[Chem. Pharm. Bull. 28(4)1307—1310(1980)]

Cylic Guanidines. VIII.[1] Synthesis of Imidazo-1,3- and -2,4-benzodiazepine Derivatives as Blood Platelet Aggregation Inhibitors

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(Received August 1, 1979)

The imidazo[2,1-*b*][1,3]- and -[2,4]benzodiazepin-2-one derivatives (**4**) and (**13**), and imidazo[1,2-*a*][1,3]benzodiazepin-2-one derivative (**9**), of a potent blood platelet aggregation inhibitor, the imidazo[2,1-*b*]quinazolin-2-one derivative (**14**), were synthesized as ring expansion analogs. Compound **9** showed potent activity but **4** and **13** showed poor activity and no activity, respectively.

Keywords——2,3,5,6-tetrahydro-1H-imidazo[2,1-*b*][1,3]benzodiazepin-2-one; 2,3,5,6-tetrahydro-1H-imidazo[2,1-*b*][2,4]benzodiazepin-2-one; 2,3,5,6-tetrahydro-1H-imidazo-[1,2-*a*][1,3]benzodiazepin-2-one; platelet aggregation inhibitor: structure-activity relationship

Beverung *et al.*[3] have reported that imidazo[2,1-*b*]quinazolin-2-one derivatives (**14**) are potent blood platelet aggregation inhibitors. It would be of interest to examine the activity of compounds in which the pyrimidine ring in the imidazoquinazoline structure of **14** is replaced by a 1,3-diazepine ring. This report deals with the syntheses of related heterocycles, imidazo[2,1-*b*][1,3-]- (**4**) and -[2,4]benzodiazepin-2-one (**13**), and imidazo[1,2-*a*][1,3]-benzodiazepin-2-one (**9**) derivatives, and describes the influence of structual modification on the activity.

Syntheses of imidazobenzodiazepine ring systems, 2,3,5,6-tetrahydro-1H-imidazo[2,1-*b*]-[1,3]- and [1,2-*a*][1,3]benzodiazepine, have been reported by Jen *et al.*[4] but their 2-one derivatives have not been reported.

Reaction of N-2-(2-nitrophenyl)ethylbenzylamine (**1**)[5] with ethyl bromoacetate gave the N-substituted derivative (**2**) in good yield. Catalytic reduction of **2** over palladium-on-charcoal (Pd-C), followed by reaction with cyanogen bromide afforded the desired 2,3,5,6-tetrahydro-1H-imidazo[2,1-*b*][1,3]benzodiazepin-2-one (**4**), but the yield was very poor.

Hydrogenation of **1** over platinum oxide gave N-2-(2-aminophenyl)ethylbenzylamine (**5**). Heating **5** with dimethyl cyanoimidodithiocarbonate at 160° yielded 2-cyanoimino-1,3-benzodiazepine (**6**). Reaction of **6** with ethyl bromoacetate gave the 1-ethoxycarbonylmethyl derivative (**7**). In the course of cyclizing **7** to **8**, where the cyano group of **7** is removed, it is necessary to avoid the hydrolysis of the 1-acetate ester group. Compound **7** was treated under mild conditions, such as refluxing in *tert*-butyl alcohol (*tert*-BuOH) containing 3-4 molar equivalents of hydrochloric acid,[6] to give the 3-benzyl derivative (**8**). Catalytic reduction of **8** over Pd-C gave the desired 2,3,5,6-tetrahydro-1H-imidazo[1,2-*a*][1,3]benzodiazepin-2-one (**9**). Heating o-xylenediamine (**10**)[7] with dimethyl cyanoimidodithiocarbonate at 150° gave

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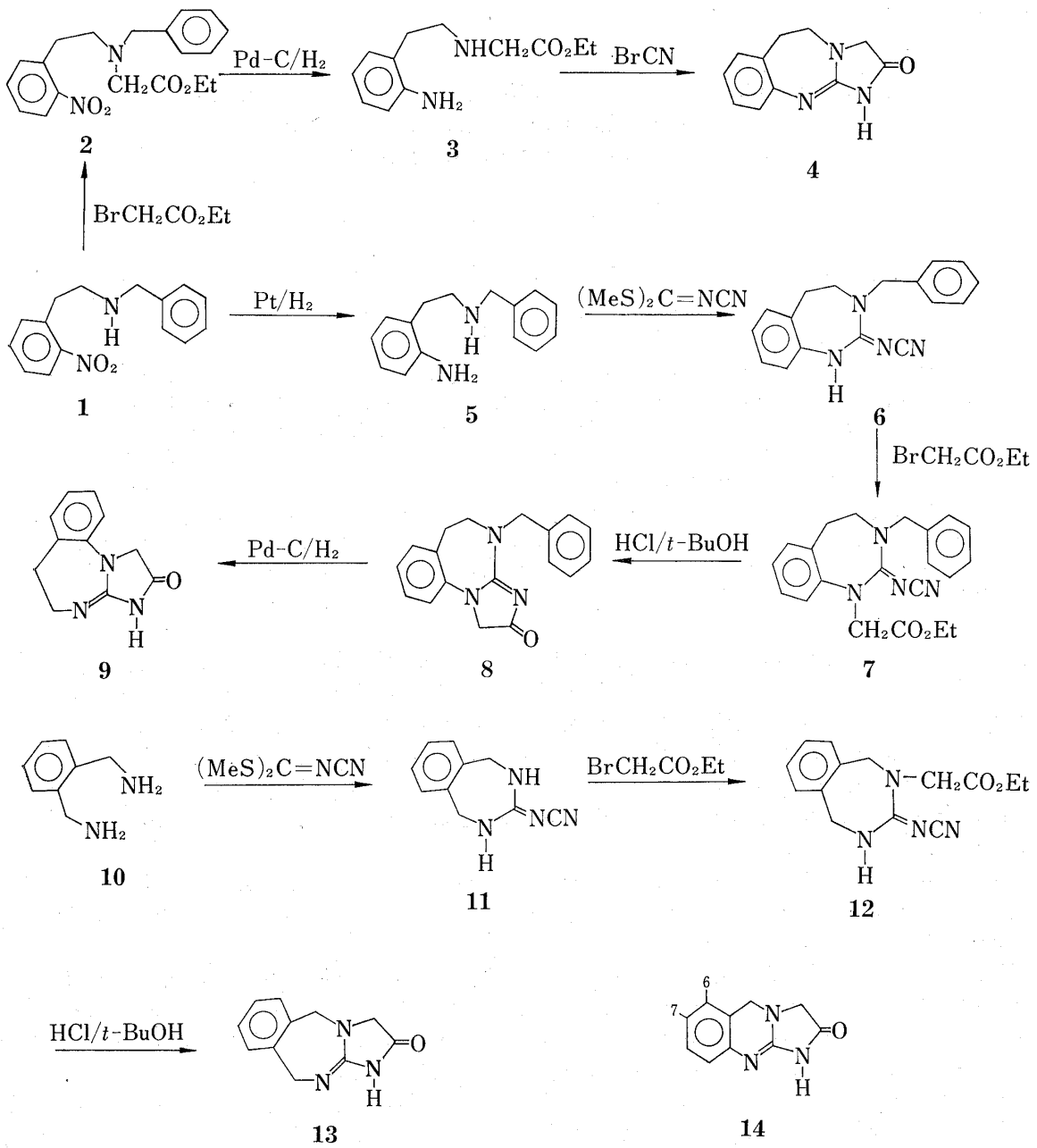

Chart 1

3-cyanoimino-2,4-benzodiazepine (**11**) in good yield. Treatment of **11** with ethyl bromoacetate, followed by heating in *tert*-BuOH containing hydrochloric acid afforded 2,3,5,10-tetrahydro-1H-imidazo[2,1-*b*][2,4]benzodiazepin-2-one (**13**).

The blood platelet aggregation inhibitory activities of the compounds obtained here are shown in Table I. Compound **9** has potent activity against the aggregation induced by collagen or adenosine diphosphate. Compound **4** and **13** showed poor activity and no activity, respectively. On the other hand, the 6- and or 7-alkyl or halo substituted imidazo[2,1-*b*] quinazolin-2-one derivatives (**14**) reported by Beverung *et al.*[3b] have high activity. It is conceivable, therefore, that the location of the benzene ring in **9**, which corresponds to that of the substituent at the 6-position of **14**, could be important for the activity. The fact that **13** has no activity may be due to a difference of physical properties, such as the stronger basicity of **13** compared with **9**.

Table I. Inhibition of Blood Platelet Aggregation by Imidazo-1, 3- and/or -2,4-benzodiazepin-2-one Derivatives[a]

Comound	Collagen (EC_{50}: μM)	ADP[b] (% Inhibition)
4	180	46
9	1	93
13	500	0

a) *In vitro* effect in rat blood platelet-rich plasma.
b) Concentration at 0.25 mM test compound.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer. MS spectra were determined on a JEOL OISG-2 mass spectrometer. NMR spectra were taken with a Hitachi Perkin-Elmer R-20B (60 MHz) or a Varian EM-360 (60 MHz) spectrometer with tetramethylsilane as an internal standard (δ value). The abbreviations used are as follows: s, singlet: d, doublet; t, triplet; q,quartet; m, multiplet; br, broard. For column chromatography, silica gel (Merck, 0.05—0.2 mm) was used.

Ethyl N-Benzyl-N-[2-(2-nitrophenyl)ethyl]glycinate (2)——A mixture of 3.42 g (13.3 mmol) of **1**, 3.00 g (18 mmol) of ethyl bromacetate, and 2 ml of Et_3N in 30 ml of EtOH was refluxed for 8 hr and then concentrated to dryness *in vacuo*. The residue was mixed with 10% K_2CO_3 solution and extrated with $CHCl_3$. The extract was washed with H_2O, and concentrated. The residue was purified by silica gel (50 g) chromatography. The eluate with $CHCl_3$ gave 3.70 g (81%) of **2** as a pale yellow oil. NMR ($CDCl_3$) δ: 7.90 (1H, m, aromatic proton), 7.30—7.65 (3H, m, aromatic protons), 7.25 (5H, s, Ph), 4.13 (2H, q, OCH_2), 3.81 (2H, s, CH_2Ph), 3.26 (2H, s, CH_2CO), 3.00 (4H, m, CH_2CH_2), 1.22 (3H, t, CH_3).

The free base was treated with HCl–EtOH to give the hydrochloride, mp 173—175°. IR ν_{max}^{KBr} cm^{-1}: 1755, 1525. *Anal.* Calcd for $C_{19}H_{23}ClN_2O$: C, 60.24; H, 6.12; N, 7.39. Found: C, 60.45; H, 5.92; N, 7.42.

Ethyl N-[2-(2-Aminophenyl)ethyl]glycinate (3)——Compound **2** (2.84 g, 8.3 mmol) in 60 ml of 50% aqueous EtOH was hydrogenated over 1.40 g of 10% Pd-C in the presence of 1 ml of conc. HCl for 1 hr, and then the catalyst was removed by filtration. The filtrate was concentrated *in vacuo*. The residue was mixed with 10% K_2CO_3 solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated. The residue was purified by silica gel (30 g) chromatography. The eluate with $CHCl_3$–EtOH (20: 1) gave 1.30 g (71%) of **3** as a pale yellow oil. NMR ($CDCl_3$) δ: 6.55—7.20 (4H, m, aromatic protons), 4.18 (2H, q, OCH_2), 3.39 (2H, s, CH_2CO), 3.05 (3H, br s, NH), 2.80 (4H, m, CH_2CH_2), 1.23 (3H, t, CH_3).

The free base was treated with HCl–EtOH to give the hydrochloride, mp 198—200°. IR ν_{max}^{KBr} cm^{-1}: 1735, 1580. *Anal.* Calcd for $C_{12}H_{20}Cl_2N_2O_2$: C, 48.82; H, 6.14; N, 9.49. Found: C, 48.76; H, 6.55; N, 9.28.

2,3,5,6-Tetrahydro-1H-imidazo[2,1-*b*][1,3]benzodiazepin-2-one (4)——A mixture of 6.00 g (27 mmol) of **3** and 6 ml of Et_3N in 100 ml of EtOH was treated with 2.90 g (27 mmol) of BrCN with stirring at 0—5°. After stirring at room temperature for 3 hr the mixture was concentrated *in vacuo*. The residue was mixed with 30 ml of 10% K_2CO_3 solution and 30 ml of $CHCl_3$. An insoluble crystalline material was collected by filtration to give 0.20 g of **4**. The filtrate was separated and the $CHCl_3$ layer was concentrated *in vacuo*. The residue was purified by silica gel (50 g) chromatography. The eluate with $CHCl_3$–EtOH (20: 1) gave 0.74 g of **4**. Total yield was 0.94 g (17%), mp>280°

The free base was treated with HCl–EtOH to give the hydrochloride, mp 255—258°. IR ν_{max}^{KBr} cm^{-1}: 1770, 1660, 1575. NMR (CF_3CO_2H) δ: 9.92 (1H, s, NH). 7.36 (4H, m, aromatic protons), 4.65 (2H, s, CH_2), 3.95, 3.37 (2H×2, m, CH_2CH_2). *Anal.* Calcd for $C_{11}H_{12}ClN_3O$: C, 55.59; H, 5.09; N, 17.68. Found: C, 55.52; H, 5.17; N, 17.97.

N-[2-(2-Aminophenyl)ethyl]benzylamine (5)——Compound **1** (10.0 g 40 mmol) in 100 ml of MeOH was hydrogenated over 1.0 g of PtO_2 for 2 hr and then the catalyst was removed. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel (90 g) chromatography. The eluate with $CHCl_3$–EtOH (25: 1) gave 7.37 g (84%) of **5** as a pale yellow oil. NMR ($CDCl_3$) δ: 7.28 (5H, s, Ph), 6.50—7.20 (4H, m, aromatic protons), 3.76 (2H, s, CH_2Ph), 3.13 (3H, br s, NH), 2.79 (4H, m, CH_2CH_2).

The free base was treated with HCl–EtOH to give the hydrochloride, mp 208—210°. IR ν_{max}^{KBr} cm^{-1}: 3450, 3360, 1630, 1500. *Anal. Calcd* for $C_{15}H_{19}ClN_2$: C, 68.56; H, 7.29; N, 10.66. Found: C, 68.31; H, 7.27; N, 10.76.

3-Benzyl-2-cyanoimino-2,3,4,5-tetrahydro-1H-1,3-benzodiazepine (6)——A mixture of 2.26 g (10 mmol) of **5** and 1.50 g (10 mmol) of dimethyl cyanoimidodithiocarbonate was heated at 160° for 30 min. After cooling, the reaction mixture was treated with Me_2CO to give 0.45 g (16%) of **6**, mp 177—179°. IR ν_{max}^{KBr} cm^{-1}: 2160, 1630, 1575, 1520, 1490. NMR ($CDCl_3$) δ: 9.12 (1H, br s, NH), 7.35 (5H, s, Ph), 6.85—7.30 (4H, m,

aromatic protons), 4.69 (2H, s, CH_2Ph), 3.49, 2.94 (2H×2, m, CH_2CH_2). *Anal.* Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.28. Found: C, 73.49; H, 5.85; N, 20.13.

3-Benzyl-2-cyanoimino-1-ethoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-1,3-benzodiazepine (**7**)——A mixture of 1.77 g (6.4 mmol) of **6** and 0.40 g (8.3 mmol) of NaH (50% oil suspension) in 100 ml of DMF was stirred for 30 min, then 1.30 g (7.8 mmol) of ethyl bromoacetate was added. After stirring at room temperature for 1 hr, the mixture was heated at 90° for 2 hr with stirring. The mixture was concentrated *in vacuo*. The residue was mixed with H_2O and extracted with $CHCl_3$. The extract was concentrated *in vacuo* and the residue was recrystallized from Et_2O to give 1.65 g (72%) of **7**, mp 131—133°. IR ν_{max}^{KBr} cm^{-1}: 2160, 1735, 1545. NMR ($CDCl_3$) δ: 6.75—7.35 (9H, m, aromatic protons), 4.66 (4H, s, CH_2Ph and CH_2CO), 4.20 (2H, q, OCH_2), 3.55, 3.10 (2H×2, m, CH_2CH_2), 1.23 (3H, t, CH_3). *Anal.* Calcd for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 6.12; N, 15.45. Found: C, 69.42; H, 6.21; N, 15.68.

4-Benzyl-1,2,5,6-tetrahydro-4H-imidazo[1,2-*a*][1,3]benzodiazepin-2-one (**8**)——A mixture of 0.90 g (2.5 mmol) of **7** and 1.00 ml (10 mmol) of conc. HCl in 50 ml of *tert*-BuOH was refluxed for 7 hr and then concentrated *in vacuo*. The residue was purified by silica gel (30 g) chromatography. The eluate with $CHCl_3$ gave 0.38 g (58%) of **8**, mp 164—166° (benzene–Et_2O) IR ν_{max}^{KBr} cm^{-1}: 1700, 1590, 1570. NMR ($CDCl_3$) δ: 7.33 (5H, s, Ph), 6.90—7.30 (4H, m, aromatic protons), 4.95 (2H, s, CH_2Ph), 4.51 (2H, s, CH_2CO), 3.53, 3.00 (2H×2, m, CH_2CH_2). *Anal.* Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.35; H, 5.88; 14.63.

2,3,5,6-Tetrahydro-1H-imidazo[1,2-*a*][1,3]benzodiazepin-2-one (**9**)——Compound **8** (1.00 g, 3.43 mmol) in 150 ml of MeOH containing 2 ml of conc. HCl was hydrogenated over 1.0 g of 10% Pd-C, then the catalyst was removed. The filtrate was concetrated *in vacuo*. The residue was mixed with 10% Na_2CO_3 solution and a separated crystalline solid was collected to give 0.40 g (58%) of **9**, mp>280°. NMR (CF_3CO_2H) δ: 8.80 (1H, br s, NH), 7.10—7.80 (4H, m, aromatic protons), 5.11 (2H, s, C^1–CH_2), 4.00, 3.40 (2H×2, m,, CH_2CH_2).

The free base was treated with HCl–EtOH to give the hydrochloride, mp>280°. IR ν_{max}^{KBr} cm^{-1}: 1770, 1690, 1600. *Anal.* Calcd for $C_{11}H_{12}ClN_3O$: C, 55.59; H, 5.09; N, 17.68. Found: C, 55.57; H, 5.11; N, 17.37.

3-Cyanoimino-2,3,4,5-tetrahydro-1H-2,4-benzodiazepine (**11**)——Compound **10** (4.47 g, 32.8 mmol) was treated with 4.88 g (32.8 mmol) of dimethyl cyanoimidodithiocarbonate. After evolution of MeSH, the mixture became a colorless oil, which was heated at 150° for 30 min. The cooled mixture was treated with Me_2CO to give 4.80 g (78%) of **11**, mp 249—251° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 2170, 1620, 1570, *Anal.* Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.35; H, 5.48; N, 29.74.

3-Cyanoimino-2-ethyoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-2,4-benzodiazepine (**12**)——By a procedure similar to that used for the synthesis of **7**, 3.37 g (18.6 mmol) of **11** was treated with 3.72 g (22 mmol) of ethyl bromoacetate in the presence of 1.00 g (20 mmol) of NaH (50% oil suspension) in 50 ml of DMF. The reaction mixture was worked up in the usual manner to yield 3.30 g (65%) of **12**, mp 189—191° ($CHCl_3$–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3225, 1735, 1590, 1540. NMR ($CDCl_3$) δ: 7.25 (4H, m, aromatic protons), 6.95 (1H, br s, NH), 4.54, 4.50, 4.20 (2H×3, s, CH_2N and CH_2CO), 4.15 (2H, q, OCH_2), 1.21 (3H, t, CH_3). *Anal.* Calcd for $C_{24}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.74; H, 5.86; N, 20.96.

2,3,5,10-Tetrahydro-1H-imidazo[2,1-*b*][2,4]benzodiazepin-2-one (**13**)——A mixture of 2.55 g (9.4 mmol) of **12** and 3.0 ml of conc. HCl in 100 ml of *tert*-BuOH was heated for 30 hr and then the mixture was concetrated *in vacuo*. The residue was mixed with 10% K_2CO_3 solution. Insoluble material was collected and recrystallized from $CHCl_3$–MeOH to give 1.30 g (59%) of **13**, mp>280°.

The free base was treated with HCl–EtOH to give the hydrochloride, mp 246—248° (iso-PrOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1760, 1670, 1570. NMR (CF_3CO_2H) δ: 8.32 (1H, br, NH), 7.45 (4H, m, aromatic protons), 4.95, 4.86, 4.63 (2H×3, s, CH_2N). *Anal.* Calcd for $C_{11}H_{12}ClN_3O$: C, 55.59; H, 5.09; N, 17.68. Found: C, 55.23; H, 5.08; N, 17.28.

Acknowledgement The authors thank Dr. Y. Abiko, S. Ashida and Miss K. Sakuma for carrying out biological assays. Thanks are also due to staff of this Institute for elemental analysis.