compared to the pretreatment blood glucose values as shown in Table II.
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Glucose-Primed, Adrenalectomized Rat.[14] The hypoglycemic activity of 13, 33, and the control drugs was measured in male Sprague–Dawley rats that were adrenalectomized 7 days prior to testing. At the end of 7 days, the rats were deprived of food for 16 h and then injected subcutaneously with 100 mg of glucose per rat. Immediately thereafter, the treatment groups received the test drug orally, and the control group was administered an equal volume of saline. Blood samples were withdrawn after 2 h by cardiac puncture. The results are expressed as percent change in blood glucose as compared to the pretreatment blood glucose values as shown in Table II.

Non-Glucose-Primed Rat.[18] Male Sprague–Dawley rats (120–160 g) were fasted for a period of 18 h prior to and during treatment. Blood samples were obtained from the tail vein. The drug was administered at zero time, and blood samples were drawn 3 and 5 h after drug administration. The results are expressed as percent change in blood glucose as compared to the pretreatment blood glucose values as shown in Table II.

Acute Toxicity Determinations. Male and female Carworth Farms CF-1 strain mice, weighing 16–25 g, were used. Four mice per dose level were used in this procedure. LD_{50}'s (the dose that produces lethality in 50% of mice dosed) for all drugs were determined following oral and intraperitoneal routes of administration. Drugs were dissolved in distilled water or suspended in 0.5% carboxymethylcellulose or 0.5% gelatin mixtures. Drugs were also solubilized by pH adjustment with 1 N HCl or 1 N NaOH if the drugs were not affected by such treatment. Dosages were logarithmically spaced and the mice were observed for 7 days after drug administration. The determination of the LD_{50}'s was based on the method of Bliss.[19]

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Efficient Synthesis of 14-Hydroxymorphinans from Codeine

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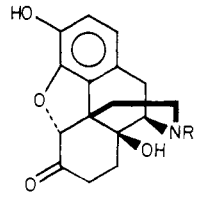
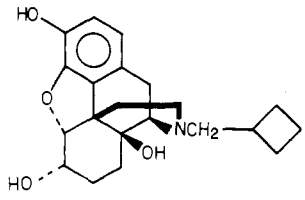
Codeine is converted to 7,8-dihydro-14-hydroxynorcodeinone (noroxycodone) in six steps and 52% overall yield or to noroxymorphone in seven steps and 43% overall yield. N-Demethylation and oxidation of codeine afford *N*-(ethoxycarbonyl)norcodeinone, which is converted to its dienol acetate derivative and oxidized with singlet oxygen to give *N*-(ethoxycarbonyl)-14-hydroxynorcodeinone in the key step. Hydrogenation of the latter affords *N*-(ethoxycarbonyl)noroxycodone, which upon acid hydrolysis yields noroxycodone. Alternatively, O-demethylation of *N*-(ethoxycarbonyl)noroxycodone with boron tribromide and subsequent acid hydrolysis gives noroxymorphone. The results of the singlet oxygen oxidation of the pyrrolidine dienamine derived from *N*-(ethoxycarbonyl)norcodeinone are also described.

14-Hydroxymorphinans, such as naloxone (**1a**), naltrexone (**1b**), and nalbuphine (**2**), have become important



1a, R = $CH_2CH{=}CH_2$
b, R = $CH_2CH(CH_2)_2$
c, R = H



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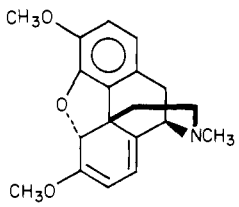

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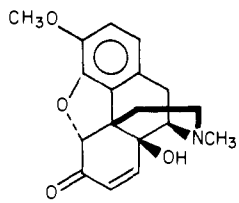

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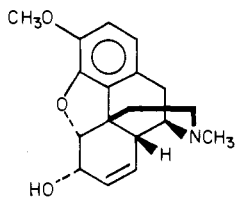

5

morphine derivatives due to their behavior as potent analgesics and/or narcotic antagonists.[1] The currently most practical synthetic route to these pharmaceuticals requires thebaine (**3**) as starting material and centers on oxidation of **3** to 14-hydroxycodeinone (**4**) with hydrogen peroxide–formic acid[2] or *m*-chloroperbenzoic acid in acetic acid–trifluoroacetic acid;[3] subsequent hydrogenation of **4**, followed by application of O- and N-demethylation procedures, then affords the essential intermediate noroxymorphone (**1c**)[4] in six steps overall from thebaine. In view of the relative scarcity of natural thebaine, however, alternate practical synthetic routes to noroxymorphone have been sought.

Codeine (**5**) is an attractive and readily available potential precursor to noroxymorphone, the required key transformation being oxidation at the allylic position to give the corresponding 14-hydroxy derivative. The direct allylic oxidation of codeine has met with only limited success, however. Treatment of codeine with chromic anhydride in sulfuric acid,[5] with manganese dioxide,[6] or

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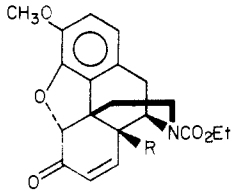
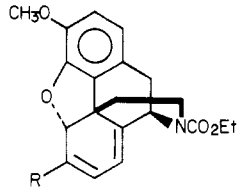
with selenium dioxide and *tert*-butyl hydroperoxide[7] led in each case only to low yields of 14-hydroxylated products. Attempts have also been made to convert codeine or codeinone to thebaine or analogues of thebaine in order to facilitate subsequent hydroxylation. Seki[8] reported the preparation of a pyrrolidine dienamine and various dienol ether derivatives of codeinone; however, subsequent oxidation of these thebaine analogues with hydrogen peroxide–formic acid gave only poor overall yields of 14-hydroxycodeinone (4) (15–30% overall from codeinone). The more recent report by Rapoport and Barber[9] of a two-step conversion of codeine to thebaine in 66% overall yield, via dehydrogenation of codeine methyl ether with γ-manganese dioxide, constituted the first potentially practical synthetic link between codeine and the 14-hydroxy derivatives.

Previous work in our laboratory had shown that singlet oxygen smoothly oxidized an *N*-acyl-9,17-secothebaine[10a] and an *O,N*-diacyl-2-hydroxynorthebaine[10b] to the corresponding 14-hydroxycodeinone derivatives in good yields. We therefore decided to subject an *N*-acylnorcodeinone to a combination of the Seki[8] approach and the singlet oxygen oxidation procedure in an attempt to achieve a shorter, more efficient conversion of codeine to noroxymorphone.

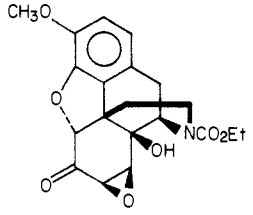
Codeine (5) was N-demethylated with ethyl chloroformate according to the method of Rice and May[11a] and then was oxidized with manganese dioxide to give *N*-(ethoxycarbonyl)norcodeinone (6) in 90% overall yield.[11b]



6, R = H
8, R = OH



7a, R = $(CH_2)_4N$
b, R = CH_3CO_2



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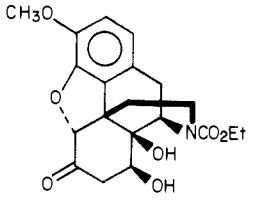

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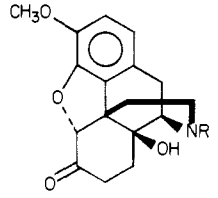

11, R = CO_2Et
12, R = H

The pyrrolidine dienamine 7a was prepared from 6 in 97% yield by Seki's[8] procedure and was subjected to photochemically generated (Rose Bengal sensitization) singlet oxygen. Two products were obtained after reduction of the crude reaction mixture with thiourea; the desired *N*-(ethoxycarbonyl)-14-hydroxynorcodeinone (8) was isolated in 6% yield, but the major product (35% yield) was identified as the epoxide 9. That the latter compound was the C-7,8 epoxide was confirmed by its ^{13}C NMR spectrum; the peaks at 134.03 and 147.63 ppm assigned[12] to C-7 and C-8, respectively, of *N*-(ethoxycarbonyl)-14-hydroxynorcodeinone (8) were absent in the spectrum of 9, and new absorptions at 58.72 and 55.71 ppm were observed. The β stereochemistry of the epoxide moiety in 9 was assigned based on the expected steric hindrance involved in α attack in these systems.[3b] The remaining 50% of material isolated from the singlet oxygen reaction mixture consisted of a complex mixture of polar compounds that could not be separated or identified. Epoxide 9 could be converted back to 8 by chromous chloride reduction[13] to diol 10 (82% yield), followed by dehydration of the latter with thionyl chloride in pyridine (70% yield), resulting in a combined yield of 26% for the preparation of *N*-(ethoxycarbonyl)-14-hydroxynorcodeinone (8) from dienamine 7a. Attempts to convert the crude mixture of 8 and 9 to the single product 8 without purification of intermediates proved to be impractical because 8 was unstable to the reduction–elimination sequence.

In view of these poor results, another easily accessible dienol derivative of the *N*-acylnorcodeinone was sought. It was found that 6 could be readily converted to the dienol acetate 7b in 87% yield by treatment with sodium acetate in refluxing acetic anhydride.[14] Oxidation of 7b with singlet oxygen then proceeded very smoothly to afford the 14-hydroxy derivative 8 as the major product, isolated in 71% yield; none of the epoxide 9 was apparent from TLC examination of the reaction mixture. Once the reaction conditions for the key transformations were thus in hand, it proved possible to carry out the entire four-step sequence for conversion of codeine (5) to 8 in 66% overall yield and without purification of any of the intermediates.

Completion of the syntheses of noroxycodone and noroxymorphone from 8 was then routine. Hydrogenation of 8 over Pd/C gave *N*-(ethoxycarbonyl)noroxycodone (11) in 90% yield, and the *N*-acyl group was removed by acid hydrolysis[2b,4a] to afford noroxycodone (12) in 88% yield. Alternatively, 11 was demethylated with boron tribromide[15] and then was subjected to acid hydrolysis to give noroxymorphone (1c) in 73% overall yield.

An efficient seven-step synthesis of noroxymorphone from codeine has thus been achieved using singlet oxygen to hydroxylate the dienol acetate of *N*-(ethoxycarbonyl)-norcodeinone. Since this approach involves essentially the same number of steps as currently required for conversion of thebaine to noroxymorphone, the sequence outlined above should provide a viable alternative route to 14-hydroxymorphinan derivatives.

Experimental Section

Melting points were determined with a Kofler microscope hot stage and are uncorrected. Infrared spectra were obtained in chloroform solution using a Beckman Acculab 8 spectrophotometer. NMR spectra were recorded on a Bruker HX-270 spectrometer in deuteriochloroform solution; chemical shifts are re-

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(10) (a) Schwartz, M. A.; Wallace, R. A. *Tetrahedron Lett.* **1979**, 3257. (b) Zoda, M. F. Ph.D. Dissertation, The Florida State University, 1981.
(11) (a) Rice, K. C.; May, E. L. *J. Heterocycl. Chem.* **1977**, *14*, 665. (b) Enone 6 has been previously prepared by a very similar procedure: Lawson, J. A.; DeGraw, J. I.; Anbar, M. *Ibid.* **1976**, *13*, 593.
(12) (a) Terui, Y.; Tori, K.; Maeda, S.; Sawa, Y. K. *Tetrahedron Lett.* **1975**, 2853. (b) Carroll, F. I.; Moreland, C. G.; Brine, G. A.; Kepler, J. A. *J. Org. Chem.* **1976**, *41*, 996.
(13) Cole, W.; Julian, P. L. *J. Chem. Soc.* **1953**, 131.
(14) Small, L.; Turnbull, S. G.; Fitch, H. M. *J. Org. Chem.* **1939**, *3*, 204.
(15) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.

ported in parts per million downfield from tetramethylsilane (δ), and coupling constants are in hertz. Mass spectra were obtained on an Associated Electronics Industries MS902 instrument by electron impact at 70 eV unless noted otherwise; relative intensities of the ions are given in parentheses. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. Thin-layer chromatography was carried out on silica gel; developed plates were visualized under ultraviolet light and/or by spraying with saturated ceric sulfate in 10% aqueous sulfuric acid, followed by heating on a hot plate. Preparative TLC plates were prepared at a thickness of 1 mm from Merck PF254 silica gel. All solvents were reagent grade, redistilled before use. Rotations were obtained in chloroform solution unless otherwise noted, using a Bendix Ericsson automatic polarimeter.

***N*-(Ethoxycarbonyl)norcodeinone (6).** A mixture of 1.00 g (3.34 mmol) of codeine (Mallinckrodt), 1.90 mL (20.0 mmol) of ethyl chloroformate, and 0.386 g (3.86 mmol) of anhydrous K_2CO_3 in 100 mL of chloroform was refluxed under nitrogen for 8 h.[11] The cooled solution was washed several times with water, dried over anhydrous Na_2SO_4, and evaporated to give 1.19 g (3.34 mmol, 100%) of *N*-(ethoxycarbonyl)norcodeine as a colorless oil: IR 2.81–3.04 (br), 5.97 μm; NMR δ 6.66 (1, d, J = 8.5 Hz, H-2), 6.55 (1, d, J = 8.5 Hz, H-1), 5.74 (1, d, J = 9.0 Hz, H-7), 5.27 (1, d, J = 9.0 Hz, H-8), 4.86 (1, d, J = 7.5 Hz, H-5).

The crude product was dissolved in 500 mL of chloroform and was stirred with 10 g of manganese dioxide[16] for 10 min. The solid was then removed by filtration through Celite, and the filtrate was evaporated to afford 1.10 g of an oil. The crude product was purified by column chromatography using silica gel/15% water with 50% chloroform/hexane as eluent to yield 1.07 g (3.01 mmol, 90%) of **6** as a colorless oil. All attempts to crystallize the oil were unsuccessful: IR 5.96 μm; NMR δ 6.65 (1, d, J = 9.0 Hz, H-2), 6.62 (1, d, J = 10.0 Hz, H-8), 6.58 (1, d, J = 9.0 Hz, H-1), 6.08 (1, d, J = 10.0 Hz, H-7), 4.66 (1, s, H-5); ^{13}C NMR 193.71 (C-6), 155.37 (carbamate C=O), 146.88 (C-8), 145.16 (C-4), 142.97 (C-3), 133.16 (C-7), 128.12 (C-12), 124.93 (C-11), 120.47 (C-1), 116.00 (C-2), 87.88 (C-5), 61.69 (carbamate CH_2), 57.11 (C-3 OMe), 50.65 (C-9), 43.63 (C-13), 40.36 (C-14), 38.15 (C-16), 33.64 (C-15), 29.30 (C-10), 14.70 (carbamate CH_3); UV λ_{max} (MeOH) 229 nm (ϵ 15780), 282 (2127); $[\alpha]^{26}_D$ −280° (c 0.30). Anal. ($C_{20}H_{21}NO_5$) C, H, N.

***N*-(Ethoxycarbonyl)norcodeinone Pyrrolidine Dienamine (7a).** A solution of 450 mg (1.27 mmol) of **6**, 0.13 mL (1.6 mmol) of pyrrolidine, and 11 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 40 mL of toluene was refluxed under nitrogen for 1.5 h, with removal of water via a Dean–Stark trap. The solution was cooled, washed successively with 10% sodium carbonate and water, dried over Na_2SO_4, and evaporated to yield 507 mg (1.24 mmol, 98%) of **7a** as a brown glass: IR 5.97, 6.36 μm; NMR δ 6.64 (1, d, J = 9.0 Hz, H-2), 6.55 (1, d, J = 9.0 Hz, H-1), 5.63 (1, br m, H-8), 5.45 (1, s, H-5), 5.16 and 5.03 (1, br s, H-9), 4.41 (1, d, J = 6.0 Hz, H-7); mass spectrum, m/e 408 (M^+, 100); UV λ_{max} (MeOH) 375 nm (ϵ 7592).

Reaction of Dienamine 7a with Singlet Oxygen. Oxygen was bubbled through a solution of 100 mg (0.25 mmol) of dienamine **7a** and 10 mg (0.01 mmol) of Rose Bengal in 50 mL of 10% methanol/methylene chloride, and the solution was maintained at 12 °C (cooling in a water–ethanol bath) while being irradiated with two visible lamps (GE Quartzline, DWY 120V, 650 W) for 30 min. To the resulting solution was added 100 mg of thiourea, and the mixture was then stirred for 12 h. Evaporation of solvents left a residue which was dissolved in chloroform, washed with water, dried over Na_2SO_4, and evaporated to give 101 mg of a red oil. Separation of the mixture by preparative TLC (ether) yielded two compounds. The lower R_f component (5 mg, 0.013 mmol, 6%) was a yellow oil, which was identified as **8** by comparison of spectral data, vide infra. The higher R_f component (34 mg, 0.088 mmol, 36%) was an oil, which was identified as epoxide **9**: IR 5.80, 5.95, 6.25 μm; NMR δ 6.75 (1, d, J = 9.0 Hz, H-2), 6.68 (1, d, J = 9.0 Hz, H-1), 4.89 and 4.74 (1, s, H-9), 4.56 (1, s, H-5); mass spectrum, m/e 387.1319 (M^+, 79; calcd for $C_{20}H_{21}NO_7$, 387.1317), 201 (100); ^{13}C NMR 199.40 (C-6), 156.40 (carbamate C=O), 145.36 (C-4), 143.58 (C-3), 128.71 (C-12), 125.34 (C-11), 120.76 (C-1), 117.28 (C-2), 87.60 (C-5), 67.94 (C-14), (carbamate CH_2) 58.72 (C-7), 57.38 (C-3 OMe), 55.81 (C-9), 55.71 (C-8), 50.43 (C-13), 37.78 (C-16), 31.41 (C-10), 27.69 (C-15), 14.67 (carbamate CH_3).

Reduction and Elimination of Epoxide 9. To a nitrogen-degassed solution of 34 mg (0.088 mmol) of epoxide **9** in 1.2 mL of glacial acetic acid was added 0.24 mL of 0.8 N chromous chloride solution.[13] The blue solution was stirred for 5 min, then it was diluted with water, made basic with solid sodium bicarbonate, and extracted with chloroform. The organic layer was washed with water and dried over Na_2SO_4 to give 33 mg of crude material. Purification of the latter by preparative TLC (ethyl acetate) afforded 28 mg (0.072 mmol, 82%) of diol **10** as an oil. Crystallization of the oil from ethyl acetate/hexane gave **10** as a white solid, mp 108–110 °C; IR 5.80, 6.03, 6.25 μm; NMR δ 6.73 (1, d, J = 8.5 Hz, H-2), 6.65 (1, d, J = 8.5 Hz, H-1), 4.60 (1, s, H-5); mass spectrum, m/e 389 (M^+, 45), 201 (100). Anal. ($C_{20}H_{23}NO_7$) C, H, N.

To 28 mg (0.072 mmol) of diol **10** in 3 mL of anhydrous pyridine (distilled from BaO) was added 0.012 mL of thionyl chloride (distilled from triphenyl phosphite). The resulting orange solution was stirred for 30 min at room temperature under nitrogen and then was quenched with water. The solvents were removed under reduced pressure, and the residue was dissolved in chloroform, washed with water, dried over Na_2SO_4, and evaporated. The resulting crude product was purified by preparative TLC (5% methanol/chloroform/a few drops of ammonium hydroxide) to give 19 mg (0.051 mmol, 70%) of **8**, identified by comparison of spectral data, vide infra.

***N*-(Ethoxycarbonyl)norcodeinone Dienol Acetate (7b).** A solution of 100 mg (0.282 mmol) of **6** and 10 mg of fused anhydrous sodium acetate in 2 mL of acetic anhydride was refluxed for 1.5 h under nitrogen.[14] The excess acetic anhydride was removed at 25 °C under high vacuum, and the residue was diluted with water and extracted with chloroform to afford 116 mg of a brown oil. The crude product was purified by chromatography using a short column of silica gel/15% water, with ether as eluent, to yield 97 mg (0.244 mmol, 87%) of dienol acetate **7b** as a colorless oil: IR 5.70, 5.94 μm; NMR (60 MHz) δ 6.67 (1, d, J = 9.0 Hz, H-2), 6.51 (1, d, J = 9.0 Hz, H-1), 5.69 (1, d, J = 6.5 Hz, H-8), 5.52 (1, d, J = 6.5 Hz, H-7), 5.44 (1, s, H-5), 5.27–4.94 (1, br s, H-9), 2.14 (3, s, $OCOCH_3$); mass spectrum, m/e 397 (M^+, 40), 355 (78), 253 (100).

***N*-(Ethoxycarbonyl)-14-hydroxynorcodeinone (8).** A solution of 97 mg (0.24 mmol) of enol acetate **7b** and 10 mg of Rose Bengal in 50 mL of 10% methanol/methylene chloride was entrained with oxygen and was irradiated for 1 h as previously described for **7a**. Treatment with 100 mg of thiourea as before, followed by the usual workup, afforded 103 mg of crude product as a red oil. Isolation of the major component by preparative TLC (ether) gave 63 mg (0.17 mmol, 71%) of **8** as a yellow oil, which crystallized from ethyl acetate/hexane, mp 154–155 °C; IR 5.96 μm; NMR δ 6.74 (1, br d, J = 9.0 Hz, H-8), 6.71 (1, d, J = 8.5 Hz, H-2), 6.61 (1, d, J = 8.5 Hz, H-1), 6.14 (1, d, J = 9.0 Hz, H-7), 4.72 (1, s, H-5); ^{13}C NMR 194.13 (C-6), 156.93 (carbamate C=O), 147.79 (C-8), 144.55 (C-4), 143.08 (C-3), 133.87 (C-7), 130.13 (C-12), 124.22 (C-11), 120.06 (C-1), 115.75 (C-2), 86.82 (C-5), 68.13 (C-14), 62.12 (carbamate CH_2), 56.96 (C-3 OMe), 55.90 (C-9), 47.32 (C-13), 37.60 (C-16), 31.61 (C-10), 27.57 (C-15), 14.60 (carbamate CH_3); $[\alpha]^{26}_D$ −201° (c 0.30). Anal. ($C_{20}H_{21}NO_6$) C, H, N.

In a separate experiment, the conversion of codeine (**5**) to **8** was performed without purification of the intermediates. When 1.00 g (3.34 mmol) of codeine was demethylated with ethyl chloroformate and oxidized with manganese dioxide as previously described, 1.00 g of crude **6** was obtained. This material was refluxed for 1.5 h with 100 mg of sodium acetate in 20 mL of acetic anhydride to yield 1.27 g of enol acetate **7b** as a dark brown gum. Reaction of the latter with singlet oxygen as previously described (100 mg of Rose Bengal in 500 mL of solvent, for 1.25 h) afforded 1.40 g of a red oil, which was purified by chromatography over silica gel/15% water using ether as eluent to yield 0.81 g (2.2 mmol, 66% overall from codeine) of **8** as a yellow-orange oil, homogeneous to TLC analysis, which crystallized as described above.

***N*-(Ethoxycarbonyl)noroxycodone (11).** Hydrogen was bubbled through a mixture of 200 mg (0.539 mmol) of **8** and 100 mg of 10% Pd/C in 100 mL of absolute ethanol with stirring for 1 h. The suspension was filtered and the filtrate was evaporated

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to give 180 mg (0.483 mmol, 90%) of 11 as a clear oil, which crystallized from methanol/ether, mp 113–115 °C; IR 5.79, 5.95 μm; NMR δ 6.72 (1, d, J = 8.5 Hz, H-2), 6.62 (1, d, J = 8.5 Hz, H-1), 4.65 (1, s, H-5); $[\alpha]^{26}_D$ −317° (c 0.30). Anal. ($C_{20}H_{23}NO_6$) C, H, N.

Noroxycodone (12). A suspension of 150 mg (0.402 mmol) of 11 in 5 mL of 5 N sulfuric acid was refluxed under nitrogen for 12 h. The solution was cooled, made basic with solid sodium bicarbonate, and extracted with chloroform to give 107 mg (0.355 mmol, 88%) of 12 as a solid: mp 170–172 °C (lit.[17] mp 174–175 °C); IR 5.80 μm; NMR δ 6.68 (1, d, J = 8.5 Hz, H-2), 6.60 (1, d, J = 8.5 Hz, H-1), 4.63 (1, s, H-5), 3.87 (3, s, OMe); mass spectrum, m/e 301 (M^+, 20), 117 (71), 103 (100), 101 (85); $[\alpha]^{26}_D$ −232° (c 0.20) [lit.[17] $[\alpha]_D$ −205° (c 0.4)]. An authentic sample of 12 (Mallinckrodt, Inc.) exhibited mp 170–173 °C; $[\alpha]^{26}_D$ −237° (c 0.20).

The hydrochloride salt of 12 was prepared by adding saturated methanolic hydrogen chloride to a solution of 12 in methanol. Subsequent addition of ether gave a precipitate, which was crystallized from methanol/ether to give 12·HCl, mp 280–283 °C dec. Anal. ($C_{17}H_{20}NO_4Cl·CH_3OH$) C, H, N.

Noroxymorphone (1c). A solution of 50 mg (0.134 mmol) of 11 in 0.5 mL of chloroform was added via syringe to a solution of 0.13 mL (1.3 mmol) of boron tribromide in 0.5 mL of chloroform with stirring in an ice bath under nitrogen.[15] The mixture was stirred in the ice bath for 1 h, then a solution prepared from 0.25 mL of concentrated ammonium hydroxide and 1 g of ice was added, and stirring was continued in the cold for 0.5 h. The layers were separated, and the aqueous solution was extracted with chloroform. The combined chloroform solutions were dried and evaporated. To the resulting gum (56 mg) was added 1 mL of 6 N sulfuric acid, and the mixture was refluxed under nitrogen for 12 h. The solution was cooled and basicified with ammonium hydroxide, and the resulting precipitate was isolated by centrifugation and dried under high vacuum to give 57 mg of gray solid.

The crude amine was dissolved in 0.2 mL of 6 N sulfuric acid by warming to 55 °C, then the solution was cooled in an ice bath, and the crystalline salt was isolated by centrifugation. The salt was dissolved in water and basicified with ammonium hydroxide, and the resulting precipitate was again centrifuged and dried to afford 34 mg of noroxymorphone (1c) as an off-white solid. Repetition of the above purification procedure yielded 28 mg (0.098 mmol, 73%) of 1c as a white solid, which did not melt below 300 °C (lit.[18] mp 310–313 °C); NMR (Me_2SO-d_6) δ 6.47 (1, d, J = 8 Hz), 6.41 (1, d, J = 8 Hz), 4.58 (1, s); $[\alpha]^{26}_D$ −179° (c 0.2, 10% HOAc) [lit.[2b] for enantiomer of 1c: mp 290 °C; $[\alpha]^{20}_D$ +150° (c 1.02, 10% HOAc)]. An authentic sample of 1c (Mallinckrodt, Inc.) exhibited an NMR spectrum identical with that of the synthetic material and $[\alpha]^{26}_D$ −199° (c 0.2, 10% HOAc).

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Purine Acyclic Nucleosides. Nitrogen Isosteres of 9-[(2-Hydroxyethoxy)methyl]guanine as Candidate Antivirals

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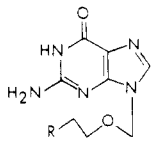
A number of nitrogen analogues of 9-[(2-hydroxyethoxy)methyl]guanine [acylovir, Zovirax] containing amine functions in the side chain were synthesized and tested for antiviral activity. These purine acyclic nucleosides were prepared by reaction of tris(trimethylsilyl)guanine or 2,6-diaminopurine sodium salt with the chloromethyl ethers prepared from *N*-(2-hydroxyethyl)phthalimide, *N*-[2-(2-hydroxyethoxy)ethyl]phthalimide, or *N*-(2-hydroxyethyl)oxazolidin-2-one to give the N-blocked intermediates **5**–**8**. Deprotection with hydrazine or by alkaline hydrolysis gave 9-[(2-aminoethoxy)methyl]guanine (**9**), 9-[(2-aminoethoxy)methyl]-2,6-diaminopurine (**10**), 9-[[2-(2-aminoethoxy)ethoxy]methyl]guanine (**11**), and 9-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]guanine (**12**). When tested against herpes simplex virus type 1, only **9** was active with an IC_{50} = 8 μM. Little or no activity was observed against a range of other DNA and RNA viruses.

Acyclovir [9-[(2-hydroxyethoxy)methyl]guanine, Zovirax (**1**)] is a potent antiherpetic drug with activity against



1, R = OH
2, R = OCH_2CH_2OH

herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).[1,2] This purine acyclic nucleoside contains an acyclic side chain which mimics the cyclic carbohydrate of natural nucleosides. Although acyclovir (**1**) is essentially nontoxic to uninfected host cells, it possesses potent antiviral activity in cells infected with HSV.[2,3] This selective toxicity is related to acyclovir (**1**) being a substrate for HSV-encoded thymidine kinase.[4] Phosphorylation to the monophosphate occurs preferentially in HSV-infected cells, with subsequent selective inhibition of viral replication.[2,4]

A number of pyrimidine acyclic nucleosides analogous to acyclovir (**1**) were found to have little or no in vitro antiviral activity.[5,6] An extended chain analogue, **2**, of

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