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

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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 structural 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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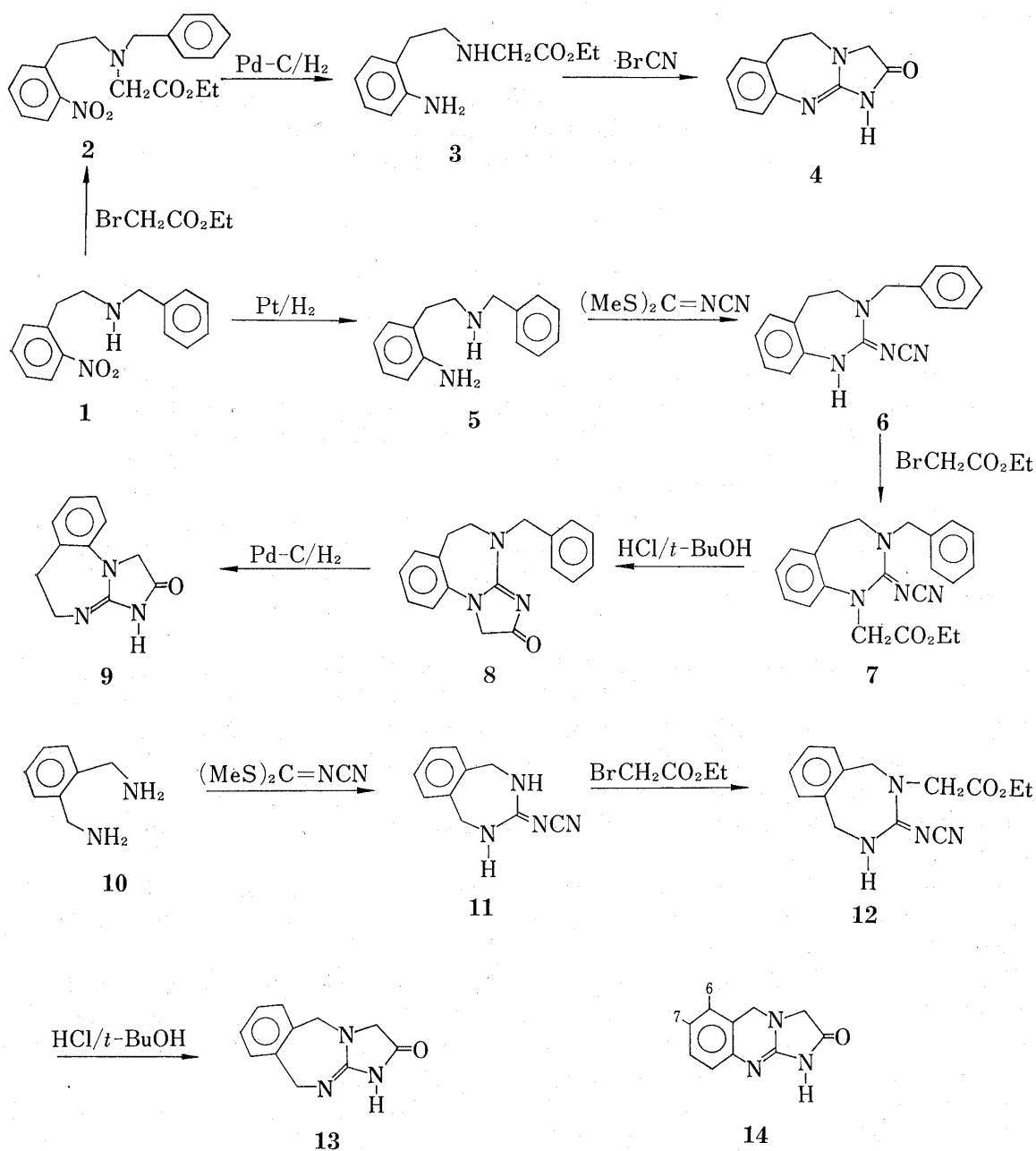


Chart 1

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)}

Compound	Collagen (EC ₅₀ : μ M)	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, broad. 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 Et₃N in 30 ml of EtOH was refluxed for 8 hr and then concentrated to dryness *in vacuo*. The residue was mixed with 10% K₂CO₃ solution and extracted with CHCl₃. The extract was washed with H₂O, and concentrated. The residue was purified by silica gel (50 g) chromatography. The eluate with CHCl₃ gave 3.70 g (81%) of 2 as a pale yellow oil. NMR (CDCl₃) δ : 7.90 (1H, m, aromatic proton), 7.30–7.65 (3H, m, aromatic protons), 7.25 (5H, s, Ph), 4.13 (2H, q, OCH₂), 3.81 (2H, s, CH₂Ph), 3.26 (2H, s, CH₂CO), 3.00 (4H, m, CH₂CH₂), 1.22 (3H, t, CH₃).

The free base was treated with HCl–EtOH to give the hydrochloride, mp 173–175°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1755, 1525. *Anal.* Calcd for C₁₉H₂₃ClN₂O₂: 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% K₂CO₃ solution and extracted with CHCl₃. The extract was washed with H₂O, dried, and concentrated. The residue was purified by silica gel (30 g) chromatography. The eluate with CHCl₃–EtOH (20: 1) gave 1.30 g (71%) of 3 as a pale yellow oil. NMR (CDCl₃) δ : 6.55–7.20 (4H, m, aromatic protons), 4.18 (2H, q, OCH₂), 3.39 (2H, s, CH₂CO), 3.05 (3H, br s, NH), 2.80 (4H, m, CH₂CH₂), 1.23 (3H, t, CH₃).

The free base was treated with HCl–EtOH to give the hydrochloride, mp 198–200°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1735, 1580. *Anal.* Calcd for C₁₂H₂₀Cl₂N₂O₂: 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 Et₃N 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% K₂CO₃ solution and 30 ml of CHCl₃. An insoluble crystalline material was collected by filtration to give 0.20 g of 4. The filtrate was separated and the CHCl₃ layer was concentrated *in vacuo*. The residue was purified by silica gel (50 g) chromatography. The eluate with CHCl₃–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 $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1770, 1660, 1575. NMR (CF₃CO₂H) δ : 9.92 (1H, s, NH), 7.36 (4H, m, aromatic protons), 4.65 (2H, s, CH₂), 3.95, 3.37 (2H $\times$ 2, m, CH₂CH₂). *Anal.* Calcd for C₁₁H₁₂ClN₃O: 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 PtO₂ 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 CHCl₃–EtOH (25: 1) gave 7.37 g (84%) of 5 as a pale yellow oil. NMR (CDCl₃) δ : 7.28 (5H, s, Ph), 6.50–7.20 (4H, m, aromatic protons), 3.76 (2H, s, CH₂Ph), 3.13 (3H, br s, NH), 2.79 (4H, m, CH₂CH₂).

The free base was treated with HCl–EtOH to give the hydrochloride, mp 208–210°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3450, 3360, 1630, 1500. *Anal.* Calcd for C₁₅H₁₉ClN₂: 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 Me₂CO to give 0.45 g (16%) of 6, mp 177–179°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2160, 1630, 1575, 1520, 1490. NMR (CDCl₃) 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 $\times$ 2, m, CH_2CH_2). *Anal.* Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_4$: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\times$ 2, m, CH_2CH_2), 1.23 (3H, t, CH_3). *Anal.* Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_2$: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\times$ 2, m, CH_2CH_2). *Anal.* Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.35; H, 5.88; N, 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 concentrated *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 ($\text{CF}_3\text{CO}_2\text{H}$) δ : 8.80 (1H, br s, NH), 7.10–7.80 (4H, m, aromatic protons), 5.11 (2H, s, $\text{C}^1\text{-CH}_2$), 4.00, 3.40 (2H $\times$ 2, m, CH_2CH_2).

The free base was treated with HCl–EtOH to give the hydrochloride, mp >280°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1770, 1690, 1600. *Anal.* Calcd for $\text{C}_{11}\text{H}_{12}\text{ClN}_3\text{O}$: 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 $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2170, 1620, 1570. *Anal.* Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.35; H, 5.48; N, 29.74.

3-Cyanoimino-2-ethoxycarbonylmethyl-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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\times$ 3, s, CH_2N and CH_2CO), 4.15 (2H, q, OCH_2), 1.21 (3H, t, CH_3). *Anal.* Calcd for $\text{C}_{24}\text{H}_{16}\text{N}_4\text{O}_2$: 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 concentrated *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 $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1760, 1670, 1570. NMR ($\text{CF}_3\text{CO}_2\text{H}$) δ : 8.32 (1H, br, NH), 7.45 (4H, m, aromatic protons), 4.95, 4.86, 4.63 (2H $\times$ 3, s, CH_2N). *Anal.* Calcd for $\text{C}_{11}\text{H}_{12}\text{ClN}_3\text{O}$: C, 55.59; H, 5.09; N, 17.68. Found: C, 55.23; H, 5.08; N, 17.28.

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