with acetonitrile. The oily residue was dissolved in methanol (20 mL) and stirred with excess basic ion-exchange resin (Dowex 1, 20–50 mesh, OH^- form, 5 mL) for 10 min. The resin was removed by filtration and washed with methanol (50 mL). Evaporation of the combined filtrates gave **4** as a white crystalline solid: yield 155 mg (93.3%). Recrystallization from methanol–ether gave an analytical sample: mp 124–125 °C dec; UV λ_{max} ($\epsilon \times 10^{-3}$), in methanol, 275 (20.6); at pH 1, 268 (20.3); at pH 14, 276 (20.9). Anal. ($C_{22}H_{28}ClN_7O_4$) C, H, N, Cl.

6-(Dimethylamino)-9-(3′-amino-3′,5′-dideoxy-β-D-ribofuranosyl)purine. 5′-Deoxy-PAN (5). To a solution of **1** (2.35 g, 8.0 mmol) in anhydrous tetrahydrofuran (100 mL) were added azobisisobutyronitrile (0.50 g, 3.04 mmol) and tributyltin hydride (6.0 g, 21.0 mmol). The reaction mixture was heated under reflux for 18 h under anhydrous conditions. The solvent was removed under reduced pressure, and the residue was triturated with cold petroleum ether (50 mL). A solid product was removed by filtration, washed with cold petroleum ether (100 mL), and crystallized from ethyl acetate to give pure **5**: yield 1.25 g (90.5%); mp 202–203 °C (lit.[14] mp 204–205 °C); IR and NMR spectra were identical with an authentic sample.[14]

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Synthesis of *S*-(3-Deazaadenosyl)-L-homocysteine

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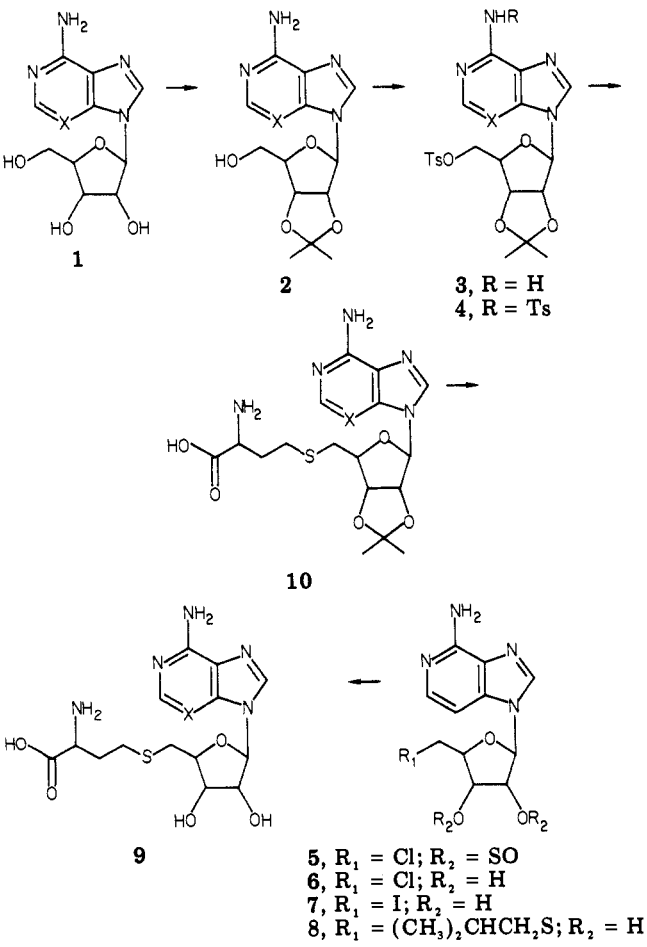
A satisfactory procedure for the preparation of *S*-(3-deazaadenosyl)-L-homocysteine, a metabolite of 3-deazaadenosine, which is a potent inhibitor of *S*-adenosyl-L-homocysteine hydrolase with antiviral activity, is described. For the first time this compound is completely characterized and its optical purity established.

S-Adenosyl-L-homocysteine (**9a**), the biochemical byproduct of methylation reactions involving adenosylmethionine, was first synthesized by displacement of the tosyloxy group of 2′,3′-*O*-isopropylidene-5′-*O*-tosyladenosine (**3a**) with the sodium salt of L-homocysteine, followed by removal of the isopropylidene group from the product.[1,2] This procedure has been applied to the synthesis of *S*-(3-deazaadenosyl)-L-homocysteine monohydrate (**9b**) in an overall yield of 12%; the intermediates were not characterized, and no information on the specific rotation or optical purity of **9b** was provided.[3]

Because of the recent interest in 3-deazaadenosine (**1b**) as a competitive inhibitor of and alternate substrate for *S*-adenosyl-L-homocysteine hydrolase,[4,5] we have reinvestigated the chemical synthesis of the enzymatic product **9b** (Scheme I). Tosylation[3] of 2′,3′-*O*-isopropylidene-3-deazaadenosine (**2b**), most satisfactorily prepared by the procedure of Zderic et al.,[6] gave a mixture of 61% unreacted **2b**, 31% 5′-*O*-tosyl-2,3-*O*-isopropylidene-3-deazaadenosine (**3b**), and a small amount of material identified by UV and mass spectral data as a ditosyl derivative of **2b** (**4b**).

The rather unsatisfactory results of the tosylation reaction led us to explore the conversion of the sulfite ester (**5**) of 5′-chloro-5′-deoxy-3-deazaadenosine (**6**) directly to **9b**, since we previously prepared the 5′-(isobutylthio)-5′-deoxy-3-deazaadenosine (**8**) from **6** itself,[7] and Borchardt et al. have prepared other analogues of *S*-adenosyl-L-homocysteine in a similar manner.[8] Unfortunately, **5**

Scheme I



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proved too unreactive in liquid ammonia to give more than traces of the desired product. Compound **5** did react with L-homocysteine in refluxing aqueous base, but these conditions were found to completely racemize L-homocysteine. Furthermore, **9b** prepared in this way from in situ generated L-homocysteine had a specific rotation of +21.9°, very close to that of **9b** prepared from DL-homocysteine in the same way, suggesting that almost complete racemization had occurred. The lack of reactivity of the chlorine of **5** suggested catalysis by the addition of KI, but this ploy was unsuccessful in liquid ammonia, failing to increase the yield of **9b** significantly.

These results caused us to turn to the preparation of the 5′-deoxy-5′-iodo compound **7**, which should be as reactive as the 5′-tosyloxy compound. Attempts to prepare **7** by means of the Rydon reagent[9] gave a low yield of product, contaminated with a diiodo compound (failed to give a metaperiodate Schiff's test), that had to be purified by column chromatography. More satisfactory was the use of triphenylphosphine, iodine, and imidazole.[10] This reagent combination gave a 46% yield of product (**7**) that appeared to contain no diiodo impurities and was suitable for the preparation of **9b**. An attempt to prepare an analytically pure sample of **7** by chromatography on thick silica gel plates resulted in the isolation of the sulfate salt of **7**, formed from the $CaSO_4$ binder in the plates because of the relatively basic nature of **7**. This salt was identified by elemental analyses, by its IR spectrum, and by conversion to the picrate salt.

Reaction of **7** with in situ generated L-homocysteine gave, after purification, a 65% yield of material (**9b**) that had a specific rotation of +32.8° and the expected UV, ^1H NMR, and mass spectra.

The ^1H NMR spectrum of **9b** was very badly resolved at ambient temperature, presumably because of an intermediate rate of exchange between tautomers or rotamers. At 77 °C, the spectrum was well resolved and assignments could be made for peaks not overlapping with the solvent absorption (see Experimental Section). When the sample was returned to ambient temperature, the spectrum slowly returned to the original appearance. The reason for this slow rate of reversal is not known. Chemical shifts are temperature dependent, and those quoted in the Experimental Section are from the spectrum obtained at 77 °C.

The ^{13}C NMR spectra of the three preparations of **9b** were obtained on approximately saturated solutions in D_2O, with dioxane as internal reference. Data were subsequently converted to the Me_4Si scale. Assignments were made on the basis of comparison with the ^{13}C NMR spectra of methionine[11] and 3-deazaadenosine.

Compound DL-**9b** showed two partially overlapping peaks of approximately equal intensity for the absorption assigned to $C_{4'}$. Compound **9b** prepared from **5** showed primarily one peak, but with an upfield shoulder, for the same absorption, while L-**9b** showed a single, well-defined peak. It is intriguing that the difference in the sugar portion of these optical isomers should be apparent only at $C_{4'}$. Perhaps this is because $C_{4'}$ is the nearest cyclic carbon to the methionine asymmetric center, with presumably less motional freedom than the methionine carbons themselves. In addition, in all three spectra, the peaks due to $C_{5'}$, $C_{6'}$, $C_{7'}$, and $C_{8'}$ are slightly broadened in comparison with the other peaks of the sugar moiety, and this broadening might obscure small differences. One further difference is apparent between the spectrum of the pure isomer and the spectra of the mixtures. One of $C_{2'}$, $C_{4'}$, or $C_{8'}$ is shifted downfield by at least 1 ppm in the pure isomer. Unfortunately these peaks have not been assigned unequivocably, since the limited solubility of these samples has precluded our obtaining the proton-coupled ^{13}C NMR spectrum. Probably, the shifted peak is due to $C_{8'}$, and the shift is caused by a change in the average torsion angle about the glycosidic bond.

The unpredictability of the effect of a new chiral center in nucleosides has been observed before; that is, the diasteriomeric mixture containing the new chiral center may show a doubling of the signal of the chiral carbon or a nearby one or it may not.[12] Thus, a single peak alone does not prove optical purity (within the limit of NMR detection), but the fact that the deliberately prepared DL-**9b** showed a doubling at $C_{4'}$ established the optical purity of L-**9b** prepared from **8**, which showed only a single signal from $C_{4'}$. Compound **9b** prepared from **5**, on the other hand, is clearly largely racemic (ca. 3:2).

Although HPLC is frequently used to resolve diasteriomers, we were unable to separate the two diasteriomers of **9b** prepared from **5** and the DL-thiolactone by reverse-phase HPLC: the elution pattern of DL-**9b** was identical with that of L-**9b** in all solvent systems investigated.

In summary, a satisfactory method for the preparation of relatively large amounts of optically pure *S*-(3-deazaadenosyl)-L-homocysteine (**9b**) has been developed involving the use of 5′-deoxy-5′-iodo-3-deazaadenosine (**7**), which is much more reactive than the chloro compound **5**; however, since it lacks the N-3 of adenosine, it cannot form an anhydronucleoside.

Experimental Section

All evaporations were carried out in vacuo with a rotary evaporator. The analytical sample was dried in vacuo over P_2O_5 at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight, by charring after spraying with saturated $(NH_4)_2SO_4$, and with ninhydrin spray where applicable. The analytical sample and intermediates were homogeneous by TLC, and the analytical sample was also homogeneous by HPLC. The UV absorption spectra were determined with a Cary 17 spectrophotometer. The NMR spectra were determined with a Varian XL-100-15 spectrometer equipped with a Gyrocode spin decoupler and Nicolet Model TT-100A data system and pulser in D_2O as described: chemical shifts (δ) quoted in the case of multiplets were measured from the approximate center. The mass spectral data were obtained with a Varian MAT 311A mass spectrometer in the electron-impact mode. The specific rotations were obtained with a Rudolph precision polarimeter, Model 80. The elemental analyses were within ±0.4% of the theoretical values.

***S*-(3-Deazaadenosyl)-L-homocysteine (9b).** To a solution of L-homocysteine (435 mg, 1.62 mmol) in liquid ammonia (30 mL) was added sodium in tiny bits until the blue color persisted for about 15 min. After discharging the color with ammonium chloride, 5′-deoxy-5′-iodo-3-deazaadenosine (**7**; 1.22 g, 3.24 mmol) was added in portions. The ammonia was allowed to evaporate over a 20- to 30-min period; the last traces were removed in vacuo. A solution of the residue in water (25 mL) was chilled, neutralized with 6 N hydrochloric acid, and applied to a column of 100 mL of Dowex 50-WX4, 50–100 mesh, NH_4^+ form. After elution of

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the column with water to remove inorganics and homocysteine, the desired product was obtained by further elution with 1 N ammonium hydroxide. Fractions containing the product were pooled and freeze-dried to give a fluffy, cream-colored solid: yield 845 mg (65%); mp indefinite; UV λ_{max} ($\epsilon \times 10^{-3}$) 262 nm at pH 1 (11.0), 262 nm at pH 7 (10.7), 265 nm at pH 13 (10.9); $[\alpha]^{23}_D$ +32.8 ± 0.7° (c 0.44, 1 N HCl); ^{1}H NMR (D_2O, chemical shifts in parts per million from DSS) 8.31 (s, H_8), 7.82 (d, H_2), 7.06 (d, $J_{2,3}$ = 6 Hz, H_3), 5.98 (d, $J_{2,3}$ = 6 Hz, $H_{1'}$), 4.65 (d of d, $J_{1',2'} = J_{2',3'}$ = 5 Hz, $H_{2'}$), 3.03 (m, $H_{5'}$), 2.78 (t, $J_{6',7'}$ = 8 Hz, $H_{6'}$), 2.23 (m, $H_{7'}$), $H_{3'}$, $H_{4'}$, and $H_{8'}$ were between δ 3.6 and 4.8 and were overlapping the solvent absorption; ^{13}C NMR [D_2O, chemical shifts referenced to internal dioxane and converted to the Me_4Si scale using the relationship δ_C (dioxane) = 67.4 ppm] 142.06, 140.36, and 139.20 (C_2, C_4, and C_8), 99.97 (C_3), 127.46 (C_5), 151.96 (C_6), 89.79 ($C_{1'}$), 74.20 ($C_{2'}$), 72.97 ($C_{3'}$), 84.30 ($C_{4'}$), 28.8 ($C_{5'}$), 34.5 and 31.5 ($C_{6'}$ and $C_{7'}$), 54.7 ($C_{8'}$), 175.29 ($C_{9'}$). Anal. ($C_{15}H_{21}N_5O_5S \cdot H_2O$) C, H, N.

S-(3-Deazaadenosyl)-DL-homocysteine (Racemic 9b). A cold (0–5 °C) solution of 3-deazaadenosine (**1b**; 265 mg, 1.0 mmol) in trimethyl phosphate (2.5 mL) was treated with thionyl chloride (290 μL, 4.0 mmol) and allowed to warm up to ambient temperature and held there for 20 h. The precipitate that formed was collected by filtration, washed thoroughly with ether, and quickly dried in vacuo: yield 330 mg (100%) of **5**; ^{1}H NMR (Me_2SO-d_6) δ 4.0 (m, 2 $H_{5'}$), 4.2 (m, $H_{3'}$ and $H_{4'}$), 4.5 (dd, $J_{1',2'} = J_{2',3'}$ = 5.2 Hz, $H_{2'}$), 6.05 (d, $J_{1',2'}$ = 5.2 Hz, $H_{1'}$), 7.34 (d, $J_{2,3}$ = 7 Hz, H_3), 7.83 (d, $J_{2,3}$ = 7 Hz, H_2), 8.7 (s, H_8); MS, *m/e* 330 (M^+), 295 [$(M - Cl)^+$], 284 [$(M - CH_2Cl)^+$], 134 [$(B + 1)^+$]. This material was added to a cold (ice–ethanol) solution prepared 30 min prior by adding DL-homocysteine thiolactone hydrochloride (203 mg, 1.32 mmol) with stirring to 1 N NaOH (4.6 mL). The resulting solution was refluxed for 3 h, neutralized with dilute HCl, and applied to a column of 100 mL of Dowex 50W-X4, 50–100 mesh, NH_4^+ form. After initial water elution to remove inorganics and unreacted starting material, the column was eluted with 1 N ammonium hydroxide to give the product. Fractions containing product were pooled and freeze-dried to give a glass: yield 245 mg (92%); MS, *m/e* 384 [$(M + 1)^+$]; UV λ_{max} ($\epsilon \times 10^{-3}$) 262 nm at pH 1 and 7 (9.97) and 265 nm at pH 13 (9.75); $[\alpha]^{24}_D$ +19.5 ± 0.5° (c 0.67, 1 N HCl); ^{13}C NMR (D_2O, see above) 141.95, 139.32, and 139.02 (C_2, C_4, and C_8), 99.75 (C_3), 127.13 (C_5), 151.45 (C_6), 89.80 ($C_{1'}$), 74.39 ($C_{2'}$), 72.96 ($C_{3'}$), 84.20 and 84.12 ($C_{4'}$), 28.73 ($C_{5'}$), 34.50 and 31.48 ($C_{6'}$ and $C_{7'}$), 54.70 ($C_{8'}$), 175.08 ($C_{9'}$).

5'-Deoxy-5'-iodo-3-deazaadenosine (7). A mixture of 3-deazaadenosine (**1b**; 2.00 g, 7.50 mmol), triphenylphosphine (2.84 g, 10.8 mmol), iodine (2.74 g, 10.8 mmol), and imidazole (1.54 g, 2.30 mmol) in dry toluene (400 mL) was stirred vigorously at 70 °C for 3 h and then the toluene was decanted. A methanol solution of the residue was applied to a dry column of silica gel (2 × 55 cm, Woelm). After the column was developed with chloroform–methanol (3:1), the product band was extracted with methanol, which was then evaporated to give the product as a glass: yield 1.29 g (46%); MS, *m/e* 134 [$(B + H)^+$], 248 [$(376 - HI)^+$], 376 (M^+).

The analytical sample was obtained in a small run which was purified by preparative thin-layer chromatography on silica gel plates developed with chloroform–methanol (3:1). Extraction of the product band with methanol gave a crystalline solid that was recrystallized from ethanol: mp 90–92 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 262 nm at pH 1 (10.6), 263 nm at pH 7 (10.5), and 264 nm at pH 13 (10.5); IR 2200–3000 cm^{-1} (br, hydrogen bonded NH^+). Anal. ($C_{11}H_{13}IN_4O_3 \cdot H_2SO_4$) C, H, N.

The picrate was obtained as a crystalline solid from an aqueous solution of picric acid and **7**. It was recrystallized from ethanol, mp 219–221 °C dec. Anal. ($C_{11}H_{13}IN_4O_3 \cdot C_6H_3N_3O_7$) C, H, N.

Analgesic Narcotic Antagonists. 9. 6-Methylene-8β-alkyl-*N*-(cycloalkylmethyl)-3-hydroxy- or -methoxymorphinans

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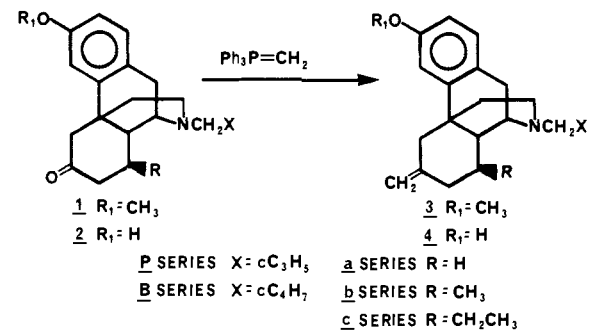
Series of *N*-(cyclopropylmethyl) (**P** series) or *N*-(cyclobutylmethyl) (**B** series) 3-methoxy (1) or 3-hydroxy (2) morphinan-6-ones with hydrogen (**a**), methyl (**b**), or ethyl (**c**) groups in the 8β position were converted to the 6-methylene compounds **3** or **4** by reaction with $Ph_3P{=}CH_2$. One member of this new series, *N*-(cyclobutylmethyl)-8β-methyl-6-methylenemorphinan-3-ol (**4Bb**), had potent mixed agonist–narcotic antagonist properties and, in contrast to the previously studied 6-oxo compound **2Bb**, did not substitute for morphine in dependent rats or monkeys.

We have recently been engaged in a program to prepare novel analgesic narcotic antagonists derived by chemical modification from the naturally occurring morphine alkaloids.[1] As an entry into this area, we initially explored the effect of lipophilic substitution at the 8β position in the C ring of dihydrocodeinone.[2] An extension of this work was the preparation of a series of *N*-(cycloalkylmethyl)-8β-alkylmorphinan-6-ones which had interesting pharmacological properties.[3] In order to extend these studies, we have now prepared and investigated the pharmacology of the 6-methylene derivatives of this latter series.

Scheme I



The replacement of the 6-oxo function in morphinone derivatives with other groups which are sp^2 hybridized has been reported. A summary of these studies[4] indicated that

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