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Reactions of 2-Hydroxytryptophol: Results of Strong Acid and Alkaline Treatments of 2-Hydroxytryptophol

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Upon being warmed at 90 °C in trifluoromethanesulfonic acid for 42—78 h, 2-hydroxytryptophol (**4a**) gave 3-ethylideneoxidoles (*E*- and *Z*-form) (**5a**), while 3-methyl- (**4b**) or 3-ethyl-2-hydroxytryptophol (**4c**) gave the corresponding 3-alkylideneoxindoles (**5b**, **5c**) and 3,4-dialkylcarbostyrils ($\mathbf{6}_{I\text{-}b,c}$, $\mathbf{6}_{II\text{-}c}$).

On tosylation in pyridine, **4a** gave spiro-(3)-cyclopropane-(**8**) and 3-chloroethyl-oxindole (**10**), and the corresponding tosylate (**7a**), but **4b** and **4c** gave only the corresponding tosylates (**7b**, **7c**).

The tosylate **7a** and the chloroethyl compound **10** reacted in alkaline ethanol to afford the spiro compound **8**, whereas the tosylates **7b**, **7c** gave 2-ethoxy-3-methyl (or ethyl)-3-hydroxyethylindolenines (**9b**, **9c**) under the same conditions.

Keywords——2-hydroxytryptophol; 3-alkyl-2-hydroxytryptophol; trifluoromethanesulfonic acid; 3-alkylideneoxindole; 3,4-dialkylcarbostyril; 2-ethoxyindolenine; tosylation; alkaline; solvolysis; Wagner–Meerwein rearrangement

In the structural study of uncarine and rhyncophylline, the neutral crystals, $C_{10}H_9NO$, obtained *in vacuo* by dehydrogenation with palladium[1] or by heating uncarine methiodide,[1] were assumed to be 2,3-dihydrofuro[2,3,*b*]indole[2] (**1**) at that time. However, **1** was later confirmed to be spiro-(3)-cyclopropaneoxindole (**8**).[3] The synthesis of **1** was attempted by Julian[4] and Kondo.[5a] We also attempted to obtain **1** through catalytic reduction of α-(*o*-nitrophenyl)-γ-butyrolactone (**3a**) in the previous paper,[6] but unexpectedly 2-hydroxytryptophol (**4a**) was produced by ring transformation; the preparation of **1** has not yet been reported.

As an extension of this work, we examined the reaction of 2-hydroxytryptophol (**4a**) with strong acid and alkali. Although **1** was not obtained, the results were interesting. Similarly, 3-methyl- (or ethyl)-2-hydroxytryptophols (**4b**, **4c**) were treated with the same reagents.

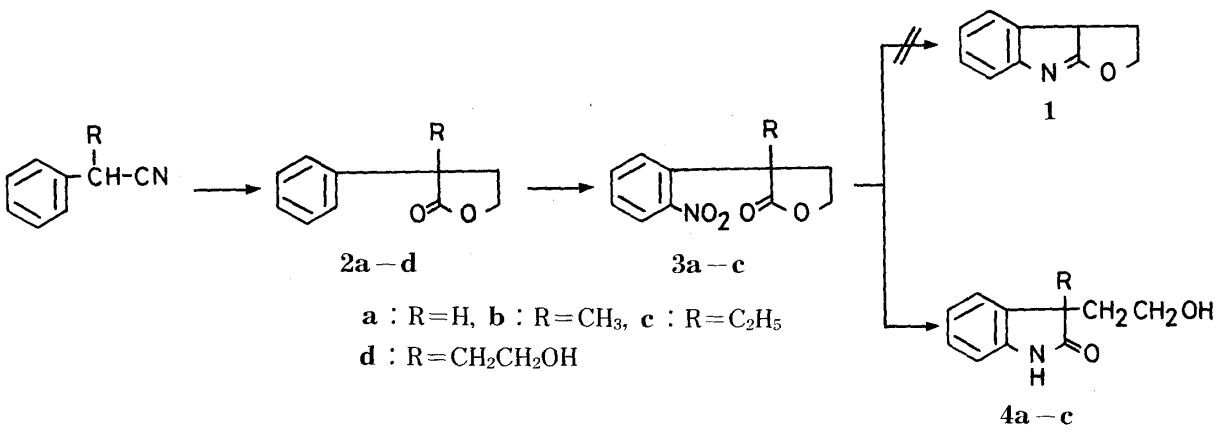

Chart 1

TABLE I. Yields of **2b**, **2d**, **3b** and **4b**

Compound No.	mp (°C)	Yield (%)	Compound No.	mp (°C)	Yield (%)
2b	[a]	38.0	**3b**	109—110	6.0[c]
2d	77[b]	9.8	**4b**	127—128	89.0[d]

a) bp 125—131 °C (2.6 mmHg). *b*) bp 174—178 °C (0.12 mmHg).
c) Chromatographed on silica with PhH–EtOAc (19:1). *p*-Isomer: mp 123—124 °C (yield 47.5%).
d) Chromatographed on silica with EtOAc.

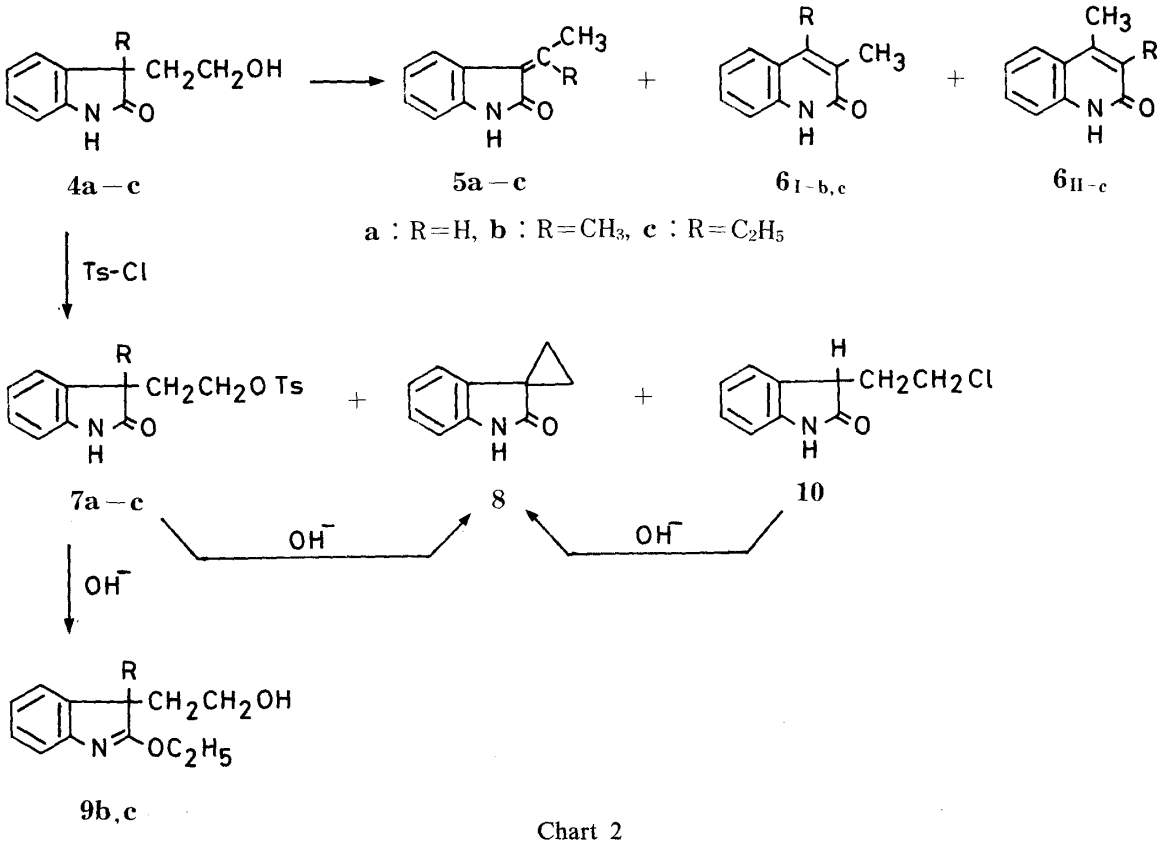

Chart 2

TABLE II. Reaction of **4a—c** with TFSA at 90 °C

Compound No.	Time (h)	Product No.	Yield (%)	mp (°C)
4a	42	**5a**-*E*	16.6	143—148[d]
		5a-*Z*	7.5	169—171[e]
4b	40	**5b**	45.3[b]	193—194[f]
		$\mathbf{6}_{\text{I-b}}$	21.6[b]	276—277[g]
4c	74	**5c**[a]	62.2[c]	—
		$\mathbf{6}_{\text{I-c}}$	14.9[c]	184—187[h]
		$\mathbf{6}_{\text{II-c}}$	3.1[c]	232—234[i]

a) A mixture of *E*- and *Z*-isomer (2:1) from the NMR spectrum.
b) Extracted with CH_2Cl_2. Chromatographed on silica with EtOAc.
c) Chromatographed on silica with *n*-hexane–EtOAc (1:1).
d) Lit.[5] 147—148.5 °C. *e*) Lit.[5] 173—174 °C.
f) Lit.[10] 189—190 °C. *g*) Lit.[7a] 269—270 °C.
h) Lit.[7a] 188.5—190 °C. *i*) Lit.[7b] 228—229 °C.

Compounds **4a**—**c** were prepared according to our previous method,[6] as shown in Chart 1. In the reaction of phenylacetonitrile with ethylene oxide to obtain **2a**, α-(2-hydroxyethyl)-α-phenyl-γ-butyrolactone (**2d**) was isolated as a by-product in 9.8% yield. The new results are summarized in Table I.

When **4a** was treated with a strong acid, trifluoromethanesulfonic acid (TFSA), at 90 °C, 3-ethylideneoxindoles (**5a**-*E* and **5a**-*Z*) were obtained. The structures of **5a**-*E* and **5a**-*Z* were confirmed by direct comparison with authentic samples[5] [infrared (IR) spectra and mixed mp].

However, alkyl migration was observed in the reactions of **4b** and **4c** with TFSA. The reaction of **4b** with TFSA gave 3-isopropylideneoxindole (**5b**) and 3,4-dimethylcarbostyril ($\mathbf{6}_{\text{I-b}}$). Similarly, **4c** gave 3-methyl-4-ethylcarbostyril ($\mathbf{6}_{\text{I-c}}$), 3-ethyl-4-methylcarbostyril ($\mathbf{6}_{\text{II-c}}$), and a mixture of 3-(2-butylidene)oxindoles (**5c**-*E* and **5c**-*Z*). The structures of $\mathbf{6}_{\text{I-b}}$, $\mathbf{6}_{\text{I-c}}$, and $\mathbf{6}_{\text{II-c}}$ were confirmed by direct comparison with authentic samples[7a,b] [thin layer chromatography (TLC), IR, and mixed mp] and that of **5b** was supported by spectral data [IR, ultraviolet (UV), and nuclear magnetic resonance (NMR) spectra, and mass spectrum (MS)][10] (Chart 2). The results are summarized in Table II.

On the other hand, **4a**—**c** did not react upon alkaline treatment (5% KOH–EtOH). Therefore, we attempted to obtain the tosylates (**7a**—**c**). At room temperature, **4a** was reacted with 2 mol of tosyl chloride (Ts-Cl) in anhydrous pyridine to give three products, **10** and a mixture of **7a** and **8**, whereas in an ice bath **4a** gave predominantly **7a** together with **8** and **10**. Compounds **4b** and **4c** afforded only the tosylates (**7b**, **7c**) in an ice bath under similar conditions (Chart 2). The results are summarized in Table III.

Compound **7a** was refluxed with 5% KOH–EtOH to yield the spiro-cyclo compound **8**, which was also formed from 3-chloroethyl-oxindole (**10**) under similar conditions. The structure of **8** was confirmed by direct comparison with an authentic sample[3] (TLC, IR, and

Table III. Reaction of **4a**—**c** with Ts-Cl in an Ice Bath

Compound No.	Time (h)	Yield (%)		
		7	**8**	**10**
4a	15.0[a]	4.1[b]		12.6
	1.5	53.9	11.5	0.5
4b	7.0	58.9	—	—
4c	7.0[c]	94.9	—	—

a) At room temperature.
b) A mixture of **7** and **8** (1 : 2.5) from the NMR spectrum.
c) Subsequently left to stand for 2 d in a refrigerator. Extracted with EtOAc.

Table IV. Reaction of **7a**—**c** and **10** with 5% KOH–EtOH (Refluxed)

Compound No.	Time (h)	Yield (%)	
		8	**9**
7a	4.0	43.1	—
7b	1.0	—	68.0
7c	1.0	—	90.0[a]
10	1.5	63.8	—

a) Chromatographed on silica with *n*-hexane–EtOAc (1 : 2).

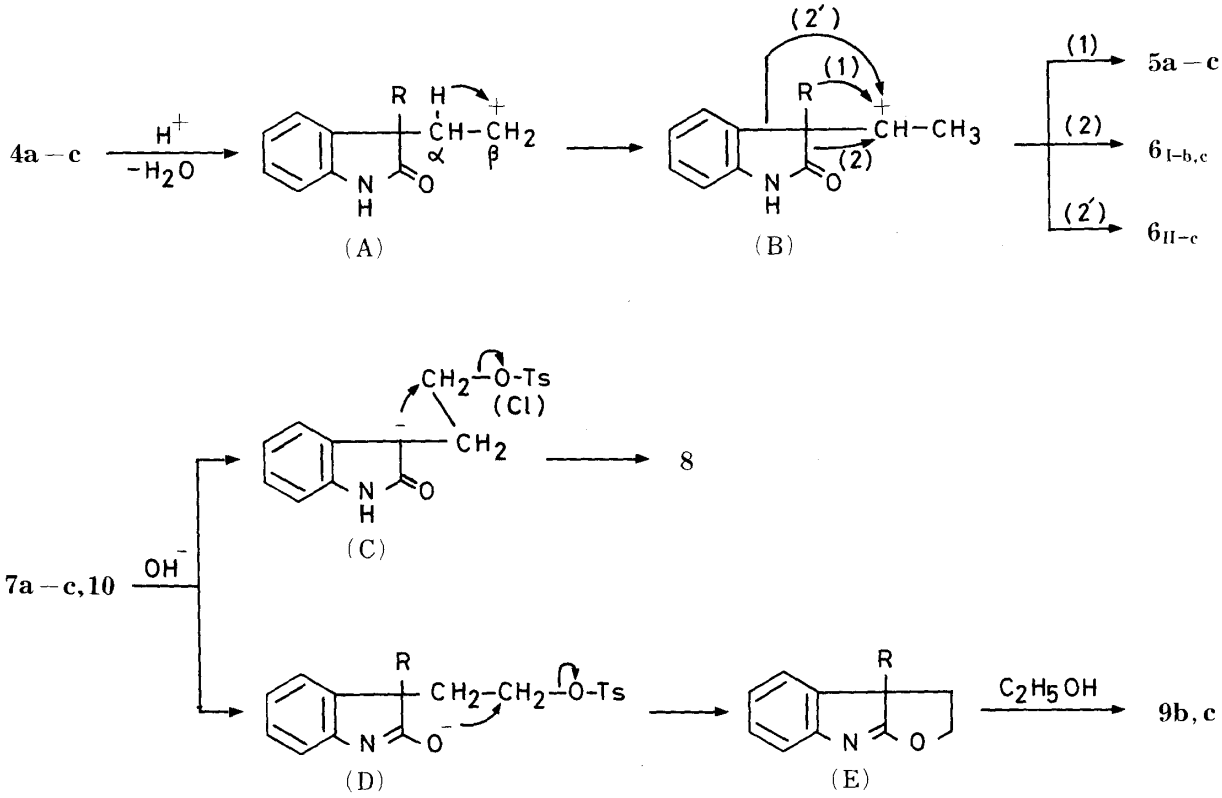

Chart 3

MS). On the other hand, **7b** and **7c**, with a methyl or ethyl group at C-3 of the oxindole ring, gave compounds of the 2-ethoxyindolenine type (**9b**, **9c**) (Chart 2). The structures of **9b** and **9c** were supported by spectral data (MS, IR, NMR, and UV). The results are summarized in Table IV.

The formation of **5a**—**c**, $\mathbf{6}_{\text{I-b,c}}$ and $\mathbf{6}_{\text{II-c}}$ by treatment of **4a**—**c** with TFSA may be interpreted as follows: a carbonium ion (A) was produced from **4a**—**c**, followed by hydride ion rearrangement from α-C to β-C, giving a secondary carbonium ion (B). Then **5a**—**c** were produced by rearrangement of R to α-C, followed by deprotonation (path 1: Wagner–Meerwein rearrangement[11]). On the other hand, $\mathbf{6}_{\text{I-b,c}}$ or $\mathbf{6}_{\text{II-c}}$ was formed by opening of the C-2–C-3 bond (path 2) or the C-3—C-4a bond (path 2′), followed by deprotonation (Chart 3).

The formation of **8** on treatment of **7a** or **10** with 5% KOH–EtOH may be interpreted as follows: the anion (C) was produced from **7a** or **10**, followed by nucleophilic displacement at β-C to give **8**. In the case of **7b** or **7c**, the enol anion (D) might be formed to yield furoindolenine (E) by the attack of the anion on β-C with elimination of the tosyl group. The intermediate (E) could not be isolated and presumably afforded **9b** or **9c** by solvolysis, because it might be unstable under the reaction conditions used (Chart 3). Although the above attempts to obtain **1** from 2-hydroxytryptophol met with failure, further studies are in progress.

Experimental

All melting points were measured with a microscope (Yanaco MP-S2) and are uncorrected. UV spectra were recorded on a Hitachi 200-20 spectrophotometer and IR spectra on a JASCO IRA-1 spectrophotometer. NMR spectra were taken with a JEOL PS-100 machine using tetramethylsilane as an internal standard. MS were determined with a JEOL-01SG-2 instrument.

The abbreviations used are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, Ts=tosyl.

TABLE V. Physical Properties of **2b**, **2d**, **3b**, **3b-p** and **4b**

Compound No.	Formula	Analysis (%) Calcd (Found)			IR (KBr, cm^{-1})	MS *m/e* M^+, (100%)
		C	H	N		
2b	$C_{11}H_{12}O_2$		[c]		1735[a]	176 (117)
2d	$C_{12}H_{14}O_3$	69.88 (69.61	6.84 6.91)		3438, 1738	206 (117)
3b	$C_{11}H_{11}NO_4$	59.72 (59.79	5.01 5.03	6.33 6.17)	1758, 1515, 1360	221 (91)
3b-p[b]	$C_{11}H_{11}NO_4$	59.72 (59.54	5.01 5.05	6.33 6.19)	1758, 1520, 1350	221 (116)
4b	$C_{11}H_{13}NO_2$	69.09 (69.16	6.85 6.88	7.33 7.29)	3160, 1718	191 (147)

a) Neat. *b*) *p*-Isomer of **3b**. *c*) High resolution mass: 176.0840 (Calcd: 176.0838).

TABLE VI. Physical Properties of **7a—c**, **9b—c** and **10**

Compound No.	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)			IR (KBr cm^{-1})	UV λ_{max}^{EtOH} nm (log ε)	MS M^+ *m/e* (100%)
			C	H	N			
7a	115—116 (CH_2Cl_2–*n*-hexane)	$C_{17}H_{17}NO_4S$	61.61 (61.38	5.17 5.20	4.22 4.28)	3380 1700 1330 1162		331 (159)
7b	Oil	$C_{18}H_{19}NO_4S$		[a]		3430[d] 1715 1365 1175	227 (4.10) 250 (3.88)	345 (146)
7c	134—137 (CH_2Cl_2–*n*-hexane)	$C_{19}H_{21}NO_4S$	63.50 (63.55	5.88 5.94	3.90 3.67)	3400 1700 1355 1171	226 (3.98) 251 (3.76)	359 (158)
9b	109—110 (EtOAc–*n*-hexane)	$C_{13}H_{17}NO_2$	71.21 (71.30	7.80 7.90	6.38[b] 6.32)	3340 1610 1570	254[e] (3.85)	219 (147)
9c	Oil	$C_{14}H_{19}NO_2$		[c]		3400[d] 1620 1570	256[e] (3.62)	233 (161)
10	116 (CH_2Cl_2–*n*-hexane)	$C_{10}H_{10}ClNO$	61.38 (61.00	5.15 5.01	7.16 6.88)	3430 1680		197 (M^++2) 195 (133)

a) High resolution mass: 345.1059 (Calcd: 345.1036).
b) High resolution mass: 219.1264 (Calcd: 219.1259).
c) High resolution mass: 233.1427 (Calcd: 233.1416).
d) In $CHCl_3$ solution.
e) 2,3-Dimethyl-2-ethoxyindolenine[8]: UV λ_{max} 253 nm (log ε: 3.88).

α-Phenyl-γ-butyrolactone (2a) and α-Hydroxyethyl-α-phenyl-γ-butyrolactone (2d)——**2a** was obtained from the reaction of phenylacetonitrile (80 g, 0.68 mol) with ethylene oxide (30 g, 0.68 mol) in 34.7% yield. After **2a** had been distilled off, the residue was redistilled *in vacuo* to give 13.75 g (9.8%) of **2d** as a viscous liquid. After a while, **2d** solidified (white prisms from MeOH).

α-Methyl-α-phenyl-γ-butyrolactone (2b)——α-Phenylpropionitrile (21.4 g, 0.16 mol) was treated with ethylene oxide (7.16 g, 0.16 mol) to yield 11.01 g (38%) of **2b** as a colorless liquid.

α-(*o*- or *p*-Nitrophenyl)-α-methyl-γ-butyrolactone (3b, 3b-p)——**2b** (7.04 g, 40 mmol) was treated in acetic anhydride with fuming HNO_3 ($d=1.52$) to give a mixture of the *p*- and *o*-nitro compounds in 5.79 g (65.5%) yield. The mixture was recrystallized from benzene to afford 4.2 g (47.5%) of the *p*-nitro compound (**3b-p**). The mother liquor was chromatographed on silica to yield 528 mg (6.0%) of **3b** and 514 mg (5.8%) of a mixture of **3b** and **3b-p**.

3-Methyl-2-hydroxytryptophol (4b)——A solution of **3b** (221 mg, 1 mmol) in EtOH was hydrogenated at atmospheric pressure with 10% palladium on charcoal until the uptake of hydrogen ceased. After removal of the catalyst, evaporation of the solvent, and chromatography of the residue on silica, 170 mg (89%) of **4b** was obtained as colorless crystals from ethyl acetate. Elemental analysis, IR, and MS data for **2b**, **2d**, **3b**, and **4b** are summarized in Table V. NMR spectral data are summarized in Table VII.

General Procedure for the Reaction of 4 with TFSA——Typical Example: A solution of **4a** (190.9 mg, 1.08 mmol) in TFSA (1.2 ml) was stirred at 90 °C for 42 h under nitrogen. The reaction mixture was poured into ice water and

TABLE VII. Proton Nuclear Magnetic Resonance Data for **2**—**10**

Compound No.	δ (ppm), J (Hz)[a]
2b	1.56 (3H, s, $-C\underline{H}_3$), 2.14—2.70 (2H, m, $-C\underline{H}_2-CH_2-O-$), 3.90—4.34 (2H, m, $-C\underline{H}_2-O-$)
2d	2.17 (2H, t, $J=6.5$, $-C\underline{H}_2-$), 2.43 (1H, s, $-O\underline{H}$), 3.56 (2H, t, $J=6.5$, $-C\underline{H}_2-OH$)
3b	1.82 (3H, s, $-C\underline{H}_3$), 2.18—2.46 (1H, m) and 2.91—3.04 (1H, tt, $J=10$) ($-C\underline{H}_2-CH_2-O-$), 4.38—4.78 (2H, m, $-C\underline{H}_2-O-$)
3b-p	1.68 (3H, s, $-C\underline{H}_3$), 2.38—2.90 (2H, m, $-C\underline{H}_2-CH_2-O-$), 4.12—4.57 (2H, m, $-C\underline{H}_2-O-$), 7.64 (2H, d, $J=9$, Ph), 8.20 (2H, d, $J=9$, Ph)
4b[b]	1.20 (3H, s, $-C\underline{H}_3$), 1.87 (2H, t, $J=8$, $-C\underline{H}_2-$), 3.04 (2H, m, $-C\underline{H}_2-O-$), 4.24 (1H, t, $J=6$, $-O\underline{H}$), 10.22 (1H, br, $-N\underline{H}-$)
7a	2.26 (2H, q, $J=6$, $-C\underline{H}_2-CH_2-$), 2.43 (3H, s, $-C\underline{H}_3$), 3.50 (1H, t, $J=6$, $>C\underline{H}-$), 4.27 (2H, t, $J=6$, $-C\underline{H}_2-O-$), 7.30 (2H, d, $J=9$, Ph), 7.75 (2H, d, $J=9$, Ph), 8.86 (1H, br, $-N\underline{H}-$)
7b	1.35 (3H, s, $-C\underline{H}_3$), 2.13 and 2.25 (each 1H, t, $J=7$, $-C\underline{H}_2-CH_2-O-$), 2.36 (3H, s, $Ph-C\underline{H}_3$), 3.82 (2H, t, $J=7$, $-C\underline{H}_2-O-Ts$), 7.24 (2H, d, $J=8$, Ph), 7.60 (2H, d, $J=8$, Ph), 8.62 (1H, br, $-N\underline{H}-$)
7c	0.62 (3H, t, $J=7$, $-CH_2-C\underline{H}_3$), 1.78 (2H, m, $-C\underline{H}_2-CH_3$), 2.14 and 2.25 (each 1H, t, $J=7$, $-C\underline{H}_2-CH_2-O-$), 2.41 (3H, s, $Ph-C\underline{H}_3$), 3.86 (2H, t, $J=7$, $-C\underline{H}_2-O-Ts$), 7.26 (2H, d, $J=9$, Ph), 7.64 (2H, d, $J=9$, Ph), 8.63 (1H, br, $-N\underline{H}-$)
8	1.50 (2H, q, $J=3.5$, cyclo-$C\underline{H}_2-$), 1.72 (2H, q, $J=3.5$, cyclo-$C\underline{H}_2-$), 9.08 (1H, br, $-N\underline{H}-$)
9b	1.32 (3H, s, $-C\underline{H}_3$), 1.38 (3H, t, $J=7$, $-O-CH_2-C\underline{H}_3$), 1.65 (1H, br, $-CH_2-O\underline{H}$), 2.08 and 2.10 (each 1H, t, $J=7$, $-C\underline{H}_2CH_2OH$), 3.26 (2H, t, $J=7$, $-C\underline{H}_2-OH$), 4.41 (2H, q, $J=7$, $-O-C\underline{H}_2-CH_3$)
9c	0.50 (3H, t, $J=7$, $-CH_2-C\underline{H}_3$), 1.42 (3H, t, $J=7$, $-O-CH_2-C\underline{H}_3$), 1.84 (2H, q, $J=7$, $>C-C\underline{H}_2-CH_3$), 2.10 (2H, t, $J=7$, $-C\underline{H}_2-CH_2OH$), 3.25 (2H, t, $J=7$, $-C\underline{H}_2OH$), 4.45 (2H, q, $J=7$, $-O-C\underline{H}_2-CH_3$)
10	2.35 (2H, q, $J=7.5$, $-C\underline{H}_2-CH_2-$), 3.71 (3H, m, $J=7.5$ and 3, $>C\underline{H}-$, $-C\underline{H}_2-Cl$), 8.2—8.8 (1H, br, $-N\underline{H}-$)

a) In $CDCl_3$ solution unless otherwise noted. b) In DMSO-d_6 solution.

extracted with ethyl acetate. The extract was washed with 5% K_2CO_3 and H_2O, and dried over anhydrous Na_2SO_4. The solvent was evaporated off *in vacuo* to leave 140.4 mg of a mixture, which was chromatographed on silica with benzene–ethyl acetate (1 : 1) to obtain 12.9 mg (7.5%) of **5a**-*Z*, 28.5 mg (16.6%) of **5a**-*E*, and 125.6 mg (65.8%) of recovered **4a**.

General Procedure for the Reaction of 4 with Ts-Cl——Typical Example: A solution of **4a** (365.3 mg, 2.06 mmol) and Ts-Cl (751.3 mg, 3.94 mmol) in anhydrous pyridine (5 ml) was stirred in an ice bath for 1.5 h. The mixture was poured into ice water and extracted with CH_2Cl_2. The extract was washed with 10% HCl, H_2O, and 10% K_2CO_3, and dried over anhydrous Na_2SO_4. The solvent was evaporated off *in vacuo* to leave the crude product, which was recrystallized from CH_2Cl_2–*n*-hexane to yield 122.6 mg (18.0%) of **7a** as white crystals. The mother liquor was chromatographed on silica with *n*-hexane–ethyl acetate (2 : 1) to afford 2.1 mg (0.5%) of **10** as the first fraction, 37.7 mg (11.5%) of **8**, and 245.0 mg (53.9%) of **7a** as the last fraction. Elemental analysis, IR, and MS data for **7a**, **7b**, and **7c** are summarized in Table VI. NMR spectra data are summarized in Table VII.

General Procedure for the Reaction of 7 with 5% KOH–EtOH——Typical Example: A solution of **7a** (41.2 mg, 0.12 mmol) in 5% KOH–EtOH (5 ml) was refluxed for 4 h. The solvent was evaporated off *in vacuo*. The residue was mixed with water, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The crude product was recrystallized from ethyl acetate to give 8.1 mg (43.1%) of **8**. Elemental analysis, IR, and MS data for **9b**, **9c**, and **10** are summarized in Table VI. NMR spectra data are summarized in Table VII.

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References and Notes

1) H. Kondo and T. Nozoye, *Itsuu Kenkyusho Nempo*, **1**, 71 (1950).
2) T. Ikeda, *Yakugaku Zasshi*, **63**, 393 (1943).
3) H. Kondo, T. Nozoye and M. Tobita, *Itsuu Kenkyusho Nempo*, **5**, 80 (1954); H. Kondo, T. Nozoye and H. Tsukamoto, *ibid.*, **6**, 53 (1955); H. Kondo and T. Nozoye, *ibid.*, **7**, 44 (1956).
4) P. L. Julian, A. Magnai, J. Pikl and W. J. Karpel, *J. Am. Chem. Soc.*, **70**, 174 (1948).
5) *a*) H. Kondo, T. Nozoye and M. Tobita, *Itsuu Kenkyusho Nempo*, **1**, 74 (1950); *idem, ibid.*, **3**, 70 (1953); *b*) T. Nozoye, T. Nakai and A. Kubo, *Chem. Pharm. Bull.*, **25**, 196 (1977).
6) T. Nozoye and Y. Shibanuma, *Yakugaku Zasshi*, **95**, 710 (1975).
7) *a*) H. Ll. Bassett and C. R. Thomas, *J. Chem. Soc.*, **1954**, 1188; I. Shahak, *Tetrahedron Lett.*, **1966**, 2201; D. J. Cook and W. E. Schelwalt, *Proc. Indiana Acad. Sci.*, **74**, 183 (1965); *b*) A. L. Searles and H. G. Lindwall, *J. Am. Chem. Soc.*, **68**, 988 (1946); A. L. Searles and R. J. Kelly, *ibid.*, **78**, 2242 (1956).
8) J. Harley-Mason and T. J. Loeney, *Proc. Chem. Soc.*, London, **1964**, 364.
9) E. Wenkert, J. S. Bindra, C. J. Chan, D. W. Cochran and D. E. Rearick, *J. Org. Chem.*, **39**, 1662 (1974). **8** was obtained by mesylation of **4a** in this report but full experimental data are not given.
10) W. C. Anthony, *J. Org. Chem.*, **31**, 77 (1966).
11) P. Mayo, "Molecular Rearrangements," Vol. 1, ed. by Y. Pocker, Interscience Publishers, a division of John Wiley and Sons, New York, London, 1963, p. 6.