Table II. Dissociation Constants of α-Amino Phosphonic Acids

Compd	pK_{a_1}	pK_{a_2}	Ref
4a	3.22	6.16	4
4a	5.40	10.10	This work
4b	3.66	6.29	4
4b	6.02	9.75	This work
4c	3.55	6.33	4
4c	6.00	10.70	This work
4d	3.65	6.23	4
4d	5.53	10.68	This work
$NH_2C(CH_3)_2P(=O)(OH)_2$	6.05	10.43	6
$NH_2CH(Ph)P(=O)(OH)_2$	5.60	9.50	6

ration, Analytical Section. ^1H NMR spectra were obtained with a Varian A-60 spectrometer, ^{31}P and ^{13}C spectra with a Jeol FX-60 spectrometer operating at 24.15 and 15.04 MHz, respectively.

***N*-Benzyliminobis(methylenephosphonic) Acid (2b, R_1 = $PhCH_2$–).** In precisely the manner described[4] benzylamine (0.1 mol) was reacted with phosphorous acid (0.2 mol) and formaldehyde (0.2 mol). The yield of white crystals, virtually insoluble in ethanol, was 14 g. Recrystallization from water yielded pure **2b** (R_1 = $PhCH_2$);[1] mp 257–258 °C; NMR (D_2O) (as sodium salt) δ 3.50 (d, 4, J = 12 Hz, NCH_2P), 4.85 (s, 2, $PhCH_2$), 7.62 (s, 5, PhH).

Anal. Calcd for $C_9H_{15}NO_6P_2$: N, 4.75; P, 21.02. Found: N, 4.64; P, 20.88.

***N*-Benzyl-α-aminomethylphosphonic Acid (4a).** Diethyl *N*-benzyl-α-aminomethylphosphonate (25.7 g, 0.1 mol) was heated under reflux in 18% hydrochloric acid (200 mL) for 2 h. Evaporation of the aqueous acid yielded a gum. Crystallization from ethanol/ether yielded **4a** as its hydrochloride: mp 272–274 °C; NMR (D_2O) δ 3.28 (d, 2, J = 13 Hz, NCH_2P), 4.37 (s, 2, $PhCH_2N$), 7.50 (s, 5, PhH).

Anal. Calcd for $C_8H_{12}NO_3PHCl$: C, 40.42; H, 5.47; N, 5.89; P, 13.05. Found: C, 40.64; H, 5.66; N, 5.63; P, 13.44.

***N*-Benzyl-2-amino-2-propylphosphonic Acid (4b).** Hydrolysis of the corresponding ethyl ester as described above yielded after crystallization the acid **4b**: mp 177–180 °C from ethanol; NMR (D_2O) δ 1.68 (d, 6, J = 12 Hz, CH_3CP), 4.44 (s, 2, $PhCH_2$), 7.55 (s, 5, PhH).

Anal. Calcd for $C_{10}H_{16}NO_3P$: C, 52.40; H, 6.99; N, 6.11; P, 13.54. Found: C, 52.69; H, 7.12; N, 5.78; P, 13.35.

***N*-Benzyl-1-amino-1-propylphosphonic Acid (4c).** As in the case of **4a**, the acid crystallized from ethanol/ether as its hydrochloride: mp 182–184 °C; NMR (D_2O) δ 1.10 (t, 3, J = 7 Hz, CH_3CH_2), 2.0 (m, 2, CH_2CH_3), 3.1–3.6 (m, 1, CHP), 4.43 (s, 2, CH_2Ph), 7.55 (s, 5, PhH).

Anal. Calcd. for $C_{10}H_{16}NO_3P{\cdot}HCl$: N, 5.27; P, 11.68; Cl^-, 13.37. Found: N, 4.90; P, 11.76; Cl^-, 13.37.

Dissolution of the hydrochloride in ethanol and treatment with propylene oxide gave the free acid **4c**, mp 227–228 °C (lit.[7] mp 222–224 °C).

***N*-Benzyl-2-amino-2-butylphosphonic Acid (4d).** The acid was obtained from the corresponding ethyl ester as described above and crystallized from ethanol/ether: mp 125–128 °C; NMR (D_2O) δ 1.13 (t, 3, J = 7 Hz, CH_2CH_3), 1.60 (d, 3, J = 14 Hz, CH_3CP), 1.9–2.3 (m, 2, CH_2), 4.47 (s, 2, CH_2Ph), 7.57 (s, 5, PhH).

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.29; H, 7.40; N, 5.58; P, 12.25.

Registry No.—**2b**, 6056-53-7; **4a** HCl, 64715-31-7; **4a** diethyl ester, 50917-70-9; **4b** diethyl ester, 64715-32-8; **4c** HCl, 64715-33-9; **4c** diethyl ester, 42274-96-4; **4d** diethyl ester, 64740-22-3; benzylamine, 100-46-9; formaldehyde, 50-00-0; phosphorous acid, 13598-36-2.

References and Notes

(1) K. Moedritzer and R. R. Irani, *J. Org. Chem.*, **31**, 1603 (1966).
(2) (a) K. Moedritzer, *Synth. Inorg. Met.-Org. Chem.*, **2**, 317 (1972); **3**, 75 (1973); (b) D. Redmore, *Top. Phosphorus Chem.*, **8**, 515–585 (1976).
(3) R. R. Irani and K. Moedritzer, U. S. Patent 3 288 846 (1966).
(4) W. Szczepaniak and J. Siepak, *Rocz. Chem.*, **47**, 929 (1973).
(5) E. K. Fields, *J. Am. Chem. Soc.*, **74**, 1528 (1952).
(6) J. P. Berry, A. F. Isbell, and G. E. Hunt, *J. Org. Chem.*, **37**, 4396 (1972).
(7) R. Tyka, *Tetrahedron Lett.*, 677 (1970).

N-Iodosuccinimide for the Synthesis of Rose Oxide

S. C. Taneja, K. L. Dhar,* and C. K. Atal

Regional Research Laboratory, Council of Scientific and Industrial Research, Jammu, India

Received April 21, 1977

The use of *N*-iodosuccinimide (NIS) in the synthetic field is less explored than that of *N*-bromosuccinimide (NBS). Djerassi et al.[1,2] have found that NIS is incapable of performing certain free-radical chain iodinations typical of the radical chain brominations brought about by NBS. NIS has been shown to react with enol acetates derived from ketones to give iodo ketones.[2] The mechanism of the reaction seems to be ionic in nature. In another unusual free-radical iodination reaction characteristic of NIS, a vinylic proton is replaced by iodine.[3]

In the present note, we report the use of NIS in the synthesis of rose oxide (III) from citronellol (I) in one step. The synthesis of the same compound from citronellol or citronellyl acetate using NBS is reported to be a multistep process in which allylic bromination is followed by dehydrobromination with a base and finally hydrolysis and cyclization with an acid.[4] With the use of NIS, all these steps are combined into one, giving rose oxide in yields up to 36%. The probable mechanism of the reaction may be represented as shown in Scheme I.

From the above sequence of reactions, it appears that the mechanism involved is similar to that of allylic bromination by NBS. However, in the case of NIS, allylic iodination is immediately followed by dehydroiodination, resulting in the formation of dehydrocitronellols IIa and IIb.[5] The cyclization of dehydrocitronellol to rose oxide is facilitated by iodine, which itself is generated during the course of the reaction.

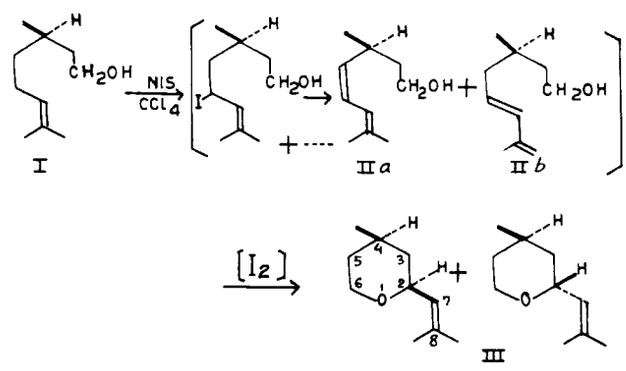
In summary, while the reaction of citronellol with NBS (in CCl_4) gives a bromo derivative of citronellol, the reaction with NIS (in CCl_4) gives rose oxide as the major product. Changing the reaction medium to dioxane and acetic acid gave only a trace amount of rose oxide.

Experimental Section

NIS was prepared by the method of Djerassi and Lenk.[6] A 10-g amount of the citronellol[7] and 22 g of *N*-iodosuccinimide were taken up in 80 mL of CCl_4, and the mixture was refluxed in a water bath for 45 min. The dark violet solution obtained was shaken several times with an aqueous solution of sodium thiosulfate until the iodine was completely removed. It was then washed with distilled water and dried over anhydrous sodium sulfate. The solution was concentrated and subjected to column chromatography on silica gel. Elution with petroleum ether–benzene (10:1) afforded pure rose oxide: 3.6 g (cis/trans, 81:19);[8] bp 48 °C (1.5 mm); $[\alpha]^{20}_D$ +27.5°; ^1H NMR (60 MHz) δ 0.90 (d, J = 8 Hz, 3 H, C-4), 1.52 (d, J = 1.2 Hz, 3 H, C-8), 1.66 (d, J = 1.2 Hz, 3 H, C-8), 3.0–4.0 (m, 3 H, C**H**–O–C$\mathbf{H}_2$), 5.10 (m, 1 H, =CH).

Acknowledgment. We wish to thank Dr. Y. V. Subbarao of the Regional Research Laboratory, Hyderabad, for the ^1H

Scheme I



0022-3263/78/1943-0997$01.00/0

NMR data, and S.C.T. wishes to thank the Council of Scientific and Industrial Research, New Delhi, for the Postdoctoral fellowship award.

Registry No.—**I**, 106-22-9; *cis*-**III**, 876-17-5; *trans*-**III**, 876-18-6; *N*-iodosuccinimide, 516-12-1.

References and Notes

(1) C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **75**, 3494 (1953).
(2) C. Djerassi, J. Grossman, and G. R. Thomas, *J. Am. Chem. Soc.*, **77**, 3826 (1955).
(3) K. H. Dudley and H. W. Miller, *Tetrahedron Lett.*, 571 (1968).
(4) C. F. Seidel and M. Stoll, *Chimia*, **15**, 311 (1961); *Chem. Abstr.*, **60**, 12059G (1964).
(5) The presence of dehydrocitronellol in the reaction mixture was confirmed by TLC and GLC only. The authentic sample was prepared by the reaction of citronellyl acetate with NBS and subsequent dehydrobromination and hydrolysis of the bromo derivative (cf. ref 4).
(6) Djerassi and Lenk, "Organic Synthesis", Collect. Vol. 5, H. E. Baumgarten, Ed., Wiley, New York, N.Y., 1973, p 663.
(7) The citronellol used was of 95% purity; $[\alpha]^{20}_{D}$ +1.5°.
(8) The ratio of the *cis*- and *trans*-(rose oxide) was calculated from GLC only.

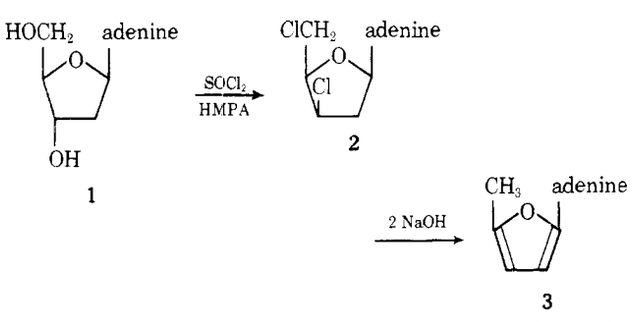
Reinvestigation of the Synthesis of 2′-Deoxyadenosylhomocysteine[1]

Yueh Wang and Harry P. C. Hogenkamp*

Department of Biochemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received, June 23, 1977

Recently two laboratories described convenient methods for the preparation of *S*-adenosylhomocysteine and some of its analogues.[2,3] Both methods employ the hexamethylphosphoramide–thionyl chloride reagent of Kikugawa and Ichino[4] to prepare the 5′-chloro-5′-deoxynucleosides, which upon condensation with either DL-homocysteine thiolactone in 2 N alkali[2] or DL-homocystine in sodium and liquid ammonia[3] yield the desired products. Borchardt and co-workers[3] reported the syntheses of *S*-adenosylhomocysteine and its analogues containing N^6-methyladenine, N^6-methyl-3-deazaadenine, and 7-deazzaadenine, as well as 2′- and 3′-deoxyadenosine. The purported synthesis of the last two analogues is surprising in light of our earlier observations that chlorination of 2′-deoxyadenosine by the method of Kikugawa and Ichino[4] does not yield 5′-chloro-2′,5′-dideoxyadenosine but rather the dichlorinated nucleoside, 9-(3,5-dichloro-2,3,5,-trideoxy-β-D-*threo*-pentofuranosyl)adenine (**2**).[5] Condensation of this dichloronucleoside with L-homocysteine could lead to the disubstituted analogue, 9-(3,5-dihomocysteinyl-2,3,5-trideoxy-β-D-*erythro*-pentofuranosyl)adenine, or the two monosubstituted analogues, 9-(3-chloro-5-*S*-homocysteinyl-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine and 9-(5-chloro-3-*S*-homocysteinyl-2,3,5-trideoxy-β-D-*erythro*-pentofuranosyl)adenine.



These compounds would be expected to undergo elimination reactions under the basic conditions of the condensation reactions. Indeed, McCarthy and co-workers[6] have demonstrated that a similar compound, 2′,5′-dideoxy-5′-*S*-ethyl-3′-*O*-*p*-toluenesulfonyl-5′-thioadenosine, is converted to 9-(5-methyl-2-furyl)adenine (**3**) via two base-catalyzed elimination reactions when treated with potassium *tert*-butoxide in dimethyl sulfoxide.

In order to resolve this inconsistency, we have reinvestigated the synthesis of the analogue of *S*-adenosylhomocysteine involving 2′-deoxyadenosine under reaction conditions used in both laboratories.[2,3] Our results demonstrate that chlorination of 2′-deoxyadenosine with thionyl chloride in hexamethylphosphoramide yields exclusively 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine (**2**). Paper chromatography of the crude reaction mixture in three solvent systems showed only **2** and adenine. Under the conditions of the condensation reactions, **2** undergoes two eliminations and an isomerization to 9-(5-methyl-2-furyl)adenine (**3**). The NMR spectra of **3** readily confirm its structure; the 270-MHz ^{1}H NMR spectrum shows the C-5′ protons as a three-proton singlet while the ^{13}C NMR spectrum shows a prominent resonance in the methyl region. Further evidence for the isomerization was obtained by conducting the reaction in a mixture of sodium deuterioxide and deuterioethanol. The ^{13}C NMR spectrum of the crystalline product demonstrates that one atom of deuterium is incorporated at carbon-5′, which now appears as a triplet, while the ^{1}H NMR spectrum indicates the presence of only two C-5′ protons. The ^{1}H NMR and ^{13}C NMR spectra also show that substitution of deuterium has occurred at C-8. The 80-MHz ^{1}H NMR spectra of **3** and its 5′-monodeuterio derivative are also in accordance with the assigned structures. The C-3′ proton of **3** appears as a set of quartets due to the long-range coupling of the three C-5′ protons, while for the deuterio derivative the C-3′ proton appears as a set of triplets.

This two-step reaction sequence provides a most convenient synthetic route to these unsaturated purine derivatives.

Experimental Section

Melting points were measured on a hot stage equipped with a microscope and are not corrected. Pulse proton and carbon-13 nuclear magnetic resonance spectra were recorded with a Bruker 270-MHz, a Varian CFT-20, and a Varian XL-100-15 spectrometer; chemical shifts are recorded in parts per million downfield from tetramethylsilane. Ultraviolet spectra were recorded with a Cary Model 15 spectrophotometer. Descending chromatography on Whatman No. 1 paper was conducted with the following solvent systems: 1-butanol–ethanol–water (50:15:35), *sec*-butyl alcohol–ammonium hydroxide–water (50:14:36), 1-butanol–acetic acid–water (40:10:50). Nucleosides on paper chromatograms were detected by their absorption of ultraviolet light; homocysteine derivatives were located with ninhydrin.

5′-Chloro-5′-deoxyadenosine and 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine were prepared as described before.[5]

***S*-Adenosylhomocysteine. Method 1.** To a solution of L-homocysteine thiolactone hydrochloride (1.15 g, 7.49 mmol) in 12 mL of 2 N sodium hydroxide was added 1.0 g (3.5 mmol) of 5′-chloro-5′-deoxyadenosine. The reaction mixture was stirred vigorously at 80 °C for 1.5 h and then acidified to pH 6 with dilute acetic acid. The solution was applied to an ion-exchange column (2 × 60 cm of Dowex 50-X2, 200–400 mesh, NH_4^+ form) and eluted with water. The fractions containing the desired product were pooled and evaporated to dryness, and the residue was crystallized from water–methanol to yield 520 mg (39%) of *S*-adenosyl-L-homocysteine: mp 195–199 °C (lit.[3] 212 °C).

Method 2. To a solution of L-homocystine (400 mg, 1.5 mmol) in 50 mL of liquid ammonia was added sufficient sodium to give a blue solution. Solid ammonium chloride was then added to just discharge the color. 5′-Chloro-5′-deoxyadenosine (600 mg, 2.1 mmol) was added and the reaction mixture was stirred at −33 °C for 12 h. The reaction mixture was evaporated to dryness, the residue was dissolved in water, and the desired product was purified as described above: yield 393 mg (49%); mp 198–202 °C; UV λ_{max} (pH 1) 257 nm (ϵ 12.8 × 10^3); UV λ_{max} (pH 7) 259 nm (ϵ 14.3 × 10^3); UV λ_{max} (pH 11) 259 nm (ϵ 14.1 × 10^3); ^{1}H NMR (Me_2SO-d_6) 1.84, 1.99 (2 m, 2, C_βH), 2.64 (t, 1, $J_{\alpha,\beta}$ = 7.5 Hz, C_αH), 2.79, 2.95 (2 m, 2, C_γH), 3.31 (q, 2, $J_{5'a,5'b}$ = −15.0 Hz,

