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# Studies on the Syntheses of Heterocyclic Compounds. CDXCIII.[1] Reaction of N-Ethoxycarbonyl-5-methoxytryptamine with Methyl Fluorosulfonate ("Magic Methyl")

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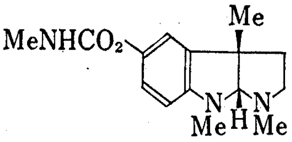
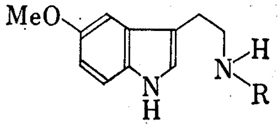
In the previous paper, we have already reported that methyl fluorosulfonate is a methylating agent,[3] and also a novel methylsulfonation reagent.[4] Thus, since we applied the reagent to tryptamine derivative, we here wish to report these results.

Supposing that the $\beta$-position of indole ring at first is electrophilically attacked by methyl or methoxysulfonyl group, followed by attacking of a lone pair of nitrogen of ethanamine side chain moiety to the $\alpha$-position of indole ring, the eserine (I) type compound would be synthesized in one step. Since 5-methoxytryptamine (II) has a primary amino group, we used N-ethoxycarbonyl-5-methoxytryptamine (III) derived from 5-methoxytryptamine (II) as a starting material in order to avoid its quaternarization.



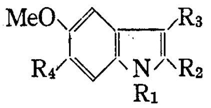
I



II : R=H

III : R=COOEt

Chart 1



IV: $R_1$=Me, $R_2$=$R_4$=H, $R_3$=$CH_2CH_2NHCOOEt$

V: $R_1$=Me, $R_2$=$CH_2CH_2\overset{+}{N}H(COOEt)(Me)$ $FSO_3^-$, $R_3$=$R_4$=H

VI: $R_1$=$R_2$=H, $R_3$=$CH_2CH_2NHCOOEt$, $R_4$=$SO_3Me$

VII: $R_1$=Me, $R_2$=$R_4$=H, $R_3$=$CH_2CH_2NHMe$

VIII: $R_1$=Me, $R_2$=$R_4$=H, $R_3$=$CH_2CH_2N(Me)(COOEt)$

Chart 2

Treatment of the amide (III) with almostly two equivalents of methyl fluorosulfonate in dichloromethane at room temperature afforded the compound (IV) and a rearranged product (V) as major products, besides, VI and unknown compound as minor products, which were separated by silica gel and preparative thick layer chromatography. The structure of V was confirmed by comparison with the compound (VIII) derived from IV.

To our best knowledge, two methods have been known as N-methylation of indole ring as yet.[5,6] Although we could not get the eserine (I) type compound, it was noteworthy that methyl fluorosulfonate acts as a very useful reagent for N-methylation of indole ring.

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1) Part CDXCII: T. Kametani, T. Honda, H. Shimanouchi, and Y. Sasada, *Chem. Commun.*, in press.

2) Location: *Aobayama, Sendai.*

3) M.G. Ahmed, R.W. Alder, G.H. James, M.L. Sinnott, and M.C. Whiting, *Chem. Commun.*, **1968**, 1533.

4) T. Kametani, K. Takahashi, and K. Ogasawara, *Synthesis*, in press.

5) R. Weissgerber, *Ber.*, **43**, 3522 (1910); A.P. Gray, *J. Am. Chem. Soc.*, **75**, 1253 (1953).

6) T. Kunieda and B. Witkop, *J. Org. Chem.*, **35**, 3981 (1970).

## Experimental[7]

**N-Ethoxycarbonyl-5-methoxytryptamine (III)**——To a mixture of 1.5 g of 5-methoxytryptamine (II), 4 g of triethylamine and 50 ml of benzene was added dropwise 2.3 g of ethyl chlorocarbonate with stirring and the mixture was stirred at room temperature for 1 hr. The mixture was washed with 5% HCl and saturated NaCl solution, and the benzene layer was dried over $K_2CO_3$ and evaporated to afford 2.2 g of III as a brownish oil, which could not be crystallized and was used in the following reaction without purification. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm$^{-1}$: 3400 (indole NH) and 1695 (amide C=O). NMR (in $CDCl_3$) $\delta$ (ppm): 1.20 ($CH_2C\underline{H}_3$, 3H, triplet, $J=7$ Hz), 2.85 ($CH_2C\underline{H}_2N\langle$, 2H, triplet, $J=6$ Hz), 3.40 ($C\underline{H}_2CH_2N\langle$, 2H, triplet, $J=6$ Hz), 3.80 ($OC\underline{H}_3$, 3H, singlet), 4.08 ($C\underline{H}_2CH_3$, 2H, quartet, $J=7$ Hz), 4.70—5.10 ($N\underline{H}$, 1H, exchanged with $D_2O$), 6.77 ($C_6$-$\underline{H}$, 1H, a pair of doublets, $J=8$ and 2.5 Hz), 6.87 ($C_2$-$\underline{H}$, 1H, singlet), 6.98 ($C_4$-$\underline{H}$, 1H, doublet, $J=2.5$ Hz), 7.15 ($C_7$-$\underline{H}$, 1H, doublet, $J=8$ Hz), 8.4—8.7 ($N\underline{H}$ of indole ring, exchanged with $D_2O$).

**The Reaction of III with Methyl Fluorosulfonate**——To a solution of 1.3 g of III in 2 ml of $CH_2Cl_2$ was added dropwise 1.2 g of methyl fluorosulfonate with stirring at room temperature for 24 hr. The reaction mixture was then basified with 10% $NH_4OH$ and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated NaCl solution, dried over $Na_2SO_4$, and evaporated to leave 1.6 g of a brown syrup, which was chromatographed on 20 g of silica gel. Evaporation of the benzene eluate gave 350 mg of a pale yellowish residue, which was purified with preparative thick layer chromatography to afford 300 mg of IV. *Anal.* Calcd. for $C_{15}H_{20}O_3N_2$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.48; H, 7.48; N, 10.07. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm$^{-1}$: 3350 (amide NH) and 1695 (amide C=O). NMR (in $CDCl_3$) $\delta$ (ppm): 1.23 ($CH_2C\underline{H}_3$, 3H, triplet, $J=7$ Hz), 2.90 ($CH_2C\underline{H}_2N\langle$, 2H, triplet, $J=6$ Hz), 3.40 ($C\underline{H}_2CH_2N\langle$, 2H, triplet, $J=6$ Hz), 3.70 (N-$C\underline{H}_3$, 3H, singlet), 3.85 ($OC\underline{H}_3$, 3H, singlet), 4.12 ($C\underline{H}_2CH_3$, 2H, quartet, $J=7$ Hz), 4.60—5.00 ($N\underline{H}$, 1H, exchanged with $D_2O$), 6.85 ($C_6$-$\underline{H}$, 1H, a pair of doublets, $J=8$ and 2.5 Hz), 6.82 ($C_2$-$\underline{H}$, 1H, singlet), 7.01 ($C_4$-$\underline{H}$, 1H, doublet, $J=2.5$ Hz), 7.17 ($C_7$-$\underline{H}$, 1H, doublet, $J=8$ Hz). Mass Spectrum *m/e*: 276 ($M^+$), 231, 187, 174, 159, 131.

Evaporation of the $CHCl_3$ eluate gave 68 mg of a yellow syrup, which was purified by preparative thick layer chromatography to afford 50 mg of VI. *Anal.* Calcd. for $C_{15}H_{20}O_6N_2S$: C, 50.60; H, 5.66. Found: C, 50.99; H, 5.97. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm$^{-1}$: 3360 (indole NH), 1695 (amide C=O), 1340, 1160 ($SO_2$). NMR (in $CDCl_3$) $\delta$ (ppm): 1.22 ($CH_2C\underline{H}_3$, 3H, triplet, $J=7$ Hz), 2.90 ($CH_2C\underline{H}_2N\langle$, 2H, triplet, $J=6$ Hz), 3.40 ($C\underline{H}_2CH_2N\langle$, 2H, triplet, $J=6$ Hz), 3.80 ($SO_3C\underline{H}_3$, 3H, singlet), 3.95 ($OC\underline{H}_3$, 3H, singlet), 4.12 ($C\underline{H}_2CH_3$, 2H, quartet, $J=7$ Hz), 4.7—5.0 ($N\underline{H}$, 1H, exchanged with $D_2O$), 7.10 ($C_2$-$\underline{H}$, 1H, singlet), 7.34 ($C_4$-$\underline{H}$, 1H, singlet), 8.0 ($C_7$-$\underline{H}$, 1H, singlet), 8.8—9.1 ($N\underline{H}$ of indole ring, exchanged with $D_2O$). Mass Spectrum *m/e*: 356, 311, 267, 260, 254, 160.

Evaporation of the $CHCl_3$–MeOH (1:1) eluate gave 600 mg of a pale yellow syrup, the recrystallization of which from MeOH–ether afforded 550 mg of V as a colorless powder, mp 169—172°. *Anal.* Calcd. for $C_{16}H_{23}O_6N_2SF \cdot H_2O$: C, 47.10; H, 5.68; N, 6.87. Found: C, 47.12; H, 5.81; N, 6.78. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm$^{-1}$: 1700 (C=O), 1600 (C=C), 1340, 1170 ($SO_2$). NMR (in $CDCl_3$) $\delta$ (ppm): 1.33 ($CH_2C\underline{H}_3$, 3H, triplet, $J=7$ Hz), 3.0—3.3 ($CH_2C\underline{H}_2$-$N^+\langle$, 2H, multiplet), 3.38 ($C\underline{H}_3$-$N^+\langle$, 3H, singlet), 3.62 (N-$C\underline{H}_3$, 3H, singlet), 3.50—3.70 ($C\underline{H}_2$-$CH_2$-$N^+\langle$, 2H, multiplet), 3.80 ($OC\underline{H}_3$, 3H, singlet), 4.25 ($C\underline{H}_2CH_3$, 2H, quartet, $J=7$ Hz), 6.32 ($C_3$-$\underline{H}$, 1H, singlet), 6.96 ($C_6$-H, 1H, a pair of doublets, $J=9$ and 2.5 Hz), 7.24 ($C_4$-H, 1H, doublet, $J=2.5$ Hz), 7.72 ($C_7$-H, 1H, doublet, $J=9$ Hz). Mass Spectrum *m/e*: 290 ($M^+$-$FSO_3H$), 276 ($M^+$-$FSO_3Me$), 245, 231, 187, 174, 159, 131, 116. IR spectrum and thin-layer chromatogram of free base of V were not identical with those of VIII derived from V.

**The Preparation of VIII**——To a stirred suspension of 150 ml of $LiAlH_4$ in 10 ml of dry tetrahydrofuran (THF) was added dropwise a solution of 48 mg of amide (IV) in 2 ml of dry THF and the mixture was gently heated under reflux for 4 hr. The excess of $LiAlH_4$ was decomposed with wet ether and the mixture was stirred with a small amount of water. After filtration, the filtrate was evaporated to leave an oil, which was extracted with ether. The extract was washed with saturated NaCl solution, dried over $K_2CO_3$, and evaporated to afford 30 mg of a yellowish-brown syrup, which was purified with preparative thick layer chromatography on silica gel to afford 25 mg of VII as a pale yellow syrup. In the IR spectrum ($CHCl_3$) of VII, NH band due to indole ring was not observed at 3360—3400 cm$^{-1}$. NMR (in $CDCl_3$) $\delta$ (ppm): 2.46 ($NC\underline{H}_3$, 3H, singlet), 2.95 ($C\underline{H}_2C\underline{H}_2N\langle$, 4H, singlet), 3.66 ($NC\underline{H}_3$, 3H, singlet), 3.82 ($OC\underline{H}_3$, 3H, singlet), 6.80—7.10 (Ar-H, 4H, multiplet). Mass Spectrum *m/e*: 218 ($M^+$).

To a mixture of 20 mg of VII, 0.5 g of triethylamine and 3 ml of benzene was added dropwise 0.5 g of ethyl chlorocarbonate with stirring and the mixture was stirred at room temperature for 1 hr. The mixture was washed with 5% HCl and saturated NaCl solution, and the benzene layer was dried over $K_2CO_3$ and evaporated to afford 20 mg of a yellowish-brown syrup, which was purified with preparative thick layer chromatography on silica gel to afford 17 mg of VIII as a pale yellow syrup. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm$^{-1}$: 1670 (amide C=O). NMR (in $CDCl_3$) $\delta$ (ppm): 1.21 ($CH_2C\underline{H}_3$, 3H, triplet, $J=7$ Hz), 2.87 ($NC\underline{H}_3$, 3H, singlet), 2.90 ($CH_2$-

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[7] Infrared (IR) spectra were recorded on a type EPI-S2 Hitachi recording spectrometer in $CHCl_3$ solution. Nuclear magnetic resonance (NMR) spectra were measured on a Hitachi H-60 instrument. Mass spectra were measured on a Hitachi RMU-7 mass spectrometer.

$CH_2N\langle$, 2H, triplet, $J=6$ Hz), 3.45 ($CH_2CH_2N\langle$, 2H, triplet, $J=6$ Hz), 6.70—7.20 (Ar-H, 4H, multiplet). Mass Spectrum $m/e$: 290 ($M^+$).

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# Quantitative Analysis of Pharmaceutical Preparations by X-Ray Diffractometry. X.[1] Direct Quantitative X-Ray Diffraction Analysis of Ethionamide in Rectal Suppositories

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In the preceding paper,[1] the direct X-ray diffraction analysis was reported which seems to be useful for the assay of salicylic acid in plasters. The use of this assay method was successful in the determination of ethionamide (2-ethyl-thioisonicotinamide) in a rectal suppository, and it was found that this procedure is rapid and reliable.

## Experimental

**X-Ray Equipment**——For the experimental work, a Rigakudenki Geigerflex diffractometer was used. X-Ray source was a copper-target X-ray tube with a Ni-foil filter. The slit system used in this work was a divergence slit 1°, scatter slit 1°, and recieving slit 0.3 mm. The time constant of rate-meter was 2 sec. A Geiger Müller tube was used as a detection device. The scanning speed of goniometer was 1/4° (2$\theta$) per minute, and the chart speed was adjusted to be 2 cm/min throughout this work.

**Preparation of Standard Rectal Suppositories**——Known amounts of ethionamide and suppository bases were weighed accurately. For the suppository bases, 8 parts of polyethylene glycol 4000 and 2 parts of polyethylene glycol 400 were used. The mixture was melted on a water bath and poured into the hinged suppository molds cooled in blocks of ice.

**Quantitative Analysis of Ethionamide in Suppositories**——The rectal suppository was placed on the center of a cardboard (a backing) and covered with a sheet of cellophane paper (a facing), and pressed with a hydraulic press under various molding pressure at 40° for 5 min. The cellophane paper was stripped off and the cardboard was cut to size of about 3.5×6.0 cm and placed in the sepcially designed sample holder made of Bakelite, which was reported in the preceding paper.[1] The holder was set on the diffractometer and scanned.

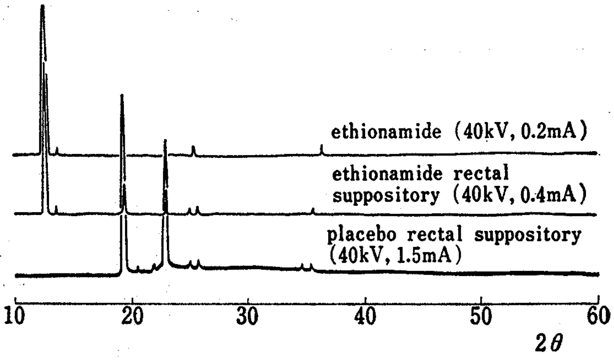

Fig. 1. X-Ray Diffraction Patterns of Ethionamide, Ethionamide Rectal Suppository, and Placebo Rectal Suppository

The diffraction patterns of powdered ethionamide, placebo rectal suppository, and ethion-

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[1] Part IX: K. Kuroda, G. Hashizume, and F. Kume, *Chem. Pharm. Bull.* (Tokyo), 17, 818 (1969).

[2] Location: *a) Kusunoki-cho, Ikuta-ku, Kobe, 650, Japan; b) Yukihira-cho, Suma-ku, Kobe, 654, Japan.*