and $2G_2$ had IR and NMR spectra and VPC retention times identical with those of the authentic samples. The IR and NMR data of 7-carbethoxy-7-azabicyclo[4.1.0]heptane ($2H_1$) and 3-cyclohexylurethane ($2H_2$) were identical with those reported by Lwowski and Mattingly.[13]

Reaction with Alcohols. In the absence and in the presence of copper, a suspension of 1 (0.02 mol) in ethanol (0.5 mol) or in 1-butanol (0.5 mol) was stirred at 50 °C under an atmosphere of nitrogen. After the reaction mixture was filtered, the excess substrate and volatile product, aldehyde, were trapped in a flask immersed in a dry ice–methanol bath under reduced pressure. The trapped solution was added to a 2,4-dinitrophenylhydrazine solution and the aldehyde was converted to the hydrazone.

Reaction in the Presence of Radical Inhibitors. The reaction was carried out in the same manner mentioned above in the addition of radical inhibitor (0.02 mol).

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Registry No.—**1**, 17510-52-0; **3**, 51-79-6.

References and Notes

(1) College of General Education, Osaka University, Toyonaka, Osaka 560, Japan.
(2) N. Torimoto, T. Shingaki, and T. Nagai, *Bull. Chem. Soc. Jpn.*, **51**, 2983 (1978).
(3) D. Carr, T. P. Seden, and R. W. Turner, *Tetrahedron Lett.*, 477 (1969).
(4) N. Torimoto, T. Shingaki, and T. Nagai, *Bull. Chem. Soc. Jpn.*, **49**, 2572 (1976).
(5) N. Torimoto, T. Shingaki, and T. Nagai, *Bull. Chem. Soc. Jpn.*, **50**, 1517 (1977).
(6) The reaction of **1** with either *cis*- or *trans*-1,4-dimethylcyclohexane gave a mixture of *N*-(*cis*-1,4-dimethylcyclohexyl)urethane and *N*-(*trans*-1,4-dimethylcyclohexyl)urethane (stereoisomers). The total yields of isomers in each reaction were less than 1%, though the yield of **3** was over 60%. In the photolyses of **4**, however, only one product isomer (14% yield in the cis isomer and 11% yield in the trans isomer) was isolated in each reaction: T. Shingaki, M. Inagaki, N. Torimoto, and M. Takebayashi, *Chem. Lett.*, 155 (1972).
(7) W. Lwowski and R. L. Johnson, *Tetrahedron Lett.*, 891 (1967).
(8) W. Lwowski and T. J. Maricich, *J. Am. Chem. Soc.*, **87**, 3630 (1965).
(9) W. Lwowski in "Nitrenes", W. Lwowski, Ed., Interscience, New York, 1970, p 185, and references quoted therein.
(10) D. S. Breslow and E. I. Edwards, *Tetrahedron Lett.*, 2123 (1967).
(11) D. Saika and D. Swern, *J. Org. Chem.*, **33**, 4548 (1968).
(12) J. A. Riddic and W. B. Bunger in "Techniques of Chemistry", Vol. VII, A. Weissberger, Ed., Wily-Interscience, New York, 1970.
(13) W. Lwowski and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, **87**, 1947 (1965).

Trimethylsulfonium Hydroxide: A New Methylating Agent

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Trimethylsulfonium hydroxide (Me_3SOH) may be considered an analogue of *S*-adenosylmethionine, which serves as a methyl group donor in biomethylation reactions.[1] In this paper we describe methylation of various kinds of compounds using Me_3SOH. We prepared Me_3SOH[2] in methanol–water (50:1 v/v) by a reaction of trimethylsulfonium iodide and silver oxide. The reagent solution is strongly basic and stable for months with negligible decomposition when stored below 10 °C.

In general, methylation reactions were carried out by concentrating a mixture of substrate and the reagent solution followed by treating the residue at 70–120 °C for 5–30 min. In a few cases, such as deoxyguanosine, when the residue forms a hard solid mass, dimethylformamide (DMF) was used as a solvent. Since the byproducts of Me_3SOH are water and dimethyl sulfide (bp 38 °C), methylated products could be isolated easily by direct distillation or recrystallization of the reaction mixture, after removal of DMF if used. Examples of methylation are shown in Table I.

Me_3SOH is well suited for methylation of COOH, SH, aromatic OH, ring –NH– groups in aromatic heterocycles, etc., which have pK_a values smaller than approximately 12. An aliphatic amido group undergoes methylation in a satisfactory yield by the employment of a large excess of Me_3SOH, but the reagent is not practical for methylation of aliphatic and aromatic NH_2 and aliphatic OH groups. The reactions can be represented by the following scheme.

$$NuH + (CH_3)_3S^+ OH^- \rightarrow Nu^- \xrightarrow{H_2O} CH_3\text{-}S^+(CH_3)_2 \rightarrow Nu\text{-}CH_3 + (CH_3)_2S$$

The main advantages of Me_3SOH as a methylating agent are easy separation and purification of products and nearly quantitative and rapid methylation with 10–30% excess of Me_3SOH. When the product is soluble in water, Me_3SOH is particularly advantageous with regard to product isolation, since most of the other methylating agents generate water-soluble byproducts, for instance, HI and $(CH_3O)SO_3H$ or their Na or K salts from CH_3I and $(CH_3O)_2SO_2$, respectively.[3,4] Methylation of deoxyguanosine illustrates a typical example; e.g., with Me_3SOH, 1-methyldeoxyguanosine (m^1dG) was isolated easily in a yield of 70%, whereas, with CH_3I,[5] m^1dG was obtained in a poor yield (29%) although the thin-layer chromatography of the reaction mixture suggested the formation of the product in >85% yield.

Diazomethane may be as useful as Me_3SOH. Its preparation and handling, however, must be conducted carefully since diazomethane and its starting materials (*N*-nitroso compounds) are carcinogens.[6]

Taking the above advantages of Me_3SOH, we have been examining methylation of nucleosides and nucleotides; the results will be reported later.

Experimental Section

Preparation of Trimethylsulfonium Hydroxide (Me_3SOH). Trimethylsulfonium iodide (10.2 g, 50.0 mmol) was dissolved in a warm mixture of methanol and water (200–1 mL) and the solution was treated by silver oxide (7.2 g, 31.1 mmol) with stirring. Occasionally a few drops of the supernatant was checked for iodide by nitric acid–silver nitrate solution. After completion of the reaction, the reaction mixture was filtered and concentrated to 50 mL. The concentration of Me_3SOH in the solution was determined by titration with 0.1 N hydrochloric acid to be 0.86 N. (The yield of Me_3SOH was 86%.) When the titrated solution was concentrated, trimethylsulfonium chloride was obtained as crystals quantitatively. The NMR of the solution was δ 3.02 [s, $(CH_3)_3S^+$]. The electron impact mass spectrum was (75 eV) *m/e* (rel intensity) 76 ($M - H_2O$, 30), 62 (CH_3SCH_3, 100), 61 (CH_3SCH_2, 85), and 47 (CH_3S, 97).

General Methylation Procedure. Reaction conditions and results are summarized in Table I. A mixture of the Me_3SOH solution and a substrate was concentrated by a rotatory evaporator and heated with stirring. The unpleasant order of dimethyl sulfide can be avoided by extending rubber tubing from the exit of the reaction flask to a sink or to a trap immersed in an acetone–dry ice bath. When methylation of the compound was incomplete as in the case of ε-caprolactam, the reaction mixture was mixed again with the Me_3SOH solution, concentrated, and heated. The similar procedure was repeated till a product was formed in a substantial yield. For methylation of deoxyguanosine, the concentrated mixture of the nucleoside and the Me_3SOH solution was heated in DMF (4 mL). The reaction mixture was occasionally analyzed by gas and thin-layer chromatographies as well as NMR spectrometry. Products were isolated by direct distillation or recrystallization of the reaction mixture. 1-Methyldeox-

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Table I. Methylation of Various Compounds by Trimethylsulfonium Hydroxide (Me_3SOH)

compd	registry no.	compd/Me_3SOH[a] mol ratio	reaction temp, °C	reaction time, min	product	registry no.	yield, %[b]
$(CH_3)_2CHCO_2H$	79-31-2	1.3	120	20	$-CO_2CH_3$	547-63-7	quant.
$(CH_3)_3CCO_2H$	75-98-9	1.3	120	20	$-CO_2CH_3$	598-98-1	quant.
$HOCH_2CH_2SH$	60-24-2	1.1	100	20	$-SCH_3$	5271-38-5	quant.
C_6H_5OH	108-95-2	1.1	100	20	$-OCH_3$	100-66-3	quant.
C_6H_5SH	108-98-5	1.1	80	20	$-SCH_3$	100-68-5	quant.
$C_6H_5NH_2$	62-53-3	2.0	110	30	$-NHCH_3$	100-61-8	<5
$CH_3(CH_2)_3CH_2OH$	71-41-0	3 (1.5 + 1.5)[c]	120	25 (5 + 20)[c]	$-OCH_3$	628-80-8	trace
	105-60-2	3 (1.5 + 1.5)[c]	120	30 (10 + 20)[c]	$>NCH_3$	2556-73-2	35
indazole	271-44-3	1.1	110	30	$>NCH_3$	13436-48-1	84
imidazole	288-32-4	1.1	70	20	$>NCH_3$	616-47-7	quant.
benzotriazole (Ben)	95-14-7	1.2	110	30	m^1Ben	13351-73-0	62
					m^2Ben	16584-00-2	11
cytosine (Cyt)	71-30-7	1.1	110	5	m^1Cyt	1122-47-0	90
deoxyguanosine (dG)	961-07-9	1.1	80	30	m^1dG	5132-79-6	70

[a] Used amount of a compound: dG, 1 mmol; all others, 10 mmol. [b] quant. refers to a quantitative yield, which was judged by gas chromatography and the NMR spectrum of the reaction mixture. Yields indicated by numbers were calculated on the basis of the isolated amounts of products. [c] Repeated addition of the Me_3SOH solution and heating of the reaction mixture for the time specified. See Experimental Section also.

yguanosine was obtained as crystals by treatment of the reaction mixture at 50 °C and 10 mmHg to remove DMF and subsequent agitation of the residue with methanol; it was recrystallized from methanol. 1-Methyl- and 2-methylbenzotriazoles were isolated according to the previous paper.[7] Products were identified by comparison of their IR and NMR spectra as well as comparison of boiling point and melting point with literature values or those of authentic samples.

Registry No.—Trimethylsulfonium hydroxide, 17287-03-5; trimethylsulfonium iodide, 2181-42-2; silver oxide, 20667-12-3.

References and Notes

(1) E. E. Conn and P. K. Stumpf, "Outlines of Biochemistry", 4th ed., Wiley, New York, 1976, p 481.
(2) A. A. Sosunov, A. P. Kilimov, and V. V. Smirnov, *Zh. Ohshch. Khim.*, **45**, 1533 (1975). Other references are cited therein. The chemistry of Me_3SOH has been little studied other than on its decomposition.
(3) L. F. Fieser and M. Fieser, "Reagents for Organic Syntheses", Vol. 1, Wiley, New York, 1976.
(4) I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods", Wiley-Interscience, New York, 1971.
(5) A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry*, **3**, 494 (1964).
(6) B. Singer in "Progress in Nucleic Acid Research and Molecular Biology", Vol. 15, W. E. Cohn Ed., Academic Press, New York, 1975, p 219. Biological Study of Me_3SOH is now under way.
(7) M. Hayashi, K. Yamauchi, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **49**, 283 (1976).

Chromic Acid Oxidation of [*n*.3.2]Propellanols

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Recently the chemistry of propellanes, particularly structure reactivity relationships, has drawn much attention.[1] We have previously reported on the synthesis and reactivity of [*n*.3.2]propellane derivatives.[2] In the course of these studies, we have noted the remarkable effect of the size of alicyclic rings (5–8) on the photochemical behavior of bicyclic enones[2d-f] and on the stereoselectivity in the hydride reduction of [*n*.3.2]propellanones[2g] and have pointed out that the ring size effect is attributable to the steric effect associated with the conformational flexibility of the ring systems. In view of the above findings, we decided to investigate the chromic acid oxidation of exo and endo [*n*.3.2]propellanols (**1–5**), involving a cyclopentanol moiety, a cyclobutane ring, and one of five- to eight-membered alicyclic rings as the third ring. Since it has been well known that the rate-determining step in the chromic acid oxidation of secondary alcohols is the decomposition of the intermediate chromate ester,[3] and the acceleration of the decomposition rate is thought to be due to the relief of unfavorable nonbonded interactions which exist in the ground state of the molecule,[4,5] remarkable distinction in steric effect of the third rings on the oxidation rate may be expected, especially in the endo alcohol system.

The alcohols were prepared as described previously;[2e,g] the bicyclo[3.2.0]heptan-2-ol moiety in these alcohols had rigid boat geometry practically independent of conformational flexibility of the third rings.[2e,g]

The rate constants of the chromic acid oxidation of propellanols are summarized in Table I.[6] The relative rate constants (k_{rel}) for the tricyclic exo alcohol system increase slightly with increasing the size of the third ring. On the other hand, k_{rel} for the endo alcohols increases remarkably with increasing the size of the third ring and, especially, in the case of endo [6.3.2]propellanol **4N**, the rate is considerably enhanced compared with other endo alcohols. These facts indicate that, in the endo alcohol system, nonbonded interactions between the endo hydroxyl group and hydrogens of the third rings become greater as they become conformationally more flexible. This seems to contradict our previous findings that conformational flexibility of alicyclic rings reduces unfavorable nonbonded interactions in the transition state of reactions such as the photocycloaddition of bicyclic enones[2d-f] and the nucleophilic addition of metal hydride to [*n*.3.2]propellanones.[2g] However, the transition state of the chromic acid oxidation of secondary alcohols (elimination of the chromate ester group in the rate-determining step) may be susceptible to acceleration due to steric crowding around the endo hydroxyl group particularly from some flexible ring such as cyclooctane as is illustrated below.

The steric environment is quite different for the exo OH group which is located at the opposite side of the third ring and at the outside of the envelope of the cyclopentane ring owing to the rigid boat conformation of the bicyclo[3.2.0]heptan-2-ol moiety.[2g] Consequently, only slight enhancement of the rate constants with increasing in the size of the third rings is expected and may be ascribed to a little increase of nonbonded interactions between the endo hydrogen (α to the OH) and the hydrogens of the third rings.

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