500 mg). The mixture was stirred at 0 °C under red lights for 10 h, the Et_2O solution was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to yield an oil. The crude product was applied to a silicic acid (30 g) column slurried in C_6H_6. Fractions (25 mL in volume) were eluted with C_6H_6. Fractions 4–6 were combined to afford methyl 17-octadecynoate (10; 230 mg, 88%) as a colorless oil. Analysis by TLC (SiO_2-GF) in C_6H_6 (R_f 0.60) indicated the presence of a single component: IR (NaCl) 3300 (C≡CH), 2920, 2860 (CH), 1745 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 26 H, CH_2), 1.9 (m, 1 H, C≡CH), 2.30 (m, 4 H, CH_2COO and C≡CCH_2), 3.66 (s, 3 H, $COOCH_3$); MS, m/z 294 (M^+, 2), 263 ($M^+ - HC{\equiv}C(CH_2)_{16}CO$, 6). Anal. ($C_{18}H_{34}O_2$) C, H.

Method B. The crude acid **9** (1.7 g) was dissolved in excess MeOH and refluxed with H_2SO_4 (1 mL) for 18 h. The solvent was removed, and the crude product was extracted into ether and chromatographed on a SiO_2 column by elution with 10% EtOAc/petroleum ether (10:90) to give 1.51 g (85%) of methyl 17-octadecynoate (10), which was identical with 10 obtained by method A.

(17-Carbomethoxyheptadec-1-en-1-yl)boronic Acid (11). Catecholborane (1.64 mL, 15 mmol) was added to methyl 17-octadecynoate (10; 2.94 g, 10 mmol) at 0 °C under nitrogen. The mixture was then heated at ~40 °C for 6 h. Ice (10 g) was added, followed by cold H_2O (100 mL), and the mixture was stirred for 18 h. The precipitate was filtered, washed thoroughly with H_2O (500 mL) and C_6H_6 (100 mL), and dried to give 2.84 g (84%) of 11: NMR (acetone-d_6/Me_2SO-d_6, 9:1) δ 1.30 (CH_2 envelope, 26 H), 2.16 (m, 4 H, C=CHCH_2 and CH_2COOCH_3), 3.54 (s, 3 H, $COOCH_3$), 5.30 (d, J = 18 Hz, 1 H, HC=CHB), 6.53 (m, 1 H, HC=CHB), 7.06 (s, OH). Anal. ($C_{18}H_{31}O_4$) C, H.

(*E*)-18-Iodo-17-octadecenoic Acid (13). (17-Carbomethoxyheptadec-1-en-1-yl)boronic acid (11; 680 mg, 2 mmol) was dissolved in 10 mL of 50% aqueous THF. Aqueous NaI (2 mL of a 1 M solution) was added, and the mixture was cooled to 0 °C. After the addition of chloramine-T (0.91 g, 4 mmol in 8 mL of 50% aqueous THF), the mixture was stirred for 15 min. Water (25 mL) was then added, followed by petroleum ether (50 mL), and the mixture was filtered and washed again with petroleum ether. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated to give the crude product. Purification by preparative TLC on silica gel GF using EtOAc/petroleum ether (2:8) gave 670 mg (79%) of 12 as a thick oil: NMR ($CDCl_3$) δ 1.25 (CH_2 envelope, 26 H), 2.11 (br m, 4 H, C=CHCH_2 and CH_2COOCH_3), 3.58 (t, 3 H, $COOCH_3$), 5.81 (d, 1 H, HC=CHI), 6.41 (m, 1 H, HC=CHI). Anal. ($C_{18}H_{35}O_2I$) C, H.

Methyl 18-[^{125}I]Iodo-17-octadecenoate ([^{125}I]12). The boronic acid 11 was dissolved in 2 mL of an H_2O–THF mixture (1:1) under argon, and the mixture was cooled to 0 °C. After the addition of sodium [^{125}I]iodide (32 mCi, 15 mg, 0.1 mmol), chloramine-T (45 mg, 0.2 mmol) was added in 1 mL of H_2O–THF, and the resulting orange-colored mixture was stirred for 30 min to give a yellow-colored solution. The mixture was poured into 50 mL of Et_2O, washed once with 50 mL of 10% sodium bisulfite and then thoroughly with H_2O, and dried over anhydrous Na_2SO_4. The dried ether solution was concentrated by a stream of argon to give an oil, which was chromatographed on silicic acid by elution (25 mL fractions) with petroleum ether (30–60 °C) (fractions 1–10) and benzene (fractions 11–20). Fractions 12–14 were combined to give 12.1 mCi (38%) of ^{125}I-labeled 12. The radiochemical and chemical purities were confirmed by TLC (SiO_2-GF) in benzene, R_f 0.50.

18-[^{125}I]Iodo-17-octadecenoic Acid ([^{125}I]13). Methyl 18-[^{125}I]iodo-17-octadecenoate ([^{125}I]12: 12.1 mCi) was dissolved in EtOH (10 mL) and refluxed with 1 N NaOH (2 mL) for 60 min. The mixture was cooled, poured into H_2O, acidified to pH 2–3 with 1 N HCl, and extracted twice with Et_2O. Following thorough washing with H_2O, the organic layer was dried over anhydrous Na_2SO_4, and the Et_2O was evaporated by a stream of argon to yield 9.43 mCi (79%) of [^{125}I]13. The chemical and radiochemical purity were confirmed by TLC (SiO_2-GF) in MeOH–$CHCl_3$ (4:96), R_f 0.40.

18-[^{123}I]Iodo-17-octadecenoic Acid ([^{123}I]13). The [^{123}I]13 was prepared in the same manner as described above for the ^{125}I-labeled analogue using iodine-123 obtained in the generator/iodination ampule from the Brookhaven National Laboratory.[7]

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cis-4-[[[(2-Chloroethyl)nitrosoamino]carbonyl]methylamino]cyclohexanecarboxylic Acid, a Nitrosourea with Latent Activity against an Experimental Solid Tumor

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cis-4-[[[(2-Chloroethyl)nitrosoamino]carbonyl]methylamino]cyclohexanecarboxylic acid (*N*-Me-*cis*-CCCNU) was synthesized in five steps from *cis*-4-aminocyclohexanecarboxylic acid via an N-tosylated intermediate. *N*-Me-*cis*-CCCNU, which is incapable of the facile decomposition that characterizes the clinically useful nitrosoureas, effected a significant cure rate of both early and established murine Lewis lung carcinoma, even though its in vitro half-life was ~5.5 times that of the unmethylated parent compound. This is the first observation of latent activity of a nitrosourea against an experimental solid tumor.

The nitrosoureas that have attracted most clinical interest as anticancer agents[2] are characterized by a 2-chloroethyl group on the nitrosated nitrogen and monosubstitution on the other nitrogen. Abstraction of the remaining proton under physiological conditions initiates an easy decomposition into alkylating and carbamoylating species that accounts for the biological effects observed.[3-5]

(1) Present address: Bristol Laboratories, Syracuse, NY.
(2) BCNU (carmustine), CCNU (lomustine), MeCCNU (semustine), PCNU, chlorozotocin, RFCNU, and ACNU (nimustine). See ref 3–5.

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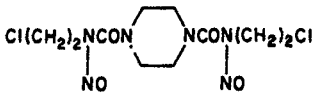
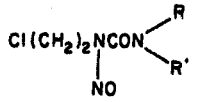
Full substitution of the ureido nitrogens, as in *N,N'*-bis-(2-chloroethyl)-*N,N'*-dinitroso-1,4-piperazinedicarboxamide (1), resulted in inactivity against murine leukemia



1

L1210[6] and stability in aqueous solution under physiological conditions.[7] Fully substituted congeners having a suitably positioned methyl group, as in *N*-(2-chloroethyl)-*N'*-methyl-*N*-nitroso-*N'*-propylurea (2), however,

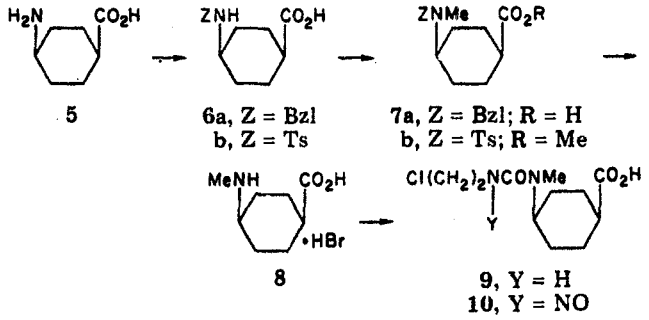


2, R = Me; R' = Pr
3, R = R' = $(CH_2)_2OH$
4, R = (2-tetrahydrofuranyl)methyl; R' = D-galactopyranosyl

were shown to be also relatively stable in aqueous solution and active against leukemia L1210 only in vivo, an observation indicative of activation via enzymatic demethylation.[8] On the other hand, fully substituted congeners having suitably positioned hydroxylated substituents, as in *N*-(2-chloroethyl)-*N',N'*-bis(2-hydroxyethyl)-*N*-nitrosourea[9] (3) and the galactopyranosyl derivative 4,[10] were recently found to be highly active against leukemia L1210 without prior enzymatic activation. The latter observation indicated a chemical activation initiated by attack of a β-hydroxyl group on the ureido carbonyl group without the coformation of a carbamoylating species.

Those results mentioned above that indicate enzymatic activation prompted a synthesis (Scheme I) of *cis*-4-[[[(2-chloroethyl)nitrosoamino]carbonyl]methylamino]-cyclohexanecarboxylic acid (10, *N*-Me-*cis*-CCCNU, *N*-Me-Cis-Acid). The unmethylated parent nitrosourea (*cis*-CCCNU) and its trans isomer were among those analogues of MeCCNU[11] that showed good activity against both early and established forms of Lewis lung carcinoma,[12] which is more discriminative in response to nitrosoureas than leukemia L1210.[13] This compound also had the advantage of convenient solubility in cold phosphate buffer of physiological pH, making it an appealing compound for further study.[14,15]

Scheme I



Chemistry. The synthesis of 10 from *cis*-4-aminocyclohexanecarboxylic acid (5) was effected in five steps, as shown in Scheme I. An initial approach (via 6a and 7a) involving protection of the amino group by benzylation as in a general method for the N-methylation of amino acids[16] was abandoned when catalytic debenzylation failed under conditions specified for less hindered amino acids. The successful approach (via 6b and 7b) involving protection of the amino group by tosylation resulted in both N- and O-methylation, but detosylation under previously reported conditions[17] was surprisingly accompanied by deesterification, a result attributed to the use of aged reagent, no longer anhydrous.

Biological Results

The single-dose LD_{10} of 10, whose half-life in phosphate buffer (pH 7.4) was ~4.2 h,[18] was >400 mg/kg; in contrast, the half-life and single-dose LD_{10} of the parent *cis*-CCCNU was ~46 min[19] and 26 mg/kg.[11] In replicate experiments, a single dose of 10 (600 mg) effected 70 and 90% cures of early Lewis lung tumors (day 2 postimplant); a dose of 400 mg/kg effected 10 and 40% cures. Against established (400-mg) Lewis lung tumors, doses of 400 mg/kg given on days 7 and 14 postimplant effected 40% cures. This response was similar to that obtained with 24 mg/kg of MeCCNU, the standard positive control for this tumor, given on days 7 and 12 (30% cures). In earlier experiments, *cis*-CCCNU effected 70% cures of the early tumor with doses of 13 and 20 mg/kg[12b] and 20% cures of the established tumor with doses of 26 mg/kg given on days 7 and 13 postimplant in comparison with 30% cures with 36 mg/kg of the standard MeCCNU in the same experiment. These experiments were carried out according to a previously described protocol[12b] with 10 and MeCCNU suspended in physiological saline with Tween-80 and *cis*-CCCNU dissolved in buffered saline for injection, with female BDF_1 mice, and with tumor measurements made

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weekly. These observations are significant in that they constitute the first demonstration of latent activity of a nitrosourea against a solid tumor—an experimental model that is distinctly less sensitive to chemotherapy than the leukemia against which latent nitrosoureas have been tested previously.[8]

Experimental Section

Melting points were determined with a Mel-Temp apparatus, unless noted otherwise, and are uncorrected. IR spectra were determined with a Perkin-Elmer 521 spectrophotometer, and NMR spectra were determined with a Varian XL-100-15 spectrometer. TLC was performed on Analtech silica gel GF plates. Analytical results indicated by element symbols were within 0.4% of the theoretical values. Elemental analyses and spectral determinations were performed in the Molecular Spectroscopy Section of Southern Research Institute under the direction of Dr. William C. Coburn, Jr., and biological evaluation was conducted in the Cancer Screening Division under the direction of Dr. W. Russell Laster, Jr.

Evaporations were carried out under reduced pressure (water aspirator) with a rotary evaporator. Products were dried in vacuo (oil pump) over phosphoric anhydride.

***cis*-4-[(Phenylmethyl)amino]cyclohexanecarboxylic Acid (6a).** A solution of 5[11,20] (28.6 g, 0.200 mol) in 1 N NaOH (200 mL) was stirred with freshly distilled benzaldehyde (20.2 mL, 0.200 mol) until the mixture became a solution, which was then hydrogenated over 5% palladium on carbon (6 g) in a Parr apparatus at 3.5 kg/cm^2 for 2.5 h. The catalyst was removed, and the filtrate was adjusted to pH 6–7 with 1 N HCl (~200 mL). The product was collected after chilling, washed with cold water, and dried: yield 41.0 g (88%); mp 206–207 °C dec; IR (KBr) 1625 (C=O, ionized carboxyl) cm^{-1}. Anal. ($C_{14}H_{19}NO_2$) C, H, N.

***cis*-4-[[(Methylphenyl)sulfonyl]amino]cyclohexanecarboxylic Acid (6b).** A solution of *p*-toluenesulfonyl chloride (22.3 g, 0.117 mol) in dichloromethane (100 mL) was added slowly to a cold, stirring solution of 5 (16.8 g, 0.117 mol) and sodium carbonate (24.9 g, 0.234 mol) in water (200 mL), and the mixture was stirred rapidly at 5 °C for 30 min and at 50–60 °C for 1 h, left overnight, and evaporated to remove dichloromethane. The mass remaining was acidified slowly with concentrated hydrochloric acid, and the product that separated was collected after cooling, washed with cold water, and dried: yield 23.5 g (68%); mp 152 °C (Kofler Heizbank); IR (KBr) 3260 (NH), 1705 (C=O, un-ionized carboxyl), 1595, 1495, 815 (Ph) cm^{-1}; TLC (water, ninhydrin for 1, UV for 2) showed homogeneity. Anal. ($C_{14}H_{19}NO_4S$) C, H, N.

***cis*-4-[Methyl(phenylmethyl)amino]cyclohexanecarboxylic Acid (7a) Formate.** Powdered **6a** (33.5 g, 0.15 mol) was mixed with concentrated formic acid (16.8 mL, 0.45 mol) and 37% formaldehyde (16.8 mL, 0.18 mol), and the mixture was boiled for 2 h after **6a** dissolved with foaming. The solution was evaporated, and the residual product was recovered after dissolving in ethanol. The product was triturated in cold acetonitrile (100 mL) and dried: yield 32.5 g (74%); mp 130–132 °C. A small sample was twice recrystallized from acetonitrile for analysis with no change in melting point: IR (KBr) 1695 (C=O, un-ionized carboxyl), 1620 (C=O, ionized carboxyl) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.2–1.88 [m, 8, CH(CH_2CH_2)$_2$CH], 1.88–2.14 (m, 1, $CHCO_2H$), 2.16 (s, 3, CH_3), 2.36–2.72 (m, 1, CHN), 3.68 (s, 2, NCH_2Ph), 7.25–7.45 (m, 5, C_6H_5), 8.24 (s, 1, HCO_2^-, overlapping with other carboxyl proton and H_2O); ^{13}C NMR (Me_2SO-d_6) δ 25.13 and 25.67 [CH(CH_2CH_2)$_2$CH], 37.02 (CH_3), 38.91 ($CHCO_2H$), 57.25 (NCH_2), 60.79 (CHN), 127.04 (C-4 of Ph), 128.16 (C-2, C-6 of Ph), 128.86 (C-3, C-5 of Ph), 138.54 (C-1 of Ph), 163.55 (HCO_2^-), 175.85 ($CHCO_2H$). Anal. ($C_{15}H_{21}NO_2 \cdot HCO_2H$) C, H, N.

Methyl *cis*-4-[Methyl[(4-methylphenyl)sulfonyl]amino]cyclohexanecarboxylate (7b). Sodium hydride (6.68 g, 0.158 mol; 57% in mineral oil) was added in portions to a cold (0–5 °C), stirring solution of **6b** (23.2 g, 78.0 mmol) in dry DMF (200 mL), and the mixture was stirred until hydrogen evolution stopped (~1 h) and treated slowly with excess methyl iodide (23.2 mL). After 1 h at room temperature, 1 h at 40 °C, and overnight at room temperature, the mixture was diluted with benzene (400 mL) and stirred more. This solution was washed with 0.5 N sodium hydroxide solution (4 × 150 mL) and water (1 × 200 mL), dried ($MgSO_4$), and evaporated to dryness. The yellow residue was triturated in hot ethanol (60 mL), and the white solid was collected after cooling and dried: yield 22.8 g (90%); mp 118–120 °C; IR (KBr) 1730 (C=O), 1595 (aromatic CH), 1330, 1310, 1160, 1145 (SO_2) cm^{-1}. Anal. ($C_{16}H_{23}NO_4S$) C, H, N.

***cis*-4-(Methylamino)cyclohexanecarboxylic Acid Hydrobromide (8).** A solution of **7b** (12.0 g, 36.9 mmol) in a 30% solution of hydrogen bromide in acetic acid (130 mL, of indefinite age) was allowed to stand for 3 days with exclusion of moisture and was then gradually added to ether (1.5 L) with stirring. The mixture was stirred at 5 °C for 20 min, and the product was collected, dried, and precipitated from methanol (35 mL) with ether (500 mL): yield 6.95 g (79%); mp 204–205 °C; IR (KBr) 1720 (C=O) cm^{-1}; mass spectrum, *m/e* 157 (M$^+$); TLC (MeOH, ninhydrin) single spot. Anal. ($C_8H_{15}NO_2 \cdot HBr$) C, H, N.

***cis*-4-[[[(2-Chloroethyl)amino]carbonyl]methylamino]cyclohexanecarboxylic Acid (9).** 2-Chloroethyl isocyanate (2.1 mL, 24 mmol) was added dropwise to a cold (5–10 °C), stirring solution of 8 (5.7 g, 24 mmol) in 1 N NaOH solution (48 mL). The resulting mixture was stirred at room temperature for 45 min, cooled, and acidified with concentrated hydrochloric acid. The product was washed with cold water and dried: yield 3.85 g (61%); mp 112–113 °C; IR (KBr) 3405 (NH), 1695 (carboxylic C=O), 1605 (ureido C=O), 1530 (CNH) cm^{-1}; TLC (EtOH, ninhydrin) single spot. The analytical sample, mp 113–114 °C, was recrystallized from acetonitrile by addition of water. Anal. ($C_{11}H_{19}ClN_2O_3$) C, H, N.

***cis*-4-[[[(2-Chloroethyl)nitrosoamino]carbonyl]methylamino]cyclohexanecarboxylic Acid (10).** Sodium nitrite was added in small portions to a cold (0–5 °C), stirring solution of **9** (5.0 g, 19 mmol) in undiluted formic acid (50 mL). After 30 min, the cold mixture was diluted with cold water (200 mL), and the resulting suspension was stirred at 0 °C for 15 min. The light-yellow product was washed with cold water and dried overnight: yield 4.9 g (90%); mp 128–129 °C dec; IR (KBr) 1690 (carboxylic C=O), 1680 (ureido C=O), 1470 (N=O) cm^{-1}; TLC (H_2O, UV for **9**, ninhydrin for **10**) single spot; ^{1}H NMR (Me_2SO-d_6) δ 1.25–2.25 [m, 8, CH(CH_2CH_2)$_2$CH], 2.44–2.68 (m, 1, $CHCO_2H$, overlap with Me_2SO-d_5), 2.86 (s, 3, CH_3), 3.6–3.8 (t, 2, CH_2Cl), 3.7–4.04 (m, 1, CHN, overlap with $ClCH_2CH_2$), 3.94–4.18 [t, 2, $N(NO)CH_2$]. Anal. ($C_{11}H_{18}ClN_3O_4$) C, H, N.

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Registry No. 5, 3685-23-2; **6a**, 87640-24-2; **6b**, 87640-25-3; **7a**·formate, 87640-27-5; **7b**, 87640-28-6; **8**·HBr, 87640-29-7; **9**, 87640-30-0; **10**, 87640-31-1; benzaldehyde, 100-52-7; 2-chloroethyl isocyanate, 1943-83-5.

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