pressure and dried over calcium chloride for 5 minutes *in vacuo* at room temperature. The residue was dissolved in 0.5 ml of ethanol, and one drop of freshly prepared ethereal diazomethane (28 mg of diazomethane per ml of ether) was added. After 10 seconds, the reaction was stopped with a few drops of 0.1 N acetic acid and to the mixture 0.1 ml of tyramine solution in 0.1 N acetic acid (containing 0.723 μg of tyramine hydrochloride) was added. The solution was evaporated to dryness under reduced pressure and dried over calcium chloride for 5 minutes. The residue was trifluoroacetylated with one drop of ethyl acetate and 10 μl of trifluoroacetic anhydride for 5 minutes, then diluted with 0.5 ml of *n*-hexane. One μl of the solution was injected to a gas chromatograph equipped with electron capture detector (Shimadzu GC 4APE, 1.4 m glass column packed with 2% GE–XF 1105 on Gas Chrom P, column temperature, 120°).

The chromatogram thus obtained was shown in Fig. 1 and 2, in which the peak of VMA was identified by its retention time and by addition treatment of the authentic compound. The chromatogram in Fig. 1 corresponds to 400 mμl of the urine of normal person, while that in Fig. 2 to 6 mμl of the urine of the patient with pheochromocytoma. The linearity between the peak height ratio of VMA to tyramine and the amount of VMA was attained as shown in Fig. 3. The average recovery percent of added VMA to urine was 103% as shown in Table I.

Table I. Recovery Percents of Added VMA (2.77 μg) to Urine of Normal Person (0.5 ml)

No.	Recovery %	No.	Recovery %
1	101	6	109
2	106	7	101
3	105	av.	103
4	99.4	st. dev.	4.02
5	97.8		

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Two Methyl Ethers of 4-Aminotropolone and Their Bromination

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Until present time, many reactions of various aminotropone derivatives have been investigated.[2]

The pK_a values of aminotropones have also been measured in order to study the correlation of their reactivities and pK_a values.[3] In the present work, two methyl ethers of 4-

1) Location: *Katahira-cho 75, Sendai.*
2) T. Nozoe, S. Seto, H. Takeda, S. Morosawa, and K. Matsumoto, *Sci. Rept. Tohoku Univ.*, I, **36**, 126 (1952); S. Ryu and T. Toda, *ibid.*, **51**, 105 (1968); K. Ogura, H. Sasaki, and S. Seto, *Bull. Chem. Soc. Japan*, **38**, 306 (1965); T. Nozoe, S. Ryu, and T. Toda, *ibid.*, **41**, 2978 (1968); T. Toda, S. Ryu, and T. Nozoe, *ibid.*, **42**, 2028 (1969); H. Toda, *Yakugaku Zasshi*, **87**, 1351 (1967).
3) S. Seto, T. Hiratsuka, H. Toda, *Yakugaku Zasshi*, **89**, 1673 (1969).

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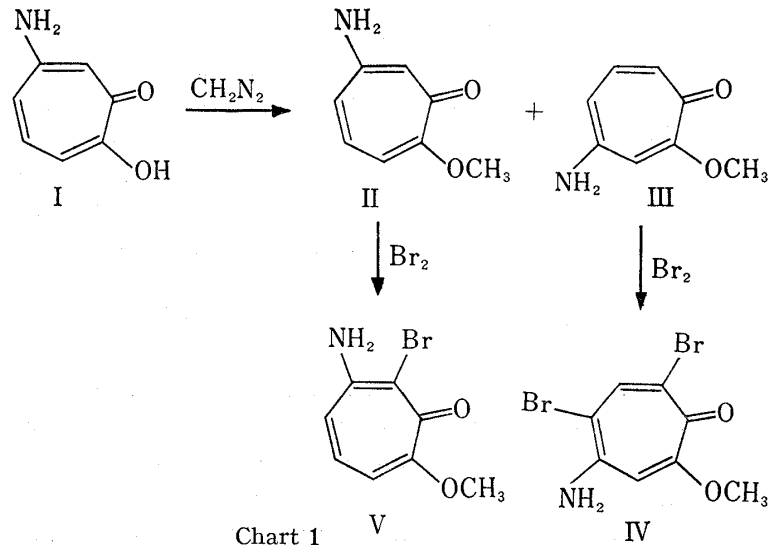

Chart 1

aminotropolone were prepared as the samples for farther investigation, and the structure of each methyl ether was elucidated from the nuclear magnetic resonance (NMR) spectral data of the methyl ethers and their bromo-derivatives.

Reaction of 4-aminotropolone (I) with diazomethane gave two methyl ethers, II (mp 257° (decomp.)) and III (mp 179° (decomp.)). The ultraviolet (UV) spectrum of II is similar to that of 3-aminotropone[4] and III shows the analogous UV

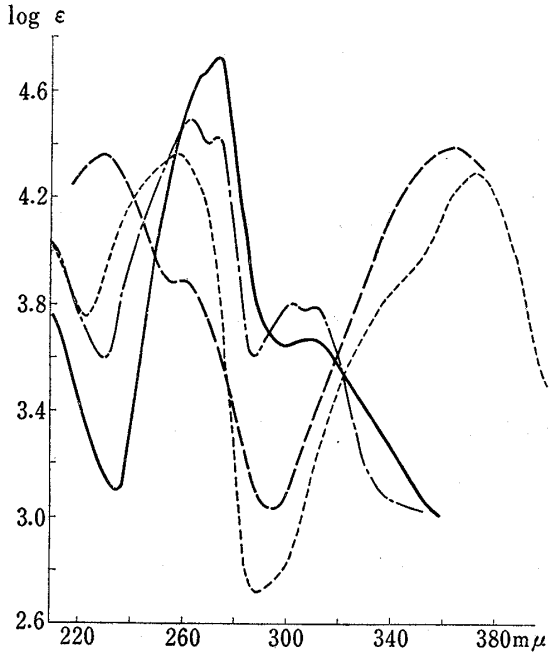

Fig. 1. UV Spectra of Aminotropone Derivatives in MeOH

-----: 3-aminotropone
———: 3-amino-7-methoxytropone (II)
– – –: 4-aminotropone[5]
--------: 4-amino-2-methoxytropone (III)

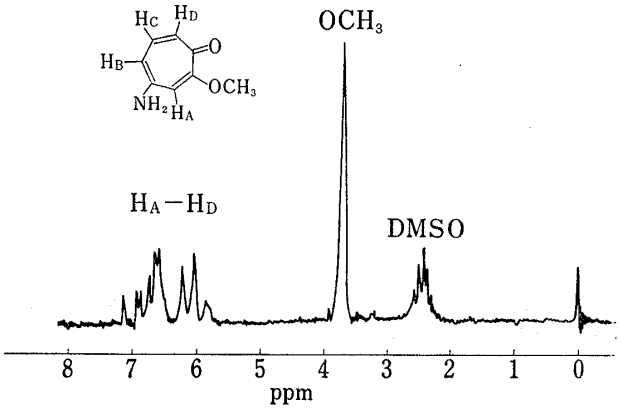

Fig. 2. NMR Spectrum of III in DMSO-d_6 (60 Mc)

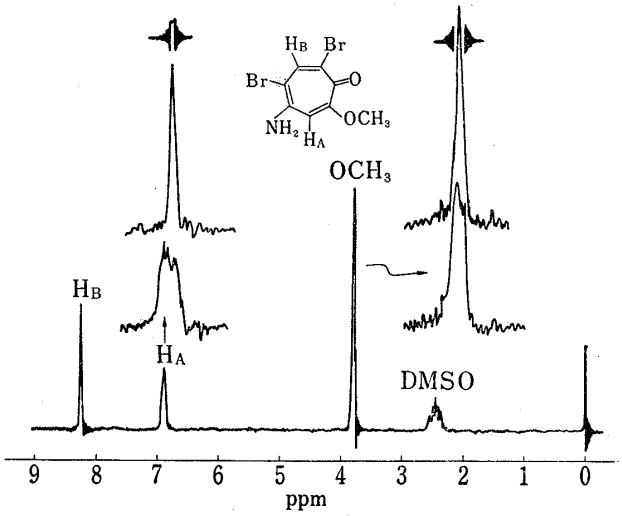

Fig. 3. NMR Spectra of IV in DMSO-d_6 showing Results (Top Two Spectra) of Spin Decoupling Experiments (60 Mc)

4) H. Toda, H. Sugiyama, and S. Seto, *Chem. Comm.*, **1968**, 562; *Chem. Pharm. Bull.* (Tokyo), **17**, 2548 (1969).

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absorption curve to 4-aminotropone[5] as is shown in Fig. 1. It is expected that if III is 4-amino-2-methoxytropone, bromination of III must afford 5-bromo- or 5,7-dibromo-derivative, because of the high electron densities at 5- and 7-positions of III caused by resonance effect of the amino group, and a bromination product must bring remarkable simplification to its NMR spectrum in the ring proton region. Actually, treatment of III with bromine afforded a dibromo-compound (IV). The NMR spectrum of IV (Fig. 3) which is more simple as compared with that of III (Fig. 2) exhibited a sharp singlet (1H) at 8.26 ppm, a broad signal (1H) at 6.97 ppm, and a broad signal due to methoxyl protons at 3.82 ppm. In the previous paper,[6] we have reported that long-range spin coupling between methoxyl protons and a neighboring ring proton has been observed in 2-methoxytropone derivatives. In the present case, it was found that both broad signals at 6.97 and 3.82 ppm were sharpened by irradiation at around 229 and 417 Hz respectively. Therefore, an isolated ring proton must be present at the adjacent position to the methoxyl group in IV. The sharp singlet at lower magnetic field (8.26 ppm) is due to another ring proton which is present between two bromine atoms on the sevenmembered ring skeleton. These NMR spectral data indicated the structure of IV to be 4-amino-5,7-dibromo-2-methoxytropone. On the other hand, bromination of II resulted in the formation of only a monobromo-derivative (V). The NMR spectrum of V shows a signal due to the methoxyl group at 3.70 ppm and complex multiplet due to three ring protons at around 6.80 ppm. Thus, it was clarified that methyl ether III is 4-amino-2-methoxytropone, and isomeric methyl ether II is 3-amino-7-methoxytropone, as expected from their UV spectra and from the results of the brominations. The methylation reaction does not need high energy.[7] Therefore, the activation energy of the methylation of I is small and the transition state of the reaction may resemble the original material as pointed out by Streitwieser.[8] The ratio of the formation of II and III is about 3:1, and thus, this result suggests the ratio of the tautomeric form in I.[9] Also, this result is consistent with the result of the UV spectrum of I as reported before.[3]

Experimental[10]

Reaction of 4-Aminotropolone with Diazomethane——Into a suspension of I (1 g) in MeOH (12 ml) ethereal diazomethane was added until no longer a portion of the solution colored to the solution of ferric chloride. The reaction mixture was allowed to stand at room temperature overnight and then the crystals (II, 60 mg) which were separated out were collected by filtration. Removal of the solvent from the filtrate afforded a yellow residue. Addition of mixture of $CHCl_3$ and MeOH (5 ml; 10 ml) to this residue gave the crystals (II, 230 mg) as the second crop, which were filtered and washed with $CHCl_3$–MeOH. The oily residue obtained by evaporation of the solvent from the filtrate crystallized by addition of a small amount of $CHCl_3$. The collected powderish crystals (III, 90 mg) were washed well with $CHCl_3$ containing a small amount of MeOH.

Methyl Ether II: Recrystallized from EtOH to give pale yellow prisms, mp 257—257.5° (decomp.). *Anal.* Calcd. for $C_8H_9O_2N$; C, 63.56; H, 6.00; N, 9.27. Found: C, 63.78; H, 5.90; N, 8.98. λ_{max}^{MeOH} mμ (log ε): 273 (4.72), 307 (3.67). ν_{max}^{KBr} cm^{-1}: 3250, 3080, 1661, 1635, 1569, 1520, 1485 (broad), 1288, 1214, 1181, 1017.

5) K. Doi, *Bull. Chem. Soc. Japan*, 33, 887 (1960).
6) S. Seto, K. Ogura, H. Toda, Y. Ikegami, and T. Ikenoue, *Bull. Chem. Soc. Japan*, **41**, 2696 (1968).
7) R. Huisgen and H. Reimlingen, *Ann.*, **599**, 183 (1956).
8) A. Streitwieser and W.D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2888 (1957).
9) The exact ratio of the formation of II and III should be known by measurement of NMR spectrum of the reaction mixture, but the signal due to the methoxyl group of II appears at the closed position to that of III that they could not be determined.
10) All melting points are uncorrected. The microanalyses were carried out by Misses Noriko Matsukawa, Emiko Yoshida and Noriko Sato of this Institute, to whom the author is indebted. The measurements of the ultraviolet and infrared absorption spectra were made with a Cary recording spectrophotometer model 14 and with a Hitachi EPI-S2 spectrophotometer, respectively. The NMR spectra were measured in a deuterodimethylsulfoxide solution, using tetramethylsilane as an internal standard, on a Varian A-60 and Hitachi H-60 spectrometer.

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Methyl Ether III: Recrystallized from $CHCl_3$–MeOH to give yellow needles, mp 179° (decomp.). *Anal.* Calcd. for $C_8H_9O_2N$; C, 63.56; H, 6.00; N, 9.27. Found: C, 63.77; H, 6.12; N, 9.19. λ_{max}^{MeOH} mμ (log ε): 257 (4.37), 372 (4.29). ν_{max}^{KBr} cm^{-1}: 3320, 3180, 1658, 1621, 1586, 1487, 1451, 1240, 1212, 1170, 987.

Bromination of II——Into a solution of II (33 mg) in EtOH (5 ml) cooled in an ice-bath, a solution of bromine (70 mg) in EtOH (3 ml) was added slowly. Colorless fine needles obtained by evaporation of the solvent were dissolved into H_2O and pH of the solution was adjusted to 7 with Na_2CO_3. The colorless needles which were separated out were filtered and washed with H_2O; 30 mg, mp 205—206°. *Anal.* Calcd. for $C_8H_8O_2NBr$; C, 41.74; H, 3.48; N, 6.09. Found: C, 41.51; H, 3.61; N, 5.86. λ_{max}^{MeOH} mμ (log ε): 274 (4.72), 322 (3.71). ν_{max}^{KBr} cm^{-1}: 3430, 3300, 3200, 1633, 1580, 1552, 1476, 1230, 800.

Bromination of III——A solution of bromine (40 mg) in EtOH (2 ml) was added dropwise to a solution of III (41 mg) in EtOH (3 ml) cooled in an ice-bath. After the reaction mixture was allowed to stand at room temperature for 1 hr, the crystals (50 mg) which were separated out were filtered and washed with EtOH. Recrystallization from EtOH gave yellow needles; mp 227—228° (decomp.). *Anal.* Calcd. for $C_8H_7O_2NBr_2$; C, 31.09; H, 2.27; N, 4.53. Found: C, 31.26; H, 2.24; N, 4.48. λ_{max}^{MeOH} mμ (log ε): 257 (4.26), 352 (3.88), 395 (4.13). ν_{max}^{KBr} cm^{-1}: 3450, 3270, 3100, 1626, 1612, 1565, 1475, 1450, 1374, 1232, 981, 742.

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A Convenient Synthesis of 1-β-D-Arabinofuranosylcytosine

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Cytosine arabinoside is effective as an antileukemic agent, and is otherwise also biologically active.[2] Therefore, the synthesis of this arabinoside seemed to be worthwhile and interesting. The purpose of this communication is to report, as a continuation of our studies of the synthesis of nucleosides, a convenient synthetic procedure for this nucleoside. Modification of the previously reported method[3] for the synthesis of the pyrimidine and purine nucleosides by using catalytic condensation reactions of acylated halogeno sugars with silyl purine and pyrimidine derivatives in organic solvents served as the basis of the synthesis.

In 1961, Goodman, *et al.*[4] successfully synthesized "Spongo" nucleosides of uracil derivatives, but did not attempt the preparation of arabinosyl cytosine (Ara-C). In their study, a 3-tosyl-D-xylofuranose derivative (II) was found suitable for synthesizing Ara-C. This together with the results of studies[3] described above, we started with the condensation of N^4-acetylcytosine (bistrimethylsilyl) (VI) with 5-O-carboethoxy-3-tosyl-2-acetylxylofuranosyl chloride (II).

Acetyl 5-O-carboethoxy-3-O-tosyl-2-O-acetyl-D-xylofuranoside (I)[4] was converted into the corresponding 1-chloroderivative (II) with hydrogen chloride in ether in the presence of acetyl chloride in the usual manner. This chloride (II) was allowed to react with bistrimethylsilyl-N^4-acetylcytosine (VI) in benzene for 12 hr at room temperature in the presence of mercuric bromide. After the solvent was removed by evaporation *in vacuo* to dryness, the

1) Location: *2–58,1-chome, Hiromachi, Shinagawa-ku, Tokyo.*
2) S. Cohen, "Progress in Nucleic Acid Research and Molecular Biology," Vol. 5, 1966 p. 1.
3) B. Shimizu and A. Saito, *Agr. Biol. Chem.* (Tokyo), 33, 119 (1969).
4) E. Reist, J. Osiecki, L. Goodman and B.R. Baker, *J. Am. Chem. Soc.*, 83, 2208 (1961).

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