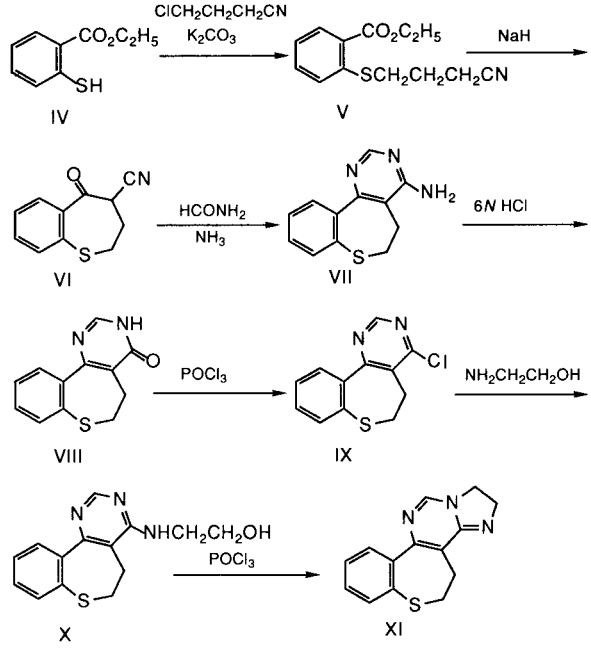
Since the discovery in our laboratory that 4-alkylamino-5,6-dihydrobenzo[*h*]quinazolines **I** had stronger inhibitory activities [1] against collagen-induced aggregation of rabbit blood platelets *in vitro* than that of aspirin which was well known as an anti-platlet agent [2], such polycyclic hetero compounds have aroused considerable recent interest for us. Indeed, it has been found that some 4-alkylamino-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines **II** and 1- or 2-alkyl-1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepines **III** showed the stronger inhibitory activities [3] (Scheme 1). One the basis of the above observations, we have designed to prepare the new compounds such as 1,2,4,5-tetrahydro[1]benzothiepino[4,5-*e*]-imidazo[1,2-*c*]pyrimidine (**XI**) having the new ring system and 4-substituted 5,6-dihydro[1]benzothiepino[5,4-*d*]-pyrimidines **VII-X** which were analogous to **III** and **II**, respectively. In order to explore more effective inhibitory agents, this paper deals with a simple and highly efficient methodology for the synthesis of the title compound **XI** and its precursors.

Scheme 1



As the sequential synthetic pathway is shown in Scheme 2, the first key intermediate, 5-oxo-2,3,4,5-tetrahydro[1]-benzothiepin-4-carbonitrile (**VI**) was prepared starting from ethyl thiosalicylate (**IV**) [4] *via* ethyl *S*-(3-cyanopropyl)thiosalicylate (**V**). That is, refluxing of **IV** with 4-chlorobutyronitrile in dioxane containing anhydrous potassium carbonate afforded the compound **V** (90%, colorless oil). Then, treatment of **V** with sodium hydride in toluene under reflux gave the desired compound **VI** (92%, colorless needles). The structures of **V** and **VI** were determined by satisfactory analytical and spectral data. In particular the ir spectra of **V** and **VI** showed the characteristic C≡N bands at 2250 cm^{-1} and C=O bands at 1705 and 1687 cm^{-1}, respectively. The pmr spectrum of **VI** indicated one proton multiplet at 4.66-4.75 ppm which was attributable to the presence of a proton at the 4-position and was exchangeable with deuterium oxide.

Scheme 2



Next ring closure of the compound **VI** to the tricyclic compound **VII** was carried out by heating of **VI** with excess formamide under an ammonia stream at 150° to yield 4-amino-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidine

(**VII**) (73%, colorless needles). The subsequent hydrolysis of the amino group at the 4-position of **VII** by heating under reflux with 6*N* hydrochloric acid solution gave the corresponding 5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4(3*H*)-one (**VIII**) (95%, colorless needles). Transformation of the compound **VIII** to the 4-chloro derivative **IX** was achieved by heating with excess phosphoryl chloride to afford 4-chloro-5,6-dihydro[1]benzothiepino[5,4-*d*]-pyrimidine (**IX**) (89%, colorless needles). The precursor, 4-(2-hydroxyethylamino)-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidine (**X**), of the tetracyclic compound **XI** was then prepared by refluxing of **IX** with excess ethanolamine in dioxane (86%, colorless powder). The pmr spectra of the tricyclic compounds **VII-X** demonstrated one proton singlet at 8.35 ppm (**VII**), 8.21 ppm (**VIII**), 8.44 ppm (**X**) in DMSO-d_6 and at 8.99 ppm (**IX**) in deuteriochloroform, respectively. Namely, the presence of it was attributable to the proton at the 2-position on newly formed pyrimidine ring of them.

Finally, the title compound, 1,2,4,5-tetrahydro[1]benzothiepino[4,5-*e*]imidazo[1,2-*c*]pyrimidine (**XI**), was synthesized by the intramolecular cyclization of the compound **X** thus obtained with excess phosphoryl chloride in the usual way (77%, colorless powder). Its structure was verified by elemental analysis, FAB mass spectrometry, and pmr spectroscopy as shown in the experimental part. It is noteworthy that this ring system has not been reported up to the present time and the tricyclic ring system for the precursors **VI-X** has been reported only in a few references in literature since the first report [5] in 1971.

Compound **XI** and its precursors **VI-X** were screened for inhibitory activity against rabbit platelet aggregation by a turbidimetric method by Born *et al.* [6] using an aggregometer. Among them, the compounds **IX**, **X** and **XI** were found to have potent inhibitory activities compared with that of aspirin. Further comprehensive studies of this series are currently under investigation and will be reported in due course.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were recorded in potassium bromide pellets except for **V** (chloroform) on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. The pmr spectra were measured on a Varian VXR-200 spectrometer (200 MHz) with tetramethylsilane as an internal standard and deuteriochloroform as a solvent unless otherwise stated. Chemical shifts are reported in parts per million (δ) and signals are quoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dt, double triplet. The FAB mass spectra were taken with a VG-70SE instrument.

Ethyl *S*-(3-Cyanopropyl)thiosalicylate (**V**).

A mixture of ethyl thiosalicylate (**IV**) [4] (5.0 g, 27.4 mmoles), 4-chlorobutyronitrile (4.26 g, 41.1 mmoles), and anhydrous potassium carbonate (5.69 g, 41.2 mmoles) in dioxane (80 ml) was refluxed with stirring for 20 hours. The mixture was concentrated *in vacuo*, diluted with water (100 ml), and extracted with methylene chloride (3 x 40 ml). The methylene chloride layers were combined, washed with water (2 x 40 ml), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give an oily residue which was distilled to provide the pure compound **V** (6.15 g, 90%), bp 186-187° (1 mm Hg); ir: ν 2250 (C≡N), ν 1705 (C=O), ν 1248 and 1145 (COC) cm^{-1}; pmr: δ 1.39 (t, J = 7.14 Hz, 3H, CH_3), 2.06 (m, 2H, $SCH_2CH_2CH_2CN$), 2.56 (t, J = 7.07 Hz, 2H, $SCH_2CH_2CH_2CN$), 3.07 (t, J = 6.97 Hz, 2H, $SCH_2CH_2CH_2CN$), 4.38 (q, J = 7.14 Hz, 2H, CH_2CH_3), 7.19 (ddd, J = 1.22, 7.40, 7.70 Hz, 1H, 5-H), 7.31 (dd, J = 1.22, 8.06 Hz, 1H, 3-H), 7.46 (ddd, J = 1.60, 7.40, 8.06 Hz, 1H, 4-H), 7.97 (dd, J = 1.60, 7.70 Hz, 1H, 6-H); ms: m/z 250 (MH^+).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.35; H, 6.02; N, 5.24.

5-Oxo-2,3,4,5-tetrahydro[1]benzothiepin-4-carbonitrile (**VI**).

A solution of **V** (14.8 g, 59.4 mmoles) in toluene (300 ml) was added dropwise to a suspension of sodium hydride (4.0 g, 100 mmoles, as 60% oil dispersion) in toluene (300 ml) at 10° with stirring. The reaction mixture was stirred at room temperature for 30 minutes and then refluxed under an inert atmosphere of argon for 24 hours. After the solvent was evaporated *in vacuo*, the residue was taken up carefully in ice-water (300 ml) and acidified (*p*H 5-6) with 2*N* hydrochloric acid. The resulting precipitate was collected by filtration and recrystallized from a mixture of benzene and ethyl acetate to give the pure compound **VI** (11.1 g, 92%), mp 104-105°; ir: ν 2250 (C≡N), ν 1687 (C=O) cm^{-1}; pmr: δ 2.58-2.87 (m, 3H, one of 2-H and 3-H), 3.22-3.33 (m, 1H, one of 2-H), 4.66-4.75 (m, 1H, deuterium exchangeable 4-H), 7.32 (dt, J = 1.66, 6.95, 7.56 Hz, 1H, 7-H), 7.41 (dt, J = 1.74, 6.95, 7.76 Hz, 1H, 8-H), 7.49 (dd, J = 1.66, 7.76 Hz, 1H, 9-H), 7.93 (dd, J = 1.74, 7.56 Hz, 1H, 6-H); ms: m/z 204 (MH^+).

Anal. Calcd. for $C_{11}H_9NOS$: C, 65.00; H, 4.46; N, 6.89. Found: C, 64.74, H, 4.37; N, 6.60.

4-Amino-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidine (**VII**).

A mixture of **VI** (3.65 g, 18.0 mmoles) and formamide (50 ml) under an ammonia stream was heated at 150° with stirring for 24 hours. In completing the reaction within a short period of time, further addition of formamide (10 ml) was necessary every 6 hours. Upon cooling the reaction solution in a refrigerator, a part of the product crystallized out and the separated product was filtered off. The filtrate was diluted with water (70 ml) and extracted with ethyl acetate (3 x 50 ml). Concentration of the combined extracts dried over magnesium sulfate *in vacuo* gave the second crop. The combined crude product was recrystallized from a mixture of benzene and ethyl acetate to get the pure compound **VII** (3.0 g, 73%), mp 268-269°; ir: ν 3410, 3320 and 1658 (NH_2) cm^{-1}; pmr (DMSO-d_6): δ 2.59 (t, J = 6.60 Hz, 2H, 5-H), 3.38 (t, J = 6.60 Hz, 2H, 6-H), 6.94 (s, 2H, deuterium exchangeable NH_2), 7.40 (dt, J = 1.77, 7.41, 7.41 Hz, 1H, 9-H), 7.51 (dt, J = 1.66, 7.41, 7.51 Hz, 1H, 10-H), 7.57 (dd, J = 1.66, 7.41, 1H, 8-H), 7.65 (dd, J = 1.77, 7.51 Hz, 1H, 11-H), 8.35 (s, 1H, 2-H); ms: m/z 300 (MH^+).

Anal. Calcd. for $C_{12}H_{11}N_3S$: C, 62.86; H, 4.84; N, 18.33. Found: C, 62.81; H, 4.72; N, 18.14.

5,6-Dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4(3*H*)-one (**VIII**).

A mixture of **VII** (4.11 g, 17.9 mmoles) with 6*N* hydrochloric acid solution (150 ml) was refluxed for 20 hours. After 10 hours, the reaction was accelerated with additional the acid (75 ml). The resulting solution was concentrated to dryness *in vacuo* and recrystallized from a mixture of ethanol and ethyl acetate to give the compound **VIII** (3.9 g, 95%), mp 282-284°; ir: ν 3150 (NH), ν 1670 (C=O), ν 1322 (C-N) cm^{-1}; pmr (DMSO-d_6): 2.58 (t, J = 6.62 Hz, 2H, 5-H), 3.42 (t, J = 6.62 Hz, 2H, 6-H), 7.43 (dt, J = 1.36, 7.49, 7.60 Hz, 1H, 9-H), 7.53 (dt, J = 1.49, 7.49, 7.60 Hz, 1H, 10-H), 7.62 (dd, J = 1.36, 7.60 Hz, 1H, 8-H), 7.67 (dd, J = 1.49, 7.60 Hz, 1H, 11-H), 8.21 (s, 1H, 2-H), 12.30 (br, 1H, deuterium exchangeable N*H*); ms: m/z 231 (MH^+).

Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.29; H, 4.34; N, 11.95.

4-Chloro-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidine (**IX**).

A mixture of **VIII** (3.97 g, 17.2 mmoles) and phosphoryl chloride (30 ml) was refluxed for 2 hours. The reaction mixture was concentrated *in vacuo* and ice-water (50 ml) was poured at once to the residue. The solution was neutralized with sodium hydrogen carbonate and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with water, dried over magnesium sulfate, evaporated *in vacuo*, and recrystallized from ethanol to give the compound **IX** (3.8 g, 89%), mp 105-106°; ir: ν 758 (CCl) cm^{-1}; pmr: δ 3.01 (t, J = 6.62 Hz, 2H, 5-H), 3.49 (t, J = 6.62 Hz, 2H, 6-H), 7.47 (dt, J = 1.76, 7.35, 7.43 Hz, 1H, 9-H), 7.55 (dt, J = 1.60, 7.35, 7.50 Hz, 1H, 10-H), 7.67 (dd, J = 1.60, 7.43 Hz, 1H, 8-H), 7.78 (dd, J = 1.76, 7.50 Hz, 1H, 11-H), 8.99 (s, 1H, 2-H); ms: m/z 249 (MH^+).

Anal. Calcd. for $C_{12}H_9ClN_2S$: C, 57.95; H, 3.65; N, 11.26. Found: C, 58.17; H, 3.69; N, 11.28.

4-(2-Hydroxyethylamino)-5,6-dihydro[1]benzothiepino[5,4-*d*]-pyrimidine (**X**).

A mixture of **IX** (1.0 g, 4.02 mmoles) and ethanolamine (1.24 g, 20.1 mmoles) in dioxane (20 ml) was refluxed with stirring for 3 hours. Concentration of the solution *in vacuo* and treatment with water gave the product **X** which was filtered, washed with cold water, and recrystallized from benzene (0.95 g, 86%), mp 179-180°; ir: ν 3340 (OH), ν 3150 (NH), ν 1050 (COH) cm^{-1}; pmr (DMSO-d_6): δ 2.63 (t, J = 6.45 Hz, 2H, 5-H), 3.41 (t, J = 6.45 Hz, 2H, 6-H), 3.54 (m, 4H, NCH_2CH_2O), 4.77 (t, J = 5.40 Hz, 1H, deuterium exchangeable O*H*), 7.29 (t, J = 5.22 Hz, 1H, deuterium exchangeable N*H*), 7.42 (dt, J = 1.71, 7.40, 7.41 Hz, 1H, 9-H), 7.52 (dt, J = 1.62, 7.40, 7.50 Hz, 1H, 10-H), 7.59 (dd, J = 1.62, 7.41 Hz, 1H, 8-H), 7.66 (dd, J = 1.71, 7.50 Hz, 1H, 11-H), 8.44 (s, 1H, 2-H) ms: m/z 274 (MH^+).

Anal. Calcd. for $C_{14}H_{15}N_3OS$: C, 61.51; H, 5.53; N, 15.37. Found: C, 61.75; H, 5.59; N, 15.18.

1,2,4,5-Tetrahydro[1]benzothiepino[4,5-*e*]imidazo[1,2-*c*]pyrimidine (**XI**).

A mixture of **X** (1.0 g, 3.66 mmoles) and phosphoryl chloride (10 ml) was refluxed for 3 hours. The reaction mixture was concentrated *in vacuo* and ice-water (25 ml) was poured at once to the residue. The solution was neutralized with sodium hydrogen carbonate and extracted with ethyl acetate (4 x 10 ml). The organic layer was washed with water, dried over magnesium sulfate, evaporated *in vacuo*, and recrystallized from a mixture of ethanol and ethyl acetate to give the compound **XI** (0.72 g, 77%), mp >270° dec; pmr (DMSO-d_6): δ 2.82 (t, J = 6.40 Hz, 2H, 4-H), 3.53 (t, J = 6.40 Hz, 2H, 5-H), 4.05 (t, J = 9.70 Hz, 2H, 1-H), 4.75 (t, J = 9.70 Hz, 2H, 2-H), 7.55 (dt, J = 1.90, 7.33, 7.33 Hz, 1H, 8-H), 7.63 (dt, J = 1.76, 7.33, 7.60 Hz, 1H, 9-H), 7.70 (dd, J = 1.76, 7.33 Hz, 1H, 7-H), 7.73 (dd, J = 1.90, 7.60 Hz, 1H, 10-H), 8.95 (s, 1H, 12-H); ms: m/z 256 (MH^+).

Anal. Calcd. for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.46. Found: C, 65.75; H, 5.24; N, 16.51.

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