187–189 °C; ^{1}H NMR (Me_2SO) δ 1.45–1.69 (m, 12 H), 1.95 (br s, 6 H), 3.77 (d, 2 H), 3.81 (t, 2 H), 3.87 (m, 2 H), 4.18–4.36 (m, 3 H, α-H), 4.81 (s, 6 H, CH_2Ph), 7.41 (s, 15 H, phenyl), 7.99 (d, 1 H, NH), 8.1 (d, 1 H, NH), 8.15 (d, 1 H, NH), 8.25 (t, 1 H, NH), 11.08 (d, 3 H, $NHOCH_2Ph$).

Anal. Calcd for $C_{45}H_{57}N_9O_{12}\cdot CH_3OH\cdot{}^1/_2H_2O$: C, 57.74; H, 6.53; N, 13.16. Found: C, 57.43; H, 6.51; N, 13.18.

Method B. TFA salt **19** (180 mg, 0.17 mmol) and triethylamine (0.03 mL, 0.2 mmol) in dry DMF (150 mL) were cooled to 0 °C. To this cold solution diphenylphosphoryl azide (DPPA) (0.08 mL, 0.4 mmol) was added and the mixture was stirred at 0 °C for 5 h and at room temperature for 4 days, during which time the pH of 7.5 was maintained by the addition of triethylamine. The reaction mixture was concentrated to a small volume (5 mL) and partitioned between *n*-BuOH/EtOAc/0.5 M aqueous citric acid (50:100:50 mL). The organic extract was washed with 0.5 M citric acid (25 mL), 1 N HCl (25 mL), 1 N $NaHCO_3$ (25 mL), H_2O (20 mL), and brine, dried (Na_2SO_4), and evaporated to dryness in vacuo. The crude product was purified as described in method A to give **20**, 30 mg (19%).

Method C. TFA salt **19** (0.52 g, 0.5 mmol) and 1-hydroxybenzotriazole (220 mg, 1.6 mmol) in dry DMF (100 mL) was cooled to 0 °C and diluted with dry CH_2Cl_2 (100 mL). *N*-Methylmorpholine (0.06 mL. 0.5 mmol) in dry DMF (25 mL) was added and the mixture was stirred for 1 h at 0 °C. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (0.28 g, 1.5 mmol) in 150 mL of dry DMF/CH_2Cl_2 (50:100) was added at 0 °C over a period of 2 h. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 4 days. The solvent was removed in vacuo and the residue was taken up in 200 mL of *n*-BuOH/EtOAc (4:6). The organic phase was washed with 1 N HCl (30 mL), 1 N $NaHCO_3$ (30 mL), water (50 mL), and brine (20 mL). After drying (Na_2SO_4), the solution was evaporated to dryness, and the crude product was purified as described in method A, yield 152 mg (33%).

***cyclo*-[Triglycyltris(*N*$^\epsilon$-hydroxy-L-α-amino-δ-adipamidyl)] (21).** The cyclic hexapeptide **20** (40 mg) in DMF (25 mL) was shaken under hydrogen (10 psi) with 5% palladium–carbon (20 mg) for 6 h at room temperature. The catalyst was filtered and the filtrate evaporated to dryness. The residue was dissolved in a minimum amount of methanol and diluted with ether, which on cooling gave crystalline compound. The product was filtered, washed with ether, and dried in vacuo over P_2O_5: yield 20 mg (71%); mp >150 °C dec; ^{1}H NMR (Me_2SO) δ 1.57 (m, 12 H), 1.94 (br s, 6 H), 3.6–3.83 (m, 6 H), 4.21 (m, 3 H, α-H), 8.08–8.68 (m, 6 H, NH), 10.36 (br s, 3 H, NH).

***N*-Demethylretrohydroxamate Ferrichrome (22).** This compound was prepared by the same procedure as used for retrohydroxamate ferrichrome (**2**).

Acknowledgment. Appreciation is expressed to the National Institutes of Health (Grant GM 26711) for support of the work and to the Colorado State University Regional NMR Center (funded by National Science Foundation Grant No. CHE-8208821) for providing 360-MHz NMR data. We acknowledge the contribution of Professor T. Emery of this department for the genesis of the rationale for attempting the synthesis of a retrohydroxamate analogue of ferrichrome.

Supplementary Material Available: Additional experimental information for other compounds in this paper (7 pages). Ordering information is given on any current masthead page.

Reductive Alkylation of β-Alkanolamines with Carbonyl Compounds and Sodium Borohydride†[1]

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A synthesis of secondary alkylalkanolamines from primary alkanolamines in a rapid process in which overalkylation is virtually suppressed is described. The procedure combines the ease of formation of oxazolidines from alkanolamines with aldehydes or ketones in absolute ethanol and the lability of the newly formed C–O bond toward sodium borohydride. The entire process is carried out in 15–35 min depending on the carbonyl substrate.

In reactivity patterns, alkylalkanolamines combine the characteristics of the amine and hydroxyl groups. This combination of functionalities makes them versatile intermediates for countless industrial applications; they are of particular interest to the textile, pharmaceutical and household products industries.[2] Secondary alkylalkanolamines are also precursors for β-hydroxylated nitrosamines. These important compounds are used in the study of nitrosamine exposure in the workplace and metabolic and carcinogenesis studies.[3]

The title compounds are generally prepared by the ring opening of an epoxide with an alkylamine.[4] The addition of imidoosmium reagents to alkenes[5] and methods for the alkylation of primary amines with 2-bromo alcohols[6] are also well-established procedures for the preparation of *N*-alkyl-1,2-alkanolamines. A major limitation of some of these methods is the possibility of further alkylation to tertiary amines and quaternary ammonium compounds.

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(1) Presented at 188th National Meeting of American Chemical Society, Philadelphia, PA, Aug 1984; American Chemical Society: Washington, DC, 1984; Abstract No. ORGN 245.

(2) The Alkanolamines Handbook 1981, The Dow Chemical Co.

(3) Lijinsky, W. "Genotoxicology of N-Nitroso Compounds"; Rao, T. K., Lijinsky, W., Epler, J. L. Plenum Press: New York, 1984; Chapter 10 and references therein.

(4) (a) Knorr, L.; Schmidt, W. *Ber. Deutsch. Chem. Ges.* **1898**, *31*, 1072. (b) Berlini A. Ya.; Sycheva, T. P. *Zh. Obsch. Khim.* **1950**, *20*, 640. (c) Burfield, D. R.; Gan, S.-N.; Smithers, R. H. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 666.

(5) Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305.

(6) Goldberg, US Patent 2 139 818; English Patent 482 886.

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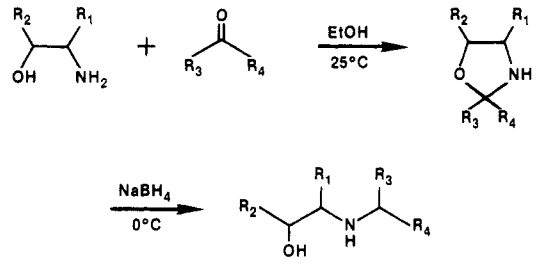
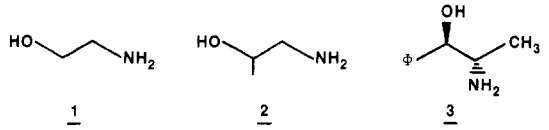
Scheme I



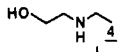
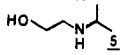
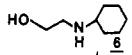
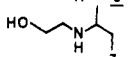
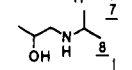
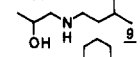
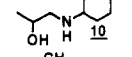
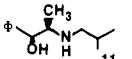
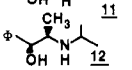
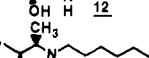
Cope and Hancock[7] successfully developed the catalytic reduction of ethanolamine and 2-aminopropanol with various aldehydes and ketones over platinum oxide–platinum catalyst in 1 or 2 atm of hydrogen. The reaction proceeded smoothly at room temperature via the oxazolidine intermediate within 4–15 h to yield the corresponding 2-alkylalkanolamine. At elevated temperatures and pressures, Raney nickel and copper chromite were also effective catalysts.[7a] Englehardt et al.[8] applied these findings to the reductive alkylation of arylalkanolamines. The need for an exogeneous source of hydrogen, the long reaction times, and high temperatures and pressure were some of the disadvantages of this method. In 1974, Shimizu et al.[9] reported the reductive cleavage of *N,N'*-, N,O-, and N,S-linked alkylidene compounds with sodium borohydride. This indicated that, since the C–N bond of the oxazolidine ring was labile in the presence of this reducing agent, the method would be a viable alternative to the catalylic reductions discussed above.

We have developed a simple, rapid, and efficient procedure for preparing secondary alkylalkanolamines uncontaminated by tertiary derivatives. Our method combines the ease of formation of oxazolidines from alkanolamines in absolute ethanol and the lability of the newly formed C–O bond toward sodium borohydride to give a superior procedure for preparing alkylalkanolamines. The outline of the procedure is described in Scheme I. In a typical run, a 1 M ethanolamine solution in absolute ethanol was stirred with 1.5 equiv of the carbonyl compound for 10–30 min at room temperature. After this time, most of the amine had been converted to the corresponding oxazolidine as indicated by gas chromatography. The reduction step was carried out in situ at 0 °C with sodium borohydrate within 5 min for amines derived from monoethanolamine (1) and 1-amino-2-propanol (2). The reduction step went to completion within 30 min at room temperature for compounds from norephedrine (3). The overall yield of pure product ranged from 70 to 99%. Examples featuring the versatility of the procedure are listed in Table I.



During the preparation of this manuscript, Morales et al.[10] reported a procedure for N-monoalkylation of amines and alkanolamines with carbonyl compounds and borane in tetrahydrofuran. This method offers an excellent alternative to the reductive alkylation described here.

Table I. Reductive Alkylation of Primary Alkanolamines with Sodium Borohydride

Amine	Carbonyl Substrate	Overall Reaction Time (minutes)[a,b]	Product	Overall Yield (%)
1	Acetaldehyde	15		76
1	Acetone	35		76
1	Cyclohexanone	35		89
1	Methyl Ethyl Ketone	35		75
2	Acetone	35		70
2	Isovaleraldehyde	15		81
2	Cyclohexanone	35		99
3	Isobutyraldehyde	30		76
3	Acetone	35		88
3	n-Heptaldehyde	35		84

[a] Reduction of oxazolidines derived from 1 and 2 took place within 5 min at 0 °C. [b] Reduction of oxazolidines of 3 went to completion within 20 min at 25 °C.

Experimental Section

Proton and carbon NMR spectra were recorded by using a Nicolet NT-300 spectrometer with $CDCl_3$ as the solvent containing 0.5% tetramethylsilane. The IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Low-resolution mass spectra were taken on a Finnigan 330 mass spectrometer equipped with a Finnigan 6000 MS data system. Gas chromatographic analyses were carried out on a Shimadzu Model 4BM gas chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame ionization detector. A 2.5-m Tenax 80/100 GC column (Applied Science Division) was used. Melting points were determined on an Electrothermal capillary melting point apparatus and were not corrected. The starting materials were obtained from Aldrich Chemical Co.

2-(Ethylamino)ethanol (4). A 1 M solution of 210 mg (3.44 mmol) of ethanolamine in absolute ethanol was stirred for 10 min at room temperature with 1.5 equiv of acetaldehyde. After this time, virtually all the starting amine had been converted to 2-methyloxazolidine[10] as indicated by gas chromatography. The solution was cooled to 0 °C and 190 mg (5 mmol) of sodium borohydride added. After 5 min at 0 °C, the mixture was quenched with 0.5 mL of water, diluted with methylene chloride, and filtered, and the solvents were removed on a rotary evaporator to give 329 mg of a viscous liquid. This residue was extracted with ether and filtered through anhydrous magnesium sulfate and the solvent evaporated. The crude product was distilled to give 234 mg (76%): bp 102–103 °C at 100 mmHg (lit.[4a] bp 167–169 °C at 751 mmHg).

2-(Isopropylamino)ethanol (5). A 1 M solution of 390 mg (6.39 mmol) of ethanolamine (1) in absolute ethanol was condensed with 1.5 equiv of acetone. This reaction was completed within 30 min. The reduction step and the workup were carried out as described above to give 498 mg (76%) of 5: bp 54–55 °C at 5.5 mmHg (lit.[7a] bp 76–77 °C at 15 mmHg).

2-(Cyclohexylamino)ethanol (6). A solution of 615 mg (10.1 mmol) of ethanolamine in 10 mL of absolute ethanol was stirred with 1.1, g (12 mmol) of cyclohexanone for 30 min at 25 °C. The reduction step was carried out with 456 mg (12 mmol) of sodium borohydride as described above to give, after vacuum distillation, a 1.29 g (89%) yield of 6: bp 89–90 °C at 2.5 mmHg (lit.[7a] bp 122–123 °C at 13 mmHg).

(7) (a) Cope, A. C.; Hancock, E. M. *J. Am. Chem. Soc.* **1942**, *64*, 1503. (b) Cope, A. C.; Hancock, E. M. *J. Am. Chem. Soc.* **1944**, *66*, 1453.
(8) Engelhardt, E. L.; Crossley, F. S.; Sprague, J. M. *J. Am. Chem. Soc.* **1950**, *72*, 2718.
(9) Shimizu, K.; Ito, K.; Sekiy, M. *Chem. Pharm. Bull.* **1974**, *22*, 1256.
(10) Morales, H. R.; Perez-Juarez, M.; Cuellar, L.; Mendoza, L.; Fernandez, H.; Contreras, R. *Synth. Commun.* **1984**, *14*, 1213.

2-(2-Butylamino)ethanol (7). Ethanolamine (1.06 g, 0.017 mol) was reacted for 30 min with 1.5 equiv of methyl ethyl ketone. The resulting oxazolidine[10] was reduced and worked up as described above to give 1.5 g (75%) of **7**: bp 70–71 °C at 5.5 mmHg (lit.[7a] bp 88–88.5 °C at 17 mmHg).

1-(Isopropylamino)-2-propanol (8). A 1 M solution of 534 mg (7.12 mmol) of 1-amino-2-propanol in absolute ethanol was stirred with 1.5 equiv of acetone. Condensation to the oxazolidine[10] took place within 45 min at 25 °C. The solution was cooled to 0 °C and reduced with 407 mg (10.7 mmol) of sodium borohydride within 5 min as described above to give 580 mg (70%) of **8**: bp 46 °C at 4 mmHg (lit.[7b] bp 75.5–76 °C at 22 mmHg).

1-(Isoamylamino)-2-propanol (9). A 1 M solution of 554 mg (7.4 mmol) of 1-amino-2-propanol (**2**) in absolute ethanol was consensed with isovaleraldehyde to form the corresponding oxazolidine[11] in 10 min. Reduction and workup were carried out as described above. Distillation of the crude product gave 862 mg (81%) of **9**: bp 70–71 °C at 2.3 mmHg (lit.[7b] bp 105.5–106 °C at 19 mmHg); the amine crystallized out on standing: mp 157–185 °C.

1-(Cyclohexylamino)-2-propanol (10). The amine **2** (531 mg, 7.08 mmol) was condensed with cyclohexanone, as described above. Oxazolidine[10] formation took place within 15 min. The solution was treated with sodium borohydride at 0 °C for 5 min and worked up as described above. The residue was dissolved in HCl and washed with methylene chloride. The aqueous portion was made basic with 5% sodium hydroxide, extracted with methylene chloride, dried, and evaporated. The crude amine was vacuum distilled to give 1.10 g (99%) of **10**: bp 77–87 °C at 2.2 mmHg (lit.[7b] 126–126.5 °C at 20 mmHg).

1-Phenyl-2-(isobutylamino)-1-propanol (11). A solution of 515 mg (3.4 mmol) of norephedrine was stirred with 1.5 equiv of isobutyraldehyde in absolute ethanol at 25 °C. The corresponding oxazolidine formed in 15 min. To the solution was added 190 mg (5 mmol) of sodium borohydride at 25 °C, and the progress of the reduction was followed by gas chromatography. The oxazolidine[10] was totally reduced in 15 min. The mixture was cooled, 10% HCl was added dropwise to adjust the solution to pH 1, and the solvent evaporated to near dryness under vacuum. The residue was taken up in 10 mL of water, filtered, made basic with sodium hydroxide, and extracted with methylene chloride. The solution was dried over sodium sulfate, the solvent removed on a rotary evaporator, and the crude product recrystallized from hexane to give 535 mg (76%) of **11**: mp 67–68 °C; mp (hydrochloride) 210–211 °C (lit.[8] mp 210–211 °C).

1-Phenyl-2-(isopropylamino)-1-propanol (12). A solution of 730 mg (4.8 mmol) of norephedrine in 5 mL of absolute ethanol was stirred with 1.5 equiv of acetone for 15 min. To the resulting oxazolidine was added 342 mg (9 mmol) of sodium borohydride, and the mixture was then stirred for 20 min. The reaction was worked up as described above and the crude product recrystallized from petroleum ether to give 816 mg (88%) of **12**, mp 89–90 °C (lit.[8] mp 91–92 °C).

1-Phenyl-2-(*n*-heptylamino)-1-propanol (13). A solution of 592 mg (3.9 mmol) of **3** in 4 mL of absolute ethanol was stirred with 1.5 equiv of *n*-heptanal for 15 min. The resulting oxazolidine was reduced with 209 mg (5.5 mmol) of sodium borohydride for 15 min at 25 °C and worked up as described above. After recrystallization from petroleum ether it gave 819 mg (84%) of **13**: mp 62–63 °C, mp (hydrochloride) 230–223 °C (lit.[8] mp 66–76 °C, mp (amine·HCl) 228–229 °C).

Registry No. **1**, 141-43-5; **2**, 78-96-6; **3**, 700-65-2; **4**, 110-73-6; **5**, 109-56-8; **6**, 2842-38-8; **7**, 35265-04-4; **8**, 41063-31-4; **9**, 96307-00-5; **10**, 103-00-4; **11**, 15145-92-3; **11**·HCl, 15263-01-1; **12**·HCl, 53457-43-5; **13**, 96307-01-6; **13**·HCl, 96307-02-7; CH_3CHO, 75-07-0; Me_2CO, 67-64-1; MeCOEt, 78-93-3; $CH_3CH(CH_3)CH_2CHO$, 590-86-3; $(CH_3)_2CHCHO$, 78-84-2; $CH_3(CH_2)_5CHO$, 111-71-7; cyclohexanone, 108-94-1; 2-methyl-2,3,4,5-tetrahydroisoxazole, 16250-70-7; 2,2-dimethyl-2,3,4,5-tetrahydroisoxazole, 20515-62-2; 2-cyclohexyl-2,3,4,5-tetrahydoisoxazole, 177-04-8; 2-methyl-2-ethyl-2,3,4,5-tetrahydroisoxazole, 17026-89-0; 2,2,5-trimethyl-2,3,4,5-tetrahydroisoxazole, 52837-54-4; 2-(2-methyl-*n*-propyl)-5-methyl-2,3,4,5-tetrahydroisoxazole, 96307-03-8; 2-cyclohexyl-5-methyl-2,3,4,5-tetrahydroisoxazole, 90267-83-7; 2-isopropyl-4-methyl-5-phenyl-2,3,4,5-tetrahydroisoxazole, 96307-04-9; 2,2,4-trimethyl-5-phenyl-2,3,4,5-tetrahydroisoxazole, 60980-85-0; 2-*n*-hexyl-4-methyl-5-phenyl-2,3,4,5-tetrahydroisoxazole, 96307-05-0.

Supplementary Material Available: Full NMR data for compounds **4** thru **13** (2 pages). Ordering information is given on any current masthead page.

(11) Fore a review on the formation and chemistry of oxazolidines see: Bergman, E. D. *Chem. Rev.* **1953**, *53*, 309.

Synthesis of Antibiotic SS-228R. Strong Base Induced Cycloaddition of Homophthalic Anhydrides

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Two types of naphthacenediones, 1,6,7-trihydroxy-9-methyl- (**2**) and 1,6,10-trihydroxy-8-methylnaphthacene-5,12-diones (**4**), were prepared by the cycloaddition of 8-methoxy-6-methyl- (**9**) and 5-methoxy-7-methylhomophthalic anhydrides (**10**) with 2-bromojuglone methyl ether (**11**), thus establishing the structure of the antibiotic SS-228R as **4**.

The antibiotic SS-228Y (**1**), obtained from a species of Chainia isolated from shallow sea mud, is known to inhibit the growth of Gram-positive bacteria and dopamine-β-hydroxylase and is very labile to light and heat, being converted into SS-228R (**2**) (Scheme I).[1] Their structures had been deduced by spectroscopic data, especially by extensive ^1H-{^1H} NOE experiments. In 1982, Ikekawa and Omura et al. reconsidered these structures based on biosynthetic studies of the antibacterial and antitumor antibiotics, the vineomycins, and proposed other biosynthetically acceptable structures (**3** and **4**) for SS-228Y and SS-228R without the synthesis of these compounds (Scheme I).[2] We have now synthesized both compounds (**2** and **4**) assigned to SS-228R by the strong base induced

(1) (a) Okazaki, T.; Kitahara, T.; Okami, Y. *J. Antibiot.* **1975**, *28*, 176. (b) Kitahara, T.; Naganawa, H.; Okazaki, T.; Okami, Y. Umezawa; H. *Ibid.* **1975**, *28*, 280. (c) Faulkner, D. J. "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Halsted Press; New York, 1978; Vol. 2, p 19.

(2) Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Omura, S. *J. Antibiot.* **1982**, *35*, 602.

0022-3263/85/1950-2273$01.50/0