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Long-Range Spin Coupling between the Methoxyl and Ring Protons in 2-Methoxytropone Derivatives and Its Applications*1

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Bromination of 5-amino-2-methoxytropone and 2-amino-7-methoxytropone afforded 5-amino-4-bromo-2-methoxytropone and 2-amino-3,5-dibromo-7-methoxytropone, respectively, as expected from the consideration of the effect of amino group in 2-methoxytropone system. Long-range spin coupling between the methoxyl group and a neighboring ring proton was observed in 2-methoxytropone derivatives. This information was applied to elucidation of the structure of the bromination products. The comparison of their NMR spectra gave the reasonable assignment for the ring protons of 5-amino-2-methoxytropone.

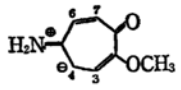
Long-range spin coupling involving methoxyl groups in aromatic compounds has been reported on the derivatives of *o*-hydroxyacetophenone and salicylaldehyde by Forsén and his co-workers.[1,2] They observed that the methyl protons are coupled to a neighboring ring proton with coupling constant of 0.24—0.31 Hz in these compounds.

During the course of our study of the reaction of amino derivatives of 2-methoxytropone, long-range spin coupling was observed between the methoxyl group and a ring proton. The fact is applicable to confirm the direction of the substitution reaction.

Results and Discussion

Bromination of 5-Amino-2-methoxytropone. It is well known that the substitution in the bromination of tropolone[3-5] and 2-aminotropone[6] takes place at 3-, 5- and 7-positions of the tropone ring, and that 2-methoxytropone is subject to addition rather than substitution on its treatment with bromine.[7] Bromination of 5-amino-2-methoxytropone (I)[8] is of interest from the standpoint of the effect of the amino group on electrophilic substitution of the 2-methoxytropone system. In the NMR spectrum of I (Fig. 1), the quartet at the highest field in the ring proton region must be due to H_4 proton or H_6 proton since it has spacings 2.5, 9.0 and 2.5 Hz due to *ortho* and *meta* couplings, respectively.[9]

It seems likely that the electron density at the position 4 of I is raised by mesomeric effect of the amino group and that such an effect is not conceivable as to the position 6. Therefore, this quartet is reasonably assigned to H_4 proton, and the other signals for ring protons can be tentatively assigned as illustrated in Fig. 1. These considerations lead to an anticipation that the substitution of bromine may occur exclusively at the position 4.

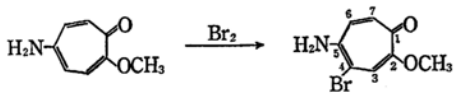


Treatment of I with bromine in methanol caused a transitory red color to appear, and then yellow crystals of a monobromo derivative (II) separated out in a high yield. The NMR spectrum of II (Fig. 2) in DMSO-d_6 shows a pair of AB type doublet (δ=6.97 and 7.13 ppm) with coupling constant of 13.9 Hz due to two adjacent ring protons and a signal with small splittings at 7.22 ppm probably due to H_3 proton. The signals corresponding to H_4 proton in I disappear in the monobromo derivative (II) and no splitting by *meta*-coupling is observed, suggesting the substitution occurred at the position 4. The splitting of the signal at 7.22 ppm was found to be due to the coupling with the methoxyl protons (J=0.5 Hz) by spin decoupling experiment; namely double irradiation at around 223 and 433 Hz sharpened the signal at 7.22 ppm and the signal for the methoxyl protons, respectively. The positional relation between methoxyl and H_3

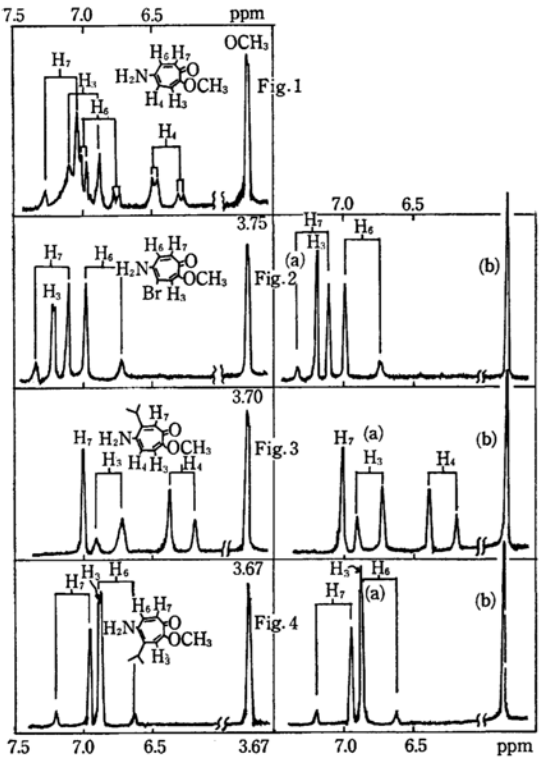
*1 Presented in part at the 85th Annual Meeting of the Pharmaceutical Society of Japan in Tokushima, Oct. 27, 1965.

1) S. Forsén, *J. Phys. Chem.*, **67**, 1740 (1963).
2) S. Forsén, B. Akermark and T. Alm, *Acta Chem. Scand.*, **18**, 2313 (1964).
3) T. Nozoe, S. Seto, T. Mukai, K. Yamane and A. Matsukuma, *Proc. Japan Acad.*, **27**, 224 (1951).
4) J. W. Look, A. R. Gibb and R. A. Raphael, *J. Chem. Soc.*, **1951**, 2244.
5) T. Nozoe, S. Seto, Y. Kitahara, M. Kunori and Y. Nakayama, *Proc. Japan Acad.*, **26**, 38 (1950).
6) T. Nozoe, S. Seto, H. Takeda, S. Morosawa and K. Matsumoto, *Sci. Repts. Tohoku Univ., Ser. I*, **36**, 126 (1952).
7) T. Nozoe, S. Seto, T. Mukai, K. Yamane and A. Matsukuma, *Proc. Japan Acad.*, **17**, 224 (1951).
8) K. Ogura, H. Sasaki and S. Seto, This Bulletin, **38**, 306 (1965).
9) H. Sugiyama, D. Sc. Thesis, Tohoku University, 1963.

proton in II is the same as that of methoxyl derivatives of 2-hydroxyacetophenone and salicylaldehyde[2] in which a coupling between methoxyl and its adjacent ring proton is reported. Accordingly, the observation of this long-range coupling also affords a strong support for the structural elucidation of II as 5-amino-4-bromo-2-methoxytropone.



I II

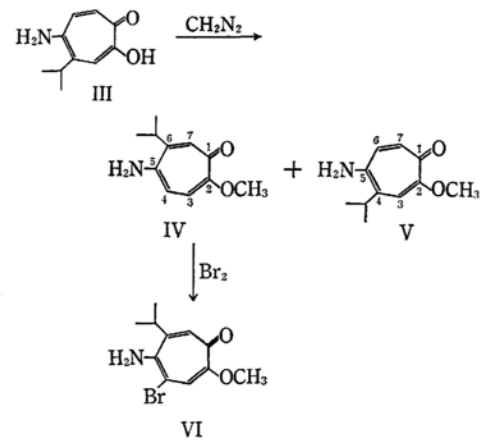


NMR Spectra
(a) OCH_3 irradiated, (b) H_3 irradiated

Fig. 1. 5-amino-2-methoxytropone (I).
Fig. 2. 5-amino-4-bromo-2-methoxytropone (II).
Fig. 3. 5-amino-6-isopropyl-2-methoxytropone (IV).
Fig. 4. 5-amino-4-isopropyl-2-methoxytropone (V).
(in DMSO-d_6)
For the sake of comparison of each spectrum, Figs. 1—4 are expressed illustratively.

Two Methyl Ethers of 5-Amino-4-isopropyltropolone. Reaction of 5-amino-4-isopropyltropolone (III)[10] with diazomethane gave two methyl ethers (IV: mp 220°C, V: mp 140°C). As shown in Fig. 3, the NMR spectrum of IV has a pair of AB type doublet (δ=6.32 and 6.82 ppm) with coupling constant of 12.0 Hz, which means an existence of two adjacent ring protons in its structure. It is noticed, moreover, that two peaks at lower fields in the pair showed further a small splitting. Spin decoupling at frequencies of 220 and 409 Hz sharpened those aromatic and methyl proton signals, respectively, indicating that the lower-field peaks in the pair of AB type doublet is assigned to a ring proton neighboring with the methoxyl group. So, the structure of IV was determined as 5-amino-6-isopropyl-2-methoxytropone. A signal at 7.00 ppm in Fig. 3 is reasonably assigned to a H_7 proton.

Isomeric methyl ether, V, is naturally assumed to be 5-amino-4-isopropyl-2-methoxytropone. The following decoupling study of its NMR spectrum supported the structure. In the spectrum shown in Fig. 4, a signal (6.84 ppm) due to an isolated ring proton appears, overlapping with a line at 6.87 ppm of a pair of doublet (δ=6.86 and 6.95 ppm, J=13.0 Hz) of two adjacent ring protons. Decoupling at frequencies of methyl protons and isolated ring-proton resonances afforded sharp and intense signals for a line at 6.84 ppm and methyl proton signal at 3.67 ppm, respectively. The phenomenon indicates that an isolated ring proton exists at a position adjacent to methoxyl group in the structure of V.



III IV V VI

Monobromo derivative (VI) of IV was obtained by its bromination, while the isomer, V, did not give any bromo derivative. Since the NMR spectrum of VI does not show any signal in the region corresponding to H_4 proton signals of IV, it is clear that the bromination of IV has occurred at 4-position similarly to the case of 5-amino-2-methoxytropone (I).

Dibromo Derivative of 2-Amino-7-methoxytropone. Reaction of 3-aminotropolone (VII) with diazomethane affords 2-amino-7-methoxytropone (VIII), together with a small amount of isomeric methyl ether (IX). The structure of VIII was confirmed by the fact that the compound (VIII) reacted with diketene giving an authentic

10) T. Nozoe, Y. Kitahara, E. Kunioka and K. Doi, *Proc. Japan Acad.*, **26**, 38 (1950).

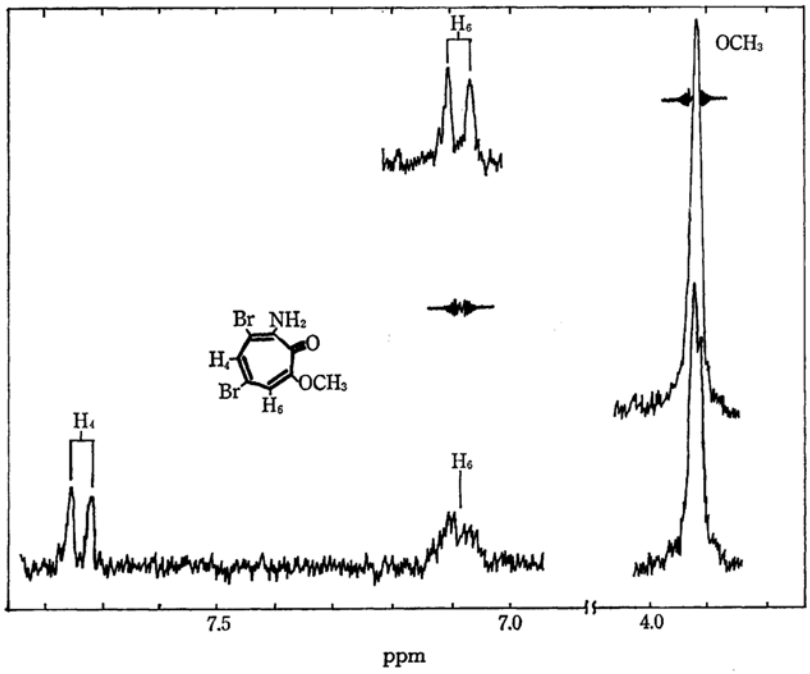
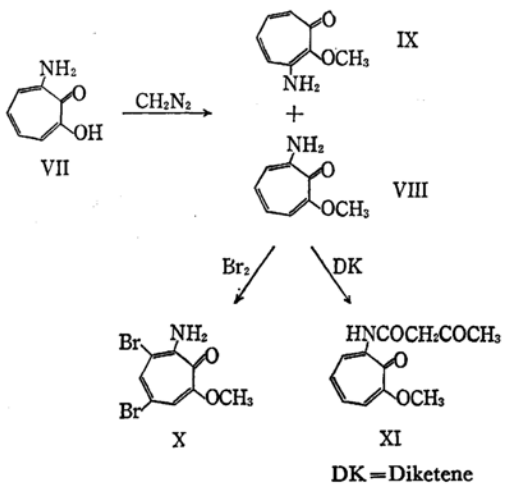


Fig. 5. NMR spectra of 2-amino-3,5-dibromo-7-methoxytropone (X) in DMSO-d_6 showing results (top two spectra) of spin decoupling experiments.

2-acetoacetamino-7-methoxytropone (XI), which had been obtained in the reaction of VII with diketene followed by methylation.[8]



Long-range spin coupling between methoxyl and ring proton was also applied to the determination of the structure of 2-amino-3,5-dibromo-7-methoxytropone (X) which is a bromination product of VIII, as follows. Since the ultraviolet and infrared spectra of the product show the existence of tropone skeleton, the dibromo derivative of VIII should be one of the six possible isomers. Analysis of the NMR spectrum excluded the structure having two adjacent ring protons, as shown in Fig. 5. The further study by proton magnetic double resonance chose a structure of X because the double resonance spectra clearly demonstrated the existence of a splitting due to long-range coupling between methyl protons and H_6 proton, the signal of which appears at 7.10 ppm, and H_6 proton couples to H_4 proton with coupling constant of 1.9 Hz.

The formation of 3,5-dibromo derivative of VIII shows that VIII has a behavior as 2-aminotropone derivative that gives 3,5,7-tribromo-2-aminotropone derivative on bromination.

Comparison of these spectra gave a confirmation of the assignment of every signal of 5-amino-2-methoxytropone (I) as given in Fig. 1. The results obtained here suggest that the long-range coupling between methoxyl and neighboring ring protons will be widely useful for the study of structural elucidation.

Experimental*2

Bromination of 5-Amino-2-methoxytropone (I). Into a cooled solution of I (100 mg) in 1 m*l* of methanol, a solution of bromine (110 mg) in 1 m*l* of methanol was added dropwise slowly. After bromine was added, the solution was stirred for 10 min and then the crystals that separated out were collected (140 mg). When the

*2 All melting points are uncorrected. The microanalyses were carried out by Misses Noriko Matsukawa, Emiko Yoshida and Hiroko Hosokawa of this Institute, to whom the authors are indebted.

crystals were dissolved in water and the solution was neutralized with sodium carbonate, yellow crystals separated out. The recrystallization of these from ethanol gave 5-amino-4-bromo-2-methoxytropone (II); yield, 90 mg. Mp 182°C (dec.). ν_{max}^{KBr} cm^{-1}: 3290, 3160, 1632, 1615, 1550, 1488, 1450, 1240. λ_{max}^{MeOH} $m\mu$ (log ε): 242 (4.32), 354 (4.02), 390 (4.02).

Found: C, 39.18; H, 4.50; N, 5.47%. Calcd for $C_8H_8O_2NBr \cdot H_2O$: C, 38.70; H, 4.02; N, 5.60%.

Two Methyl Ethers of 5-Amino-4-isopropyltropolone (III). To a suspension of III (500 mg) in a small amount of methanol, an ethereal diazomethane was added until portions of the solution were no longer colored with ferric chloride, and then the solution was allowed to stand at room temperature overnight. Yellow needles that separated out were collected by decantation and washed with benzene-methanol. A brownish yellow oil obtained by evaporation of solvent from the supernatant was dried well and chromatographed on alumina by elution with chloroform. The first fraction gave 5-amino-6-isopropyl-2-methoxytropone (IV) as yellow crystals. The third fraction, which was obtained by elution with 1% ethanolic chloroform, gave a yellow oil that crystallized by addition of benzene. The resulting yellow needles were 5-amino-4-isopropyl-2-methoxytropone (V). The second part was chromatographed again to give IV and V.

IV: mp 224—225°C; yield, 200 mg. ν_{max}^{KBr} cm^{-1}: 3740, 3320, 3200, 1640, 1610, 1576, 1500.

Found: C, 68.32; H, 7.72; N, 7.49%. Calcd for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25%.

V: mp 138—140°C; yield, 100mg. ν_{max}^{KBr} cm^{-1}: 3410, 3350, 3240, 2970, 1644, 1622, 1578, 1530, 1490.

Found: C, 68.50; H, 7.83; N, 7.10%. Calcd for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25%.

Bromination of 5-Amino-6-isopropyl-2-methoxytropone (IV). Into a solution of IV (50 mg) in 1 m*l* of methanol, a solution of bromine (50 mg) in 0.5 m*l* of methanol was added dropwise on being cooled with ice-salt. After the solution was stirred for 10 min, the removal of the solvent gave a small amount of pale yellow crystals of 5-amino-4-bromo-6-isopropyl-2-methoxytropone (VI).

Two Methyl Ethers of 3-Aminotropolone (VII). A methanolic solution of VII (670 mg), to which ethereal diazomethane was added until the solution became negative to ferric chloride coloration, was held to stand overnight. After evaporation of the solvent, the resulting hygroscopic crystalline mixture was dried in a desiccator and chromatographed on alumina with chloroform. The removal of the solvent from the first eluate gave yellow crystals of 2-amino-7-methoxytropone (VIII), which were recrystallized from benzene-ether. A yellow oily mixture of VIII and IX was obtained by the elution with 5% ethanolic chloroform. Addition of a small amount of benzene to this mixture afforded yellow prisms, which were recrystallized from benzene-methanol to give 3-amino-2-methoxytropone (IX).

VIII: mp 118—119°C; yield, 160 mg. ν_{max}^{KBr} cm^{-1}: 3370, 3290, 3150, 1613, 1588, 1525. λ_{max}^{MeOH} $m\mu$(log ε): 250(4.44), 263(4.25), 273(4.14), 340(4.14), 400(3.97).

Found: C, 62.74; H, 5.98; N, 9.72%. Calcd for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.29%.

IX: mp 157°C; yield, 30 mg. ν_{max}^{KBr} cm^{-1}: 3370, 3300, 3170, 1630, 1578, 1512. $\lambda_{max}^{H_2O}$ $m\mu$ (log ε): 264 (4.52), 313(3.90), 323(3.83), 365(3.30).

Found: C, 63.35; H, 5.81; N, 9.10%. Calcd for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.29%.

Bromination of 2-Amino-7-methoxytropone (VIII). To a solution of VIII (200 mg) in 2 m*l* of methanol that was cooled with ice-water, 220 mg of bromine in methanol was added. After the mixture was allowed to stand in a refrigerator overnight, the solvent was removed off. The crystalline residue (HBr salt of X) was dissolved in water and the pH of the solution was adjusted to 4 with sodium bicarbonate, and then extracted with chloroform. The extract that had been dried over anhydrous sodium sulfate was passed through an alumina column. Yellow crystals that were obtained from the first fraction were recrystallized from methanol to give yellow prisms of 2-amino-3,5-dibromo-7-methoxytropone (X); 45 mg, mp 172°C. ν_{max}^{KBr} cm^{-1}: 3440, 3310, 1555, 1530, 1450, 1229. λ_{max}^{MeOH} $m\mu$(log ε): 266(4.26), 350(3.91), 418(3.70).

Found: C, 30.88; H, 2.73; N, 4.55%. Calcd for $C_8H_7O_2NBr_2$: C, 31.09; H, 2.27; N, 4.53%.

Spectral Measurements. Measurements of the normal NMR spectra were carried out by using a Varian A-60 NMR spectrometer. Decoupling experiments were carried out by the frequency sweep method, using a Hitachi H-60 NMR spectrometer with a decoupling unit. The saturating field intensities were 1.0—2.0 milligauss. The spectra were taken at 34°C. In the decoupling experiments coupling constants and chemical shifts were determined with an error of ± 0.1 Hz by a frequency counter in hexadeuterodimethyl sulfoxide with concentration of *ca.* 0.3 mmol per milliliter utilizing tetramethylsilane as an internal standard. The chemical shifts were given in ppm unit.

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