Hydroxamates 48-50 were prepared as described for **47**.

***N*-Methyl-2-[4-(2,4,6-trimethylphenyl)phenyl]propenehydroxamic Acid (51).** The corresponding carboxylic acid was prepared from methyl 4-(2,4,6-trimethylphenyl)benzoate (prepared as described for **47**). The ester (3.0 g, 11.8 mmol) was dissolved in CH_2Cl_2 and cooled to -78 °C. Diisobutylaluminum hydride (27.1 mmol) was added and the reaction mixture stirred for 40 min. After warming to room temperature, the mixture was poured into 2 N HCl and the organic phase was dried with $MgSO_4$ and evaporated. 4-(2,4,6-Trimethylphenyl)benzyl alcohol was obtained in 88% yield (2.4 g) and was carried on without purification.

A mixture of the alcohol (2.0 g, 8.8 mmol) prepared above and pyridinium chlorochromate (3.36 g, 15.6 mmol) in CH_2Cl_2 (100 mL) was stirred for 2 h at room temperature. Ether was added and the mixture was filtered through a pad of silica gel to remove chromium salts. After removal of the solvent in vacuo, 1.57 g (79%) of nearly pure 4-(2,4,6-trimethylphenyl)benzaldehyde was obtained.

The benzaldehyde prepared above was converted to 2-[4-(2,4,6-trimethylphenyl)phenyl]propenoic acid in a manner similar to that described for **38** and then to hydroxamate **51** by using the standard procedure: mp 170-171 °C; ^1H NMR (Me_2SO-d_6) δ 1.92 (s, 6 H), 2.27 (s, 3 H), 3.23 (s, 3 H), 6.95 (s, 2 H), 7.18 (d, 2 H), 7.27 (d, 1 H), 7.56 (d, 1 H), 7.77 (d, 2 H), 10.12 (br s, 1 H); MS, *m/e* 295, 245. Anal. ($C_{19}H_{21}NO_2$) C, H, N.

2-(2-Naphthyl)-2-oxoethanol (25). 2-Naphthoyl chloride (2.9 g, 15.2 mmol) in ether (50 mL) was added to a solution of triethylamine (1.69 g, 16.7 mmol) and diazomethane (75 mL, ~0.5 M) in ether (100 mL) at 0 °C. After 1 h the triethylamine hydrochloride was filtered away and the solvent removed in vacuo. The resulting diazo ketone was dissolved in THF (50 mL), and a few drops of $HClO_4$ were added. Fifteen minutes later the solvent was evaporated and the residue chromatographed on 100 g of SiO_2, eluting with 25% ether in hexanes: MS, *m/e* 186, 155, 127. Anal. ($C_{12}H_{10}O_2$) C, H.

***N*-Hydroxy-2-naphthalenesulfonamide (29).** 2-Naphthalenesulfonyl chloride (2.0 g, 8.82 mmol) in CH_2Cl_2 (25 mL) was added to a solution of hydroxylamine hydrochloride (2.45 g, 35.3 mmol) and triethylamine (5.4 g, 53 mmol) in THF (30 mL)/H_2O (10 mL). After being stirred for 30 min, the mixture was poured into 2 N HCl and the organic layer was dried over $MgSO_4$ and evaporated. The residue was flash chromatographed on 80 g of SiO_2, eluting with 50% ether in hexanes. The yield was 1.51 g (77%). **29**: mp 158-160 °C; ^1H NMR (Me_2SO-d_6) δ 7.65-8.2 (m, 6 H), 8.5 (s, 1 H), 9.66 (dd, 2 H); MS, *m/e* 223, 191. Anal. ($C_{11}H_9NO_3S$) C, H, N; S: calcd, 13.63; found, 12.91.

***N*-Methyl-*N*-hydroxy-2-naphthalenesulfonamide (30)** was prepared in the same manner as for **29** with *N*-methylhydroxylamine: mp 134-135 °C. Anal. ($C_{12}H_{11}NO_3S$) C, H, N, S.

Acknowledgment. We thank Dr. Dee W. Brooks and Bruce P. Gunn for helpful discussions and Dirk Bornemeier and Thomas Clark for technical assistance. We also thank Joy Sonsalla and Dr. Dan Albert for determination of intact cell activities.

Notes

Synthesis of D-Oxa Tricyclic Partial Ergolines as Dopamine Agonists

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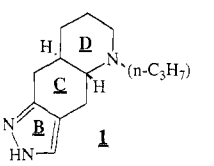
A series of hetero fused hexahydro-1,4-benzoxazines has been synthesized and evaluated for dopamine agonist activity. This class of compounds is another example in which an oxygen substitution in the D ring of a partial ergoline or ergoline retains dopaminergic properties. Compound **10**, *trans*-(±)-4,4a,5,6,8a,9-hexahydro-5-propyl-2*H*,7*H*-pyrazolo[4,3-*g*][1,4]benzoxazine, is a D-ring analogue of *trans*-(±)-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-2*H*-pyrazolo[3,4-*g*]quinoline (**1**, LY141865) and also a des-A-ring analogue of 9-oxaergoline (**2**). Compounds **10**, 2-aminohexahydrothiazolo[1,4]benzoxazine **11**, and 2-aminohexahydropyrimido[1,4]benzoxazine **12** possess dopaminergic activity in prolactin inhibition and 6-hydroxydopamine lesioned rat turning assays.

Ergoline derivatives such as bromocryptine, lergotrile, and pergolide possess dopaminergic activity.[1,2] These dopamine agonists have therapeutic utility in the treatment of Parkinson's disease,[3] inhibition of postpartum lactation,[1] and galactorrhea–amenorrhea syndrome.[1]

The BCD partial ergoline structure **1** (LY141865)[4] demonstrated that the aromatic A ring of the ergoline molecule is not necessary to retain dopaminergic properties. Furthermore, recent reports by Jones and co-workers[5,6] described new classes of dopamine agonists that are



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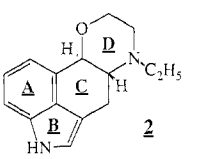

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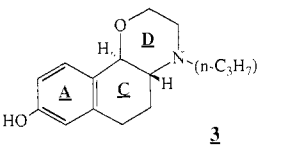

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(1) Spano, P. F.; Trabucci, M.; Eds. *Pharmacology* **1978**, *16* (Suppl. 1), 1-213. Hokfelt, B.; Nillius, S. J.; Eds. *Acta Endocrinol. (Copenhagen), Suppl.* **1978**, *No. 216*, 1-227.

(2) Fuller, R. W.; Clemens, J. A.; Kornfeld, E. C.; Snoddy, H. D.; Smalstig, E. B.; Bach, N. J. *Life Sci.* **1979**, *24*, 375.

(3) Parkes, D. *N. Engl. J. Med.* **1979**, *301*, 873. Calne, D. B.; Leigh, P. N.; Teychenne, P. F.; Bamji, A. N.; Greenacre, J. K. *Lancet* **1974**, 1355.

(4) Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481.

(5) Anderson, P. S.; Baldwin, J. J.; McClure, D. E.; Lundell, G. F.; Jones, J. H.; Randall, W. C.; Martin, G. E.; Williams, M.; Hirshfield, J. M.; Clineschmidt, B. V.; Lumma, P. K.; Remy, D. C. *J. Med. Chem.* **1983**, *26*, 363.

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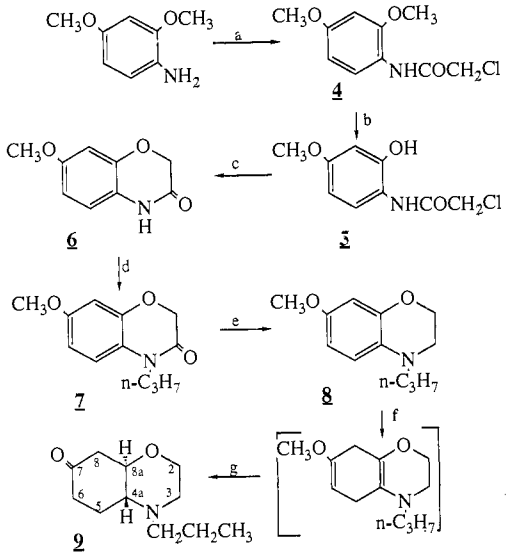
Scheme I[a]



[a] a: $ClCH_2COCl$, $N(C_2H_5)_3$. b: $AlCl_3$. c: K_2CO_3. d: K_2CO_3, n-C_3H_7I. e: 1 M BH_3 in THF. f: Li-NH_3, EtOH. g: (1) HOAc, $NaBH_4$; (2) 6 N HCl.

D-heteroergolines **2** (9-oxaergolines) and D-hetero ACD partial ergolines **3**. As an extension of the BCD partial ergolines synthesized in these laboratories,[4] a series of D-oxa BCD partial ergoline analogues of **1** was prepared.

Chemistry

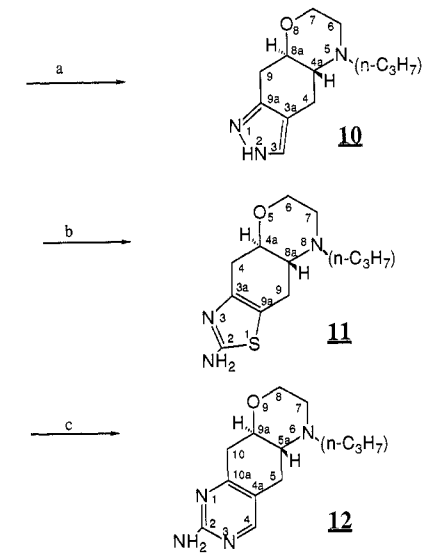
The hetero fused 1,4-benzoxazines **10–12** (Scheme II) were prepared from ketone **9** (Scheme I). Acylation of 2,4-dimethoxyaniline with chloroacetyl chloride gave amide **4**. The selective cleavage of the ortho methyl ether of amide **4** with aluminum chloride provide **5**, which was cyclized with potassium carbonate to yield lactam **6**. Alkylation of **6** with *n*-propyl iodide afforded lactam **7**. Reduction of **7** with borane gave dihydrobenzoxazine **8**. The Birch reduction of **8** was followed by a sodium borohydride reduction of the protonated enamine intermediate, and hydrolysis of the enol ether provided ketone **9** (Scheme I).

An analysis of a 270-MHz ^1H NMR spectrum of ketone **9** confirmed that the expected formation of a trans ring junction resulted from the sodium borohydride reduction of the iminium salt. Proton H_{8a} appears as a multiplet with a chemical shift of 3.38 ppm. An expansion of the data indicated H_{8a} coupled to H_8 axial (13 Hz) and H_8 equatorial (4.9 Hz). Proton H_{8a} was also coupled to H_{4a} (8.5 Hz). This pattern confirmed that H_{8a} and H_{4a} are in a trans relationship.

Ketone **9** was condensed with ethyl formate, and subsequent cyclization of the intermediate with hydrazine gave pyrazolo[4,3-g][1,4]benzoxazine **10**. Reaction of the α-bromo derivative of **9** with thiourea provided thiazolo-[5,4-*g*][1,4]benzoxazin-2-amine **11**. Condensation of ketone **9** with tris(dimethylamino)methane afforded an enamino ketone, which when reacted with guanidine carbonate gave pyrimido[5,4-*g*][1,4]benzoxazine-2-amine **12** (Scheme II).

To determine whether reactions with **9** and subsequent condensations to give compounds **10–12** occurred at position 6 rather than position 8, the ^{13}C NMR and ^1H NMR

Scheme II[a]



[a] a: (1) $HCO_2C_2H_5$, $(CH_3)_3COK$; (2) H_2NNH_2. b: (1) HOAc, Br_2; (2) thiourea. c: (1) $HC[N(CH_3)_2]_3$; (2) guanidine carbonate.

spectra of these compounds were examined.

The ^{13}C NMR spectrum of **10** indicated that the lowest field aliphatic resonance was a methine at δ 72.94. The shift of this carbon atom required that it was adjacent to an oxygen atom and therefore was C_{8a}. A ^1H, ^{13}C NMR correlation experiment showed that this methine at C_{8a} had a proton chemical shift of δ 4.15 (H_{8a}). Proton H_{8a} of **10** was resolved at 270 MHz and was found coupled to a methine (H_{4a}, δ 3.38). Also H_{8a} was coupled to a methylene (H_9 axial, δ 2.58; H_9 equatorial, δ 3.11). Assignments for the remaining proton resonances were determined by decoupling experiments.

The assigned structure for **10** was consistent with the NMR spectral data. Similar ^{13}C and ^1H NMR spectral data were collected for compounds **11** and **12**. Again, the NMR spectral data supported the assigned structures for compounds **11** and **12**. Therefore, it was concluded that products isolated from cyclization reactions with ketone **9** had occurred at position 6 to provide desired compounds **10–12**.

Pharmacology

The dopaminergic activities of compounds **10–12** were evaluated by using two standard methods. The results are listed and compared to those of **1** and pergolide in Table I. The ability of the compounds to lower serum prolactin levels in reserpinized male rats was measured by the method of Clemens.[7] The ability to induce contralateral rotational behavior in unilateral 6-hydroxydopamine nigrostriatal-lesioned rats was measured by using the method of Ungerstedt and Arbuthnott.[8]

All compounds possessed significant dopaminergic activity at doses of 0.05 mg/kg or higher in the inhibition of prolactin and rat turning models. However, none of the compounds were more potent than pergolide. At doses of 0.01 mg/kg or lower, the compounds were inactive or slightly stimulated the release of prolactin.

Compounds **10–12** represent additional examples[4–6] of hetero substitution in the D ring and removal of the A ring of partial ergolines or ergoline in which the dopaminergic properties of their parent structures are retained. Presently, however, no significant advantages exist for **10–12**

(6) After this work was completed, the following report was published. Jones, J. H.; Anderson, P. S.; Baldwin, J. J.; Clineschmidt, B. V.; McClure, D. E.; Lundell, G. F.; Randall, W. C.; Martin, G. E.; Williams, M.; Hirshfield, J. M.; Smith, G.; Lumma, P. K. *J. Med. Chem.* 1984, *27*, 1607.

(7) Crider, A. M.; Robinson, J. M.; Floss, H. G.; Cassady, J. M.; Clemens, J. A. *J. Med. Chem.* 1977, *20*, 1473.

(8) Ungerstedt, U.; Arbuthnott, G. W. *Brain Res.* 1970, *24*, 485.

Table I. Dopaminergic Activity

	prolactin inhibition[a]					rat turning[b]		
compd	dose, mg/kg ip	prolactin control, ng/mL	prolactin treatment, ng/mL	inhibn % change	signif level (p)	dose, mg/kg ip	% of rats turning	turns/1st 15 min[c]
10	0.5	46.8 ± 9.7	3.6 ± 0.3	−92	<0.001[d]	1.0	100	52
	0.1	46.8 ± 9.7	30.2 ± 3.8	−35	<0.2	0.1	60	35
	0.05	45.5 ± 4.8	27.0 ± 5.2	−41	<0.02[d]			
	0.01	58.0 ± 6.6	62.0 ± 4.4	+7	<0.7			
11	0.05	41.5 ± 3.4	20.2 ± 3.6	−51	<0.001[d]	1.0	80	95
	0.01	40.6 ± 3.7	48.9 ± 3.9	−20	<0.2			
12	0.05	45.4 ± 4.8	13.8 ± 2.7	−70	<0.001[d]	1.0	80	33
	0.01	52.0 ± 5.9	33.7 ± 2.4	−31	<0.01[d]			
	0.005	40.6 ± 3.7	41.2 ± 3.1	+1	<0.9			
1	5.0	31.7 ± 2.6	2.7 ± 0.3	−91	<0.001[d]	1.0	100	85
	0.5	31.7 ± 2.6	7.7 ± 4.0	−76	<0.001[d]	0.1	75	67
	0.05	31.7 ± 2.6	12.3 ± 1.3	−61	<0.001[d]			
pergolide	0.05	30.4 ± 3.4	1.6 ± 0.4	−95	<0.001[d]	1.0	100	93
	0.005	37.7 ± 4.0	3.5 ± 0.6	−91	<0.001[d]	0.1	83	81

[a] Values are means ± standard error for 10 rats. [b] Values are based on 6–10 rats per group. [c] After turning began. [d] Significantly different from control prolactin.

over 1, their parent BCD partial ergoline.

Experimental Section

All compounds had NMR spectra consistent with their respective structures. Mass spectra were determined for key compounds. Where analyses are indicated by symbols of the elements, the microanalytical results were within ±0.4% of theoretical values. Melting points and boiling points are uncorrected.

2-Chloro-*N*-(2,4-dimethoxyphenyl)acetamide (4). Chloroacetyl chloride (11.3 g, 0.1 mol) was added dropwise to an ice-bath-cooled solution of 2,4-dimethoxyaniline (15.3 g, 0.1 mol) and triethylamine (10.1 g, 0.1 mol) in 300 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then washed successively with 1 N HCl, 10% aqueous $NaHCO_3$, and H_2O. The CH_2Cl_2 solution was dried ($MgSO_4$) and concentrated in vacuo to provide 23 g of a solid. The solid was dissolved in EtOAc, and the solution was passed through a pad of silica gel. The EtOAc eluent was concentrated in vacuo to give 18 g of a solid. The product was recrystallized from EtOAc–hexane to afford 16.5 g (72%) of 4: mp 90–91 °C. Anal. ($C_{10}H_{12}ClNO_3$) C, H, N.

2-Chloro-*N*-(2-hydroxy-4-methoxyphenyl)acetamide (5). To a solution of 4 (22.8 g, 0.1 mol) in 500 mL of CH_2Cl_2 cooled with an ice bath was added $AlCl_3$ (39.9 g, 0.3 mol) in portions over a 15-min period. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured onto ice to provide a precipitate. The solid was dissolved in EtOAc, and the solution was washed with brine. The EtOAc solution was dried ($MgSO_4$) and concentrated in vacuo, and the crude product was recrystallized from EtOAc–hexane to afford 16.5 g (76%) of 5: mp 161–162 °C. Anal. ($C_9H_{10}ClNO_3$) C, H, Cl, N.

7-Methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (6). A mixture of 5 (19.5 g, 0.09 mol) and K_2CO_3 (13.8 g, 0.1 mol) in 500 mL of acetone was refluxed for 5 h. The reaction mixture was filtered to remove inorganic salts, and the filtrate was concentrated in vacuo. The residual solid was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to provide 14 g (78%) of 6. A sample was recrystallized from EtOAc–hexane: mp 164–165 °C. Anal. ($C_9H_9NO_3$) C, H, N.

7-Methoxy-4-propyl-2*H*-1,4-benzoxazin-3(4*H*)-one (7) and 3,4-Dihydro-7-methoxy-4-propyl-2*H*-1,4-benzoxazine (8). A mixture of 6 (22.7 g, 0.13 mol), K_2CO_3 (25.5 g, 0.15 mol), and n-C_3H_7I (20.7 g, 0.15 mol) in 600 mL of acetone was refluxed for 3 days. The reaction mixture was filtered to remove inorganic salts, and the filtrate was evaporated to dryness. The residual oil was dissolved in CH_2Cl_2, and the solution was washed with brine. The CH_2Cl_2 solution was dried ($MgSO_4$) and concentrated in vacuo to provide 25.5 g of crude 7 as an oil. The product 7 (25.5 g, 0.115 mol) was dissolved in 150 mL of THF, and the solution was added dropwise to a 1 M solution of BH_3 in THF (150 mL, 0.15 mol) at ice-bath temperature. The reaction mixture was refluxed for 2 h and then carefully decomposed at room temperature by dropwise addition of 150 mL of 6 N HCl. The organic solvent was removed in vacuo, and the aqueous acidic solution was warmed on a steam bath for 30 min. The acidic solution was cooled and extracted once with EtOAc. The acidic solution was made alkaline with excess NH_4OH, and the basic mixture was extracted with EtOAc. The EtOAc solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 21.1 g of crude 8. Distillation gave 18.8 g (70%) of 8: bp 120 °C (0.025 mm). Anal. ($C_{12}H_{17}NO_2$) C, H, N.

***trans*-(±)-3,4,4a,5,6,8a-Hexahydro-4-propyl-2*H*-1,4-benzoxazin-7(8*H*)-one (9).** In a flask fitted with a Dewar condenser was introduced 300 mL of dried (BaO) NH_3. To the liquid NH_3 was added Li (4.42 g, 0.64 mol) in pieces over a 30-min period. After all of the Li was dissolved, a solution of 8 (18.8 g, 0.09 mol) in 750 mL of THF was added dropwise. The reaction mixture was stirred for 30 min, and then anhydrous EtOH (100 mL) was added dropwise. The Dewar condenser was removed, and N_2 was blown through the reaciton mixture to remove excess NH_3. Water (100 mL) was added to the residual solution, and the aqueous mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine and dried ($MgSO_4$). The CH_2Cl_2 solvent was evaporated to provide 18 g of enamine.

To a solution of the enamine (18 g, 0.086 mol) and glacial HOAc (5.14 mL, 0.09 mol) in 150 mL of MeOH under N_2 was added dropwise a solution of $NaBH_4$ (3.78 g, 0.1 mol) in 150 mL of anhydrous EtOH. The reaction mixture was stirred at ambient temperature for 2 h. Ten milliliters of 6 N HCl was added, and the reaction mixture was stirred for an additional 1 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to afford an oily residue. The residue was dissolved in 100 mL of H_2O, and the solution was basified to pH 11 with the addition of 50% aqueous NaOH. The basic mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to provide 14 g of crude 9. The crude product 9 (14 g) was dissolved in 50 mL of CH_2Cl_2, and a solution of $NaHSO_3$ (15.6 g, 0.15 mol) in 60 mL of H_2O was added dropwise under N_2. The reaction mixture was stirred for 16 h at room temperature. The CH_2Cl_2 layer was separated, and the aqueous layer was made basic with the addition of 50% aqueous NaOH. The basic mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 9.2 g (58%) of 9. A portion was distilled: bp 88 °C (0.05 mm); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.90 (t, $CH_2CH_2CH_3$), 1.37 (br, $H5_{ax}$), 1.50 (m, $CH_2CH_2CH_3$), 2.31/2.75 (m, $CH_2C_2H_5$), 2.31 (br, $H5_{eq}$), 2.31 (br, $H6_{ax}$), 2.31 (br, H4a), 2.44 (br, $H6_{eq}$), 2.44 (br, $H8_{ax}$), 2.47 (br, $H3_{ax}$), 2.65 (br, $H8_{eq}$), 2.82 (br, $H3_{eq}$), 3.38 (br, H8a), 3.73 (br, $H2_{ax}$), 3.89 (br, $H2_{eq}$). Anal. ($C_{11}H_{19}NO_2$) C, H, N.

***trans*-(±)-4,4a,5,6,8a,9-Hexahydro-5-propyl-2*H*,7*H*-pyrazolo[4,3-*g*][1,4]benzoxazine Hydrochloride (10).** A solution of 9 (0.93 g, 0.005 mol) and ethyl formate (1.48 g, 0.02 mol) in 25 mL of THF was added dropwise at a rapid rate to a solution of potassium *tert*-butoxide (1.12 g, 0.01 mol) in 25 mL of THF

under N_2 cooled to ice-bath temperature. The reaction mixture was stirred at ice-bath temperature for 15 min and then at room temperature for 2 h. To the reaction mixture was added anhydrous hydrazine (0.96 g, 0.03 mol) followed by addition of 1 N HCl until the reaction mixture was at pH 9. The reaction mixture was stirred for an additional 2 h at ambient temperature and then poured into cold 10% aqueous NaOH (100 mL). The basic mixture was extracted twice with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to provide crude free base **10** (530 mg) as an oil. A monohydrochloride was prepared by dissolving free base **10** (530 mg, 2.4 mmol) in 25 mL of MeOH and then adding 0.1 N HCl (24 mL, 2.4 mmol). The solution was concentrated in vacuo and residual solid was recrystallized from MeOH–EtOAc to give 350 mg of **10** monohydrochloride (27%): mp 290 °C dec; ^{13}C NMR (Me_2SO-d_6) δ 10.90 ($CH_2CH_2CH_3$), 15.70 ($CH_2CH_2CH_3$), 20.25 (CH_24), 27.44 (CH_29), 49.81 (CH_26), 53.40 ($CH_2C_2H_5$), 61.82 (CH4a), 62.62 (CH_27), 72.94 (CH8a), 110.54 (C3a), 129.96 (C3), 139.96 (C9a); ^1H NMR (Me_2SO-d_6, 270 MHz) δ 0.95 (t, $CH_2CH_2CH_3$), 1.74 (m, $CH_2CH_2CH_3$), 2.58/3.11 (m, CH_29), 2.88/3.30 (m, CH_24), 3.00/3.29 (m, $CH_2C_2H_5$), 3.18/3.49 (m, CH_26), 3.38 (br, H4a), 4.04 (m, CH_27), 4.15 (br, H8a), 7.77 (s, H3). Anal. ($C_{12}H_{20}ClN_3O$) C, H, Cl, N.

***trans*-(±)-4,4a,7,8,8a,9-Hexahydro-8-propyl-6*H*-thiazolo[5,4-*g*][1,4]benzoxazin-2-amine Dihydrobromide (11).** To a solution of **9** (1.97 g, 0.01 mol) in 20 mL of glacial HOAc was introduced 2.3 mL of freshly prepared 38% HBr in glacial HOAc. The reaction mixture was irradiated with a UV lamp, and a solution of Br_2 (0.4 mL) in 5 mL of glacial HOAc was added dropwise. The reaction mixture was stirred at room temperature for an additional 30 min and then concentrated in vacuo. The crude α-bromo ketone was dissolved in 50 mL of anhydrous EtOH, and thiourea (0.84 g, 0.011 mol) was added to the solution. The reaction mixture was refluxed for 16 h under N_2. The reaction mixture was cooled, and a precipitate was collected. The solid was recrystallized from MeOH to give 1.6 g (39%) of **11** dihydrobromide: mp 297 °C dec; ^{13}C NMR (Me_2SO-d_6) δ 10.85 ($CH_2CH_2CH_3$), 15.78 ($CH_2CH_2CH_3$), 22.74 (CH_29), 28.49 (CH_24), 49.96 (CH_27), 53.76 ($CH_2C_2H_5$), 60.77 (CH8a), 71.43 (CH4a), 110.13 (C9a), 130.64 (C3a), 169.24 (C2); ^1H NMR (Me_2SO-d_6, 270 MHz) δ 0.95 (t, $CH_2CH_2CH_3$), 1.75 (m, $CH_2CH_2CH_3$), 2.52/3.05 (m, CH_24), 2.93/3.45 (m, CH_29), 3.06/3.27 (m, $CH_2C_2H_5$), 3.27/3.60 (m, CH_27), 3.65 (br, CH8a), 4.08 (m, CH_26), 4.22 (br, CH4a). Anal. ($C_{12}H_{21}Br_2N_3OS$) C, H, Br, N, S.

***trans*-(±)-5a,6,7,8,9a,10-Hexahydro-6-propyl-8*H*-pyrimido[5,4-*g*][1,4]benzoxazin-2-amine Hydrochloride (12).** A solution of **9** (2 g, 0.011 mol) and tris(dimethylamino)methane (5 g, 0.034 mol) in 40 mL of toluene was refluxed under N_2 for 2 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in 80 mL of anhydrous EtOH. To the EtOH solution was added guanidine carbonate (1.98 g, 0.011 mol), and the reaction mixture was refluxed under N_2 for 16 h. The reaction mixture was cooled to ice-bath temperature to precipitate a yellow solid. The precipitate was collected, and the filter cake was washed with H_2O. The crude product was dissolved in 100 mL of $CHCl_3$. The $CHCl_3$ solution was washed with dilute NH_4OH and brine. The $CHCl_3$ solution was dried ($MgSO_4$) and evaporated in vacuo to provide 600 mg of crude **12** as free base. A monohydrochloride was prepared by dissolving **12** free base (600 mg, 2.4 mmol) in 25 mL of THF and adding 0.1 N HCl (24 mL, 2.4 mmol). The solution was concentrated in vacuo, and the residual solid was recrystallized from MeOH–EtOAc to provide 440 mg (14%) of **12** monohydrochloride: mp 290 °C dec; ^{13}C NMR (Me_2SO-d_6) δ 10.95 ($CH_2CH_2CH_3$), 15.87 ($CH_2CH_2CH_3$), 24.18 (CH_25), 36.74 (CH_210), 49.97 (CH_27), 53.40 ($CH_2C_2H_5$), 61.12 (CH5a), 62.75 (CH_28), 72.03 (CH9a), 113.14 (CH4a), 157.83 (CH4), 161.47 (C2 or C10a), 162.16 (C10a or C2); ^1H NMR (Me_2SO-d_6, 270 MHz) δ 0.94 (t, $CH_2CH_2CH_3$), 1.73 (m, $CH_2CH_2CH_3$), 2.70/2.95 (m, CH_210), 2.95/3.20 (m, $CH_2C_2H_5$), 3.2/3.5 (m, CH_27), 3.3 (br, CH5a), 3.3 (m, CH_25), 4.04 (m, CH_28), 4.14 (br, CH9a), 8.05 (s, CH4). Anal. ($C_{13}H_{21}ClN_4O$) C, H, N.

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Synthesis and Antitumor Activity of N-Terminal Proline-Containing Peptide–(Chloroethyl)nitrosoureas

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The N^{α}-(2-chloroethyl)-*N*-nitrosocarbamoyl derivatives of H-Pro-Lys(X)-Pro-Val-NH_2 (X: *tert*-butyloxycarbonyl, formyl, (2-chloroethyl)nitrosocarbamoyl) were synthesized. It was found that the bis-substitution of the urea N^3 in these derivatives does not decrease the antitumor activity influenced mainly by the nature of the carrier molecule as a whole.

One of the most effective cytostatic (2-chloroethyl)-nitrosoureas ($ClCH_2CH_2N(NO)$-CO-NHR) is the 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU).[1] This compound, although of excellent antitumor activity, is rather toxic. Numerous analogues with modified R groups have been synthesized in order to obtain less toxic and more selective compounds.

For the same reason, we have recently prepared peptide–(chloroethyl)nitrosoureas,[2] where the peptide moieties were fragments of polypeptide hormones (α-melanotropin, gastrin) with a receptor-recognizing ability. The antineoplastic activity of these peptide derivatives against L1210 leukemia in mice[3] and against human melanoma xenograft[4] proved to be significant. The Q(NO)-Pro-Val-NH_2 (Q(NO) = $ClCH_2CH_2N(NO)CO$), although inactive as a melanotropic agent, showed strikingly good

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(1) Johnston, T. P.; McCaleb, G. S.; Montgomery, J. A. *J. Med. Chem.* **1963**, *6*, 669.
(2) Süli-Vargha, H.; Medzihradszky, K. *Int. J. Pept. Protein Res.* **1984**, 23, 650.
(3) Süli-Vargha, H.; Medzihradszky, K.; Jeney, A.; Kopper, L.; Lapis, K. *Peptides 1984*, Proceedings of the 18th European Peptide Symposium; Ragnarsson, U., Ed.; Almqvist & Wiksell: Stockholm, 1984; p 407.
(4) Jeney, A.; Kopper, L.; Nagy, P.; Lapis, K.; Süli-Vargha, H.; Medzihradszky, K. *Cancer Chemother. Pharmacol.* **1986**, *16*, 129.

0022-2623/87/1830-0583$01.50/0