[Chem. Pharm. Bull.]
31(9) 2986—2992(1983)

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

TOSHIKAZU NOZOYE, YOSHIHISA SHIBANUMA* and TATSUYA NAKAI

Meiji College of Pharmacy, Nozawa 1-35-23, Setagaya-ku,
Tokyo 154, Japan

(Received October 19, 1982)

Upon being warmed at 90 °C in trifluoromethanesulfonic acid for 42—78 h, 2-hydroxytryptophol (**4a**) gave 3-ethylideneoxindoles (*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 (**6_{I-b,c}**, **6_{II-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-hydroxy-ethylindolenines (**9b**, **9c**) under the same conditions.

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

In the structural study of uncarine and rhyncophylline, the neutral crystals, C₁₀H₉NO, obtained *in vacuo* by dehydrogenation with palladium¹⁾ or by heating uncarine methiodide,¹⁾ were assumed to be 2,3-dihydrofuro[2,3,*b*]indole²⁾ (**1**) at that time. However, **1** was later confirmed to be spiro-(3)-cyclopropanoxindole (**8**).³⁾ The synthesis of **1** was attempted by Julian⁴⁾ 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)}
		6I-b	21.6 ^{b)}	276—277 ^{g)}
4c	74	5c^{a)}	62.2 ^{c)}	—
		6I-c	14.9 ^{c)}	184—187 ^{h)}
		6II-c	3.1 ^{c)}	232—234 ⁱ⁾

^{a)} A mixture of *E*- and *Z*-isomer (2:1) from the NMR spectrum.

^{b)} Extracted with CH₂Cl₂. 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 samples⁵⁾ [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-dimethylcarbostyryl (**6_{I-b}**). Similarly, **4c** gave 3-methyl-4-ethylcarbostyryl (**6_{I-c}**), 3-ethyl-4-methylcarbostyryl (**6_{II-c}**), and a mixture of 3-(2-butylidene)oxindoles (**5c-E** and **5c-Z**). The structures of **6_{I-b}**, **6_{I-c}**, and **6_{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 sample³⁾ (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**, **6I-b,c** and **6II-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 rearrangement¹¹). On the other hand, **6I-b,c** or **6II-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 (%)			IR (KBr, cm ⁻¹)	MS <i>m/e</i> M ⁺ , (100%)
		Calcd (Found)				
		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 (%)			IR (KBr cm ⁻¹)	UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ)	MS M ⁺ <i>m/e</i> (100%)
			C	H	N			
7a	115—116 (CH ₂ Cl ₂ - <i>n</i> -hexane)	C ₁₇ H ₁₇ NO ₄ S	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 ₄ S		^{a)}		3430 ^{d)} 1715 1365 1175	227 (4.10) 250 (3.88)	345 (146)
7c	134—137 (CH ₂ Cl ₂ - <i>n</i> -hexane)	C ₁₉ H ₂₁ NO ₄ S	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- <i>n</i> -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 ₂ Cl ₂ - <i>n</i> -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 CHCl₃ solution.

^{e)} 2,3-Dimethyl-2-ethoxyindolenine⁸⁾: UV $\lambda_{\max}$ 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 HNO₃ (*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, -CH ₃), 2.14–2.70 (2H, m, -CH ₂ -CH ₂ -O-), 3.90–4.34 (2H, m, -CH ₂ -O-)
2d	2.17 (2H, t, J =6.5, -CH ₂ -), 2.43 (1H, s, -OH), 3.56 (2H, t, J =6.5, -CH ₂ -OH)
3b	1.82 (3H, s, -CH ₃), 2.18–2.46 (1H, m) and 2.91–3.04 (1H, tt, J =10) (-CH ₂ -CH ₂ -O-), 4.38–4.78 (2H, m, -CH ₂ -O-)
3b-p	1.68 (3H, s, -CH ₃), 2.38–2.90 (2H, m, -CH ₂ -CH ₂ -O-), 4.12–4.57 (2H, m, -CH ₂ -O-), 7.64 (2H, d, J =9, Ph), 8.20 (2H, d, J =9, Ph)
4b^{b)}	1.20 (3H, s, -CH ₃), 1.87 (2H, t, J =8, -CH ₂ -), 3.04 (2H, m, -CH ₂ -O-), 4.24 (1H, t, J =6, -OH), 10.22 (1H, br, -NH-)
7a	2.26 (2H, q, J =6, -CH ₂ -CH ₂ -), 2.43 (3H, s, -CH ₃), 3.50 (1H, t, J =6, >CH-), 4.27 (2H, t, J =6, -CH ₂ -O-), 7.30 (2H, d, J =9, Ph), 7.75 (2H, d, J =9, Ph), 8.86 (1H, br, -NH-)
7b	1.35 (3H, s, -CH ₃), 2.13 and 2.25 (each 1H, t, J =7, -CH ₂ -CH ₂ -O-), 2.36 (3H, s, Ph-CH ₃), 3.82 (2H, t, J =7, -CH ₂ -O-Ts), 7.24 (2H, d, J =8, Ph), 7.60 (2H, d, J =8, Ph), 8.62 (1H, br, -NH-)
7c	0.62 (3H, t, J =7, -CH ₂ -CH ₃), 1.78 (2H, m, -CH ₂ -CH ₃), 2.14 and 2.25 (each 1H, t, J =7, -CH ₂ -CH ₂ -O-), 2.41 (3H, s, Ph-CH ₃), 3.86 (2H, t, J =7, -CH ₂ -O-Ts), 7.26 (2H, d, J =9, Ph), 7.64 (2H, d, J =9, Ph), 8.63 (1H, br, -NH-)
8	1.50 (2H, q, J =3.5, cyclo-CH ₂ -), 1.72 (2H, q, J =3.5, cyclo-CH ₂ -), 9.08 (1H, br, -NH-)
9b	1.32 (3H, s, -CH ₃), 1.38 (3H, t, J =7, -O-CH ₂ -CH ₃), 1.65 (1H, br, -CH ₂ -OH), 2.08 and 2.10 (each 1H, t, J =7, -CH ₂ CH ₂ OH), 3.26 (2H, t, J =7, -CH ₂ -OH), 4.41 (2H, q, J =7, -O-CH ₂ -CH ₃)
9c	0.50 (3H, t, J =7, -CH ₂ -CH ₃), 1.42 (3H, t, J =7, -O-CH ₂ -CH ₃), 1.84 (2H, q, J =7, >C-CH ₂ -CH ₃), 2.10 (2H, t, J =7, -CH ₂ -CH ₂ OH), 3.25 (2H, t, J =7, -CH ₂ OH), 4.45 (2H, q, J =7, -O-CH ₂ -CH ₃)
10	2.35 (2H, q, J =7.5, -CH ₂ -CH ₂ -), 3.71 (3H, m, J =7.5 and 3, >CH-, -CH ₂ -Cl), 8.2–8.8 (1H, br, -NH-)

a) In CDCl₃ 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.

Acknowledgement We are grateful to Professor S. Nakano of this college for providing an authentic sample of 3,4-dimethylcarbostyryl.

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. Pikel 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. Shibamura, *Yakugaku Zasshi*, **95**, 710 (1975).
- 7) a) H. L. 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. Looney, *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.