[Chem. Pharm. Bull. 36(12)4980—4985(1988)]

Reactions of 2-Hydroxytryptophol. II.[1] Solvolysis of 3-Substituted-2-hydroxytryptophol and *N*-Methyl Derivatives with Alcoholic Alkali

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(Received April 9, 1988)

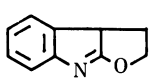
Tosylates (**2b, c**) of 3-alkyl-2-hydroxytryptophol gave 3-alkyl-2-alkoxyindolenines (**3a—f**) on treatment with 5% KOH–ROH (R = Me, iso-Pr), as expected. The *N*-methyl derivatives (**6a—c**) gave 3-alkyl-3-(2-alkoxyethyl)oxindoles (**7a—d**) except for **6a**, which afforded the 3-spirocyclopropane (**10**), and gave 3-alkyl-3-vinyloxindoles (**8a, b**) with 5% KOH–CH_3CN. The hydrolysis of **3b** was examined in the range of HCl concentration of 10^{-1}—10^{-5} M in 90% EtOH by using ultraviolet spectroscopy.

Keywords——3-alkyl-2-hydroxytryptophol; *N*-methyl-3-alkyl-2-hydroxytryptophol; 3-alkyl-2-alkoxyindolenine; *N*-methyl-3-alkyl-3-(2-alkoxyethyl)oxindole; *N*-methyl-3-alkyl-3-vinyloxindole; solvolysis; UV spectra

In the course of our synthetic studies on 2,3-dihydrofuro[2,3-*b*]indole (**1**), we showed that 3-alkyl-2-hydroxytryptophol (**2a**) did not react with 5% potassium hydroxide (KOH) in ethanol (EtOH) but its tosylates (**2b, c**) gave the iminoethers (**3**: indolenine type) under the same conditions.[1] The formation of iminoethers[2] under such basic reaction conditions is of interest. Therefore, we further studied the solvolysis of **2b, c** and its *N*-methyl derivatives (**6a—c**) with methanol (MeOH), iso-propanol (iso-PrOH) and acetonitrile (CH_3CN) as an aprotic solvent in the presence of KOH, and we also examined the stability of **3b** in an acidic medium.[3] The results are presented here.

Compounds **2b, c** were refluxed with 5% KOH in MeOH or iso-PrOH to give, as expected, the methylethers (**3a, d**) or the isopropylethers (**3c, f**), respectively, but in CH_3CN an inseparable mixture showing many spots on thin-layer chromatography (TLC) was obtained.

The structures of iminoethers were confirmed by converting **3b** to 3-methyl-2-hydroxytryptophol (**2a**) in quantitative yield by the action of hydrochloric acid (HCl) and by direct comparison with the structural isomer (**2d**),[4] which was obtained from the reaction of



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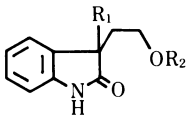
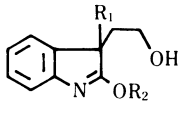


2a–d

a : $R_1=CH_3$, $R_2=H$
b : $R_1=CH_3$, $R_2=Ts$
c : $R_1=C_2H_5$, $R_2=Ts$
d : $R_1=CH_3$, $R_2=C_2H_5$



3a–f

a : $R_1=CH_3$, $R_2=CH_3$
b : $R_1=CH_3$, $R_2=C_2H_5$
c : $R_1=CH_3$, $R_2=$iso-C_3H_7
d : $R_1=C_2H_5$, $R_2=CH_3$
e : $R_1=C_2H_5$, $R_2=C_2H_5$
f : $R_1=C_2H_5$, $R_2=$iso-C_3H_7

Chart 1

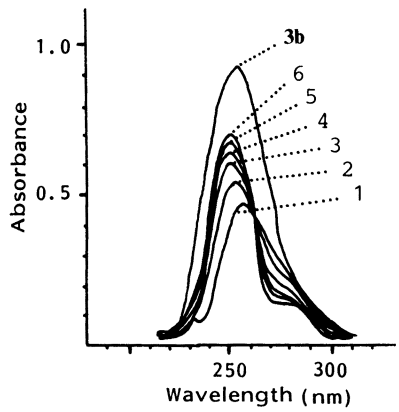


Fig. 1. UV Spectral Changes of **3b** (10^{-4} M) in 90% EtOH

Time after the start of hydrolysis in 1 N HCl–EtOH (1 : 9 in volume): 1 = 1 min, 2 = 5 min, 3 = 10 min, 4 = 15 min, 5 = 20 min, 6 = 30 min (**2a**).

TABLE I. Effects of HCl Concentration on the Rate of Hydrolysis of **3b** (10^{-4} M) in 90% EtOH

HCl (M)	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}
Time (h)[a]	0.5	0.5	2.0	48	48

a) Time required for the completion of hydrolysis.

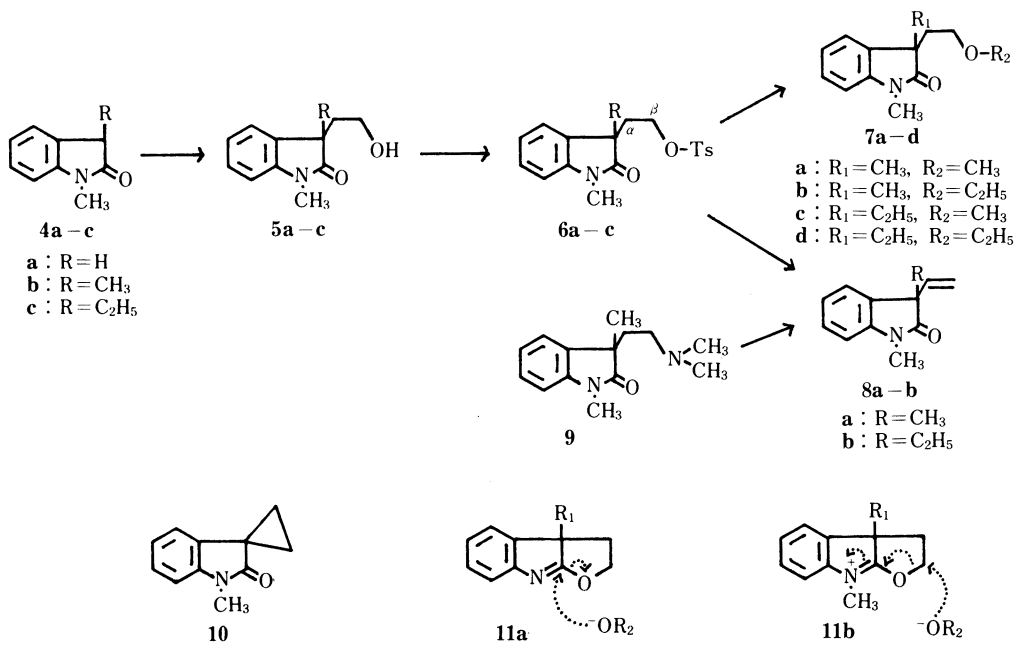


Chart 2

2a with C_2H_5I.

The effect of acidity on the hydrolysis of **3b** was precisely examined by ultraviolet (UV) spectroscopy. In the range of HCl concentration of 10^{-1}—10^{-2} M in 90% EtOH, **3b** was hydrolyzed to **2a** within about 30 min (Table I). The UV spectral changes of **3b** are shown in Fig. 1. In a basic medium (1 N KOH–EtOH), **3b** was fairly stable.

Furthermore, we examined the same reaction with *N*-methyl derivatives (**6a**—**c**) which

TABLE II. Reaction of **2b**—**c** and **6a**—**c** with 5% KOH in ROH[a] or CH_3CN[b]

Compd. No. (mmol)	Solvent[c] (ml)	Product No.	Yield[d] (%)	mp (C) (Recryst. sol.)
2b (2.3)	A (30)	**3a**	93	54—56 (EtOAc)
(0.3)[e]	B (5)	**3b**	68	109—110 (EtOAc)
(1.9)	C (30)	**3c**	39	69.5—70 (EtOAc)
2c (0.3)	A (10)	**3d**	79	72—73 (EtOAc)
(0.8)[e]	B (10)	**3e**	90	Oil
(0.25)	C (10)	**3f**	48	72—73 (EtOAc)
6a (0.2)	A (5)	**9**	Quan.	84—85 (n-C_6H_{14})
6b (0.5)	A (10)	**7a**	77	Oil
(0.5)	B (10)	**7b**	59	Oil
(0.34)	D (16)	**8a**	54	Oil
6c (0.4)	A (5)	**7c**	Quan.	42—43 (n-C_6H_{14})
(0.4)	B (10)	**7d**	49	Oil
(0.5)	D (20)	**8b**	35	Oil

a) Refluxed for 1 h. *b*) Refluxed for 4 h. *c*) A = MeOH, B = EtOH, C = iso-PrOH, D = CH_3CN. *d*) Isolated yield after chromatography, except for **3d**. *e*) Data reported in ref. 1.

TABLE III. Physicochemical and Spectral Data for **3a**—**f**, **7a**—**d** and **8a**, **b**

Compd.[a] No.	Formula	Analysis (%) Calcd (Found) C H N	MS M^+, m/z (100%)	UV λ_{max}^{EtOH} nm (log ε)	IR (neat, cm^{-1})
3a	$C_{12}H_{15}NO_2$	205.1103[b]	205	257	3352
		(205.1110)	(205)	(3.74)	1618
					1582
3c	$C_{14}H_{19}NO_2$	233.1416[b]	233	258	3352
		(233.1417)	(147)	(3.81)	1574
3d	$C_{13}H_{17}NO_2$	71.20 7.82 6.39	219	258	3324[c]
		(70.99 7.93 6.34)	(219)	(3.72)	1616
					1580
3f	$C_{15}H_{21}NO_2$	72.83 8.56 5.67	247	258	3304[c]
		(72.77 8.69 5.69)	(161)	(3.80)	1576
7a	$C_{13}H_{17}NO_2$	219.1259[b]	219	258	1714
		(219.1268)	(161)	(3.80)	1616
					1120
7b	$C_{14}H_{19}NO_2$	233.1416[b]	233	260	1714
		(233.1414)	(161)	(3.74)	1616
					1118
7c	$C_{14}H_{19}NO_2$	72.06 8.21 6.01	233	257	1714[c]
		(72.06 8.42 6.00)	(175)	(3.83)	1614
					1120
7d	$C_{15}H_{21}NO_2$	247.1572[b]	247	259	1714
		(247.1573)	(175)	(3.80)	1616
					1118
8a	$C_{12}H_{13}NO$	187.0997[b]	187	272	1720
		(187.1000)	(187)	(3.31)	1614
8b	$C_{13}H_{15}NO$	201.1154[b]	201	270	1714
		(201.1170)	(172)	(3.53)	1614

a) **3a** and **3e**: ref. 1. *b*) High-resolution mass. *c*) KBr.

TABLE IV. Physicochemical and Spectral Data for **5a—c** and **6a—c**

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	N	mp (°C) (Recryst. sol.)	Yield (%)	MS M^+, *m/z* (100%)	UV λ_{max}^{EtOH} nm (log ε)	IR (KBr, cm^{-1})
5a	$C_{11}H_{13}NO_2$	191.0946[b] (191.0947)			Oil	22	191 (160)	258 (3.77)	3416[c] 1694 1616
5b[a]	$C_{12}H_{15}NO_2$	70.21	7.37	6.83	78—80	66	205		3420
		(70.20	7.55	6.66)	(Ether)		(161)		1700 1615
5c	$C_{13}H_{17}NO_2$	71.19	7.82	6.39	98—99	23	219	258	3420
		(71.13	7.98	6.28)	(EtOAc)		(160)	(3.84)	1700 1620
6a	$C_{18}H_{19}NO_4S$	62.62	5.55	4.06	109—110	44	345	257	1706
		(62.65	5.50	3.99)	(EtOAc)		(173)	(3.78)	1352 1172
6b	$C_{19}H_{21}NO_4S$	63.52	5.90	3.90	97—98	50	359	255	1704
		(63.26	5.82	3.95)	(MeOH)		(160)	(3.86)	1352 1178
6c	$C_{20}H_{23}NO_4S$	64.35	6.22	3.75	96—99	78	373	256	1706
		(64.29	6.20	3.76)	(EtOAc)		(373)	(3.72)	1360 1172

a) Lit. 75.5—77.5 °C.[6] *b*) High-resolution mass. *c*) Neat.

were obtained from *N*-methyl-2-hydroxytryptophols (**5a—c**). Compound **6a** gave oxindole-3-spirocyclopropane (**10**), which was identified by comparing its infrared (IR) spectrum with that of an authentic sample.[5] On the other hand, **6b—c**, with a methyl or ethyl group at C-3 of the oxindole ring, gave 3-(2-alkoxyethyl)oxindoles (**7a—d**) in MeOH or EtOH, and gave 3-vinyloxindoles (**8a, b**) in CH_3CN. The structures of **7a** and **8a** were confirmed by direct comparison with authentic samples obtained from the reaction of **5b** with CH_3I, and from **9** with 5% KOH–EtOH, respectively (TLC, IR, and MS comparisons).

These transformations are considered to proceed through the solvolysis of the intermediates (**11a** or **11b**).

Experimental

All melting points were measured under a microscope (Yanaco MP-S2) and are uncorrected. IR and UV spectra were recorded on a Hitachi 270-30 spectrophotometer and a Hitachi 200-20 spectrophotometer, respectively. Nuclear magnetic resonance (NMR) spectra were taken on JEOL PS-100 and GX-400 machines with tetramethylsilane as an internal standard. Mass spectra (MS) were determined with a JEOL D-300 instrument operating at 70 eV. Column chromatography was carried out on silica gel (230—400 mesh, Merck) or alumina (70—230 mesh, Merck).

Reaction of 2b, c and 6a—c with 5% KOH–ROH——A typical experiment is described here for **2b**. A solution of **2b** (792 mg, 2.3 mmol) and 5% KOH–MeOH (30 ml) was refluxed for 1 h under nitrogen. The solvent was evaporated off *in vacuo* to give the residue, which was treated with CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was washed with 5% Na_2CO_3 and dried over KOH. Evaporation of the solvent gave the crude product, which was chromatographed on SiO_2 using CH_2Cl_2–EtOAc (1 : 1) for **3a, b** or benzene–EtOAc (2 : 1) for **7a—d** or on Al_2O_3 using benzene–EtOH (19 : 1) for **3f**. Yields, and physicochemical and spectral data are shown in Tables II, III, and V.

Reaction of 6b, c with 5% KOH–CH_3CN——A typical experiment is described here for **6b**. A solution of **6b** (121 mg, 0.34 mmol) and 5% KOH–CH_3CN (16 ml) was refluxed for 4 h under nitrogen. The solvent was evaporated off *in vacuo* to give the residue, which was treated with EtOAc and H_2O. The EtOAc layer was washed with 5% Na_2CO_3 and dried over KOH. Evaporation of the solvent gave the crude product, which was purified by preparative thin-layer chromatography (SiO_2) using benzene–EtOAc (3 : 1). Yields, and physicochemical and spectral data are shown in Tables II, III, and V.

TABLE V. ^{1}H-NMR Spectral Data for the Products (100 MHz, in $CDCl_3$)

Compd. No.	δ ppm (J in Hz)[b]
3a	1.38 (3H, s, $C\underline{H}_3$), 2.10 (2H, dt, J=4.7, $-C\underline{H}_2-$), 2.57 (1H, br, $-O\underline{H}$), 3.25 (2H, t, J=7, $-C\underline{H}_2OH$), 4.04 (3H, s, $-OC\underline{H}_3$), 6.92—7.32 (4H, m, aroma)
3c	1.38 (3H, s, $-C\underline{H}_3$), 1.41 (6H, d, J=7, $-CH(C\underline{H}_3)_2$), 1.85 (1H, br, $-O\underline{H}$), 2.10 (2H, dt, J=4, 7, $-C\underline{H}_2-$), 3.24 (2H, t, J=7, $-C\underline{H}_2OH$), 5.30 (1H, q, J=7, $-C\underline{H}(CH_3)_2$), 6.96—7.32 (4H, m, aroma)
3d[a]	0.50 (3H, t, J=7.3, $-CH_2C\underline{H}_3$), 1.70 (1H, br, $-O\underline{H}$), 1.84 (2H, q, J=$-C\underline{H}_2CH_3$), 2.12 (2H, m, $-C\underline{H}_2-$), 3.24 (2H, q, J=6.2, $-C\underline{H}_2OH$), 4.03 (3H, s, $-OC\underline{H}_3$), 7.06—7.33 (4H, m, aroma)
3f[a]	0.50 (3H, t, J=7.3, $-CH_2C\underline{H}_3$), 1.38 (6H, d, J=6.1, $-CH(C\underline{H}_3)_2$), 1.64 (1H, br, $-O\underline{H}$), 1.83 (2H, q, J=7.3, $-C\underline{H}_2CH_3$), 2.03—2.17 (2H, m, $-C\underline{H}_2-$), 3.18—3.31 (2H, m, $-C\underline{H}_2OH$), 5.29 (1H, q, J=6.1, $-C\underline{H}(CH_3)_2$), 7.04—7.30 (4H, m, aroma)
5a	2.10 (2H, q, J=7, $-C\underline{H}_2-$), 3.17 (1H, br, $-O\underline{H}$), 3.21 (3H, s, N-$C\underline{H}_3$), 3.59 (1H, t, J=6, $-C\underline{H}=$), 3.90 (2H, t, J=6.1, $-C\underline{H}_2OH$), 6.8—7.3 (4H, m, aroma)
5c	0.56 (3H, t, J=7.3, $-CH_2C\underline{H}_3$), 1.60—2.30 (4H, m, $-C\underline{H}_2CH_3$, $-C\underline{H}_2-$), 2.40 (1H, br, $-O\underline{H}$), 3.24 (3H, s, N-$C\underline{H}_3$), 3.50 (2H, m, $-C\underline{H}_2OH$), 6.80—7.36 (4H, m, aroma)
6a	2.24 (2H, q, J=7, $-C\underline{H}_2-$), 2.46 (3H, s, ph-$C\underline{H}_3$), 3.18 (3H, s, N-$C\underline{H}_3$), 3.51 (1H, t, J=7, $-C\underline{H}=$), 4.30 (2H, t, J=7, $-C\underline{H}_2-O-$), 6.76—7.18 (4H, m, aroma), 7.30 and 7.70 (each 2H, d, J=8, Ts-$\underline{H}$)
6b	1.38 (3H, s, $-C\underline{H}_3$), 1.92—2.36 (2H, m, $-C\underline{H}_2-$), 2.47 (3H, s, ph-$C\underline{H}_3$), 3.21 (3H, s, N-$C\underline{H}_3$), 3.87 (2H, t, J=6, $-C\underline{H}_2-O-$), 6.78—7.20 (4H, m, aroma), 7.26 and 7.38 (each 2H, d, J=8, Ts-$\underline{H}$)
6c[a]	0.53 (3H, t, J=7.3, $-CH_2C\underline{H}_3$), 1.71—2.35 (4H, m, $-C\underline{H}_2CH_3$, $-C\underline{H}_2-$), 2.42 (3H, s, ph-$C\underline{H}_3$), 3.15 (3H, s, N-$C\underline{H}_3$), 3.72—3.83 (2H, m, $-C\underline{H}_2-O-$), 6.82—7.31 (4H, m, aroma), 7.27 and 7.59 (each 2H, d, J=8.2, Ts-$\underline{H}$)
7a	1.40 (3H, s, $-C\underline{H}_3$), 1.82—2.46 (2H, m, $-C\underline{H}_2-$), 3.02—3.24 (2H, m, $-C\underline{H}_2-OCH_3$), 3.12 (3H, s, $-OC\underline{H}_3$), 3.24 (3H, s, N-$C\underline{H}_3$), 6.76—7.30 (4H, m, aroma)
7b	1.02 (3H, t, J=6.4, $-OCH_2C\underline{H}_3$), 1.40 (3H, s, $-C\underline{H}_3$), 1.84—2.50 (2H, m, $-C\underline{H}_2-$), 3.08—3.35 (4H, m, $-C\underline{H}_2-O-C\underline{H}_2CH_3$), 3.25 (3H, s, N-$C\underline{H}_3$), 6.78—7.30 (4H, m, aroma)
7c[a]	0.56 (3H, t, J=7.9, $-CH_2C\underline{H}_3$), 1.76—2.33 (4H, m, $-C\underline{H}_2CH_3$, $-C\underline{H}_2-$), 3.02—3.06 (2H, m, $-C\underline{H}_2-OCH_3$), 3.07 (3H, s, $-OC\underline{H}_3$), 3.20 (3H, s, N-$C\underline{H}_3$), 6.82—7.29 (4H, m, aroma)
7d	0.57 (3H, t, J=7, $-CH_2C\underline{H}_3$), 1.00 (3H, t, J=7, $-OCH_2C\underline{H}_3$), 1.68—2.48 (4H, m, $-C\underline{H}_2CH_3$, $-C\underline{H}_2-$), 3.02—3.32 (4H, m, $-C\underline{H}_2-O-C\underline{H}_2CH_3$), 3.23 (3H, s, N-$C\underline{H}_3$), 6.76—7.32 (4H, m, aroma)
8a[a]	1.49 (3H, s, $-C\underline{H}_3$), 3.21 (3H, s, N-$C\underline{H}_3$), 5.12 (1H, d, J=17.4, $=C\underline{H}_2$), 5.16 (1H, d, J=10.4, $=C\underline{H}_2$), 5.95 (1H, q, J=10.4, 17.4, $-C\underline{H}=$), 6.85—7.31 (4H, m, aroma)
8b[a]	0.66 (3H, t, J=7.3, $-C\underline{H}_3$), 1.90 (1H, m, J=7.3, $-C\underline{H}_2-$), 2.06 (1H, m, J=7.3, $-C\underline{H}_2-$), 3.21 (3H, s, N-$C\underline{H}_3$), 5.08 (1H, d, J=17.4, $=C\underline{H}_2$), 5.13 (1H, d, J=10.4, $=C\underline{H}_2$), 5.99 (1H, q, J=10.4, 17.4, $=C\underline{H}-$), 6.86—7.32 (4H, m, aroma)

a) 400 MHz. *b*) s=singlet, d=doublet, dd=double doublet, dt=double triplet, t=triplet, q=quartet, m=multiplet, br=broad, Ts=tosyl

Hydrolysis of 3b in an Acidic Medium to 2a——A solution of **3b** (92 mg, 0.4 mmol) in HCl–EtOH [1 N HCl (3 ml) in EtOH (27 ml)] was stirred at room temperature for 30 min, then brine (10 ml) was added, and the mixture was extracted with CH_2Cl_2 (20 ml); the extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give **2a** (76 mg) in quantitative yield.

Procedure for the *N*-Methyl-2-hydroxytryptophol Derivatives (5a—c)——A typical experiment is described here for **5b**. A solution of **4b** (3.2 g, 0.02 mol) in dry benzene was added to a suspension of NaH (50%, 1.2 g, 0.024 mol) in dry benzene with stirring at room temperature. The mixture was refluxed for 1 h, then stirred overnight at room temperature. Ethylene oxide (0.9 g) was slowly bubbled into the mixture through an inlet tube at 20—25 °C. Stirring was continued at room temperature for 1 h, then H_2O was added cautiously to the reaction mixture. The benzene layer was separated, washed with brine, and dried over Na_2SO_4. The aqueous layer was acidified with 10% HCl, and extracted with $CHCl_3$; the extract was dried over Na_2SO_4 after being washed with brine. The combined organic layer was evaporated *in vacuo* to give the residue, which was chromatographed on SiO_2 using benzene–EtOAc (2:1) for **5a—c**. Yields, and physicochemical and spectral data are given in Tables IV and V.

Procedure for the Tosylates (6a—c)——Compounds **6a—c** were obtained from the reaction of **5a—c** with tosyl chloride in anhydrous pyridine as described in the previous paper.[1] Yields, and physicochemical and spectral data are shown in Tables IV and V.

Acknowledgment We are grateful to the staff of the Analytical Center of this college for spectral measure-

ment and elemental analysis.

References and Note

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4) Compound **2d** was fully characterized by a combination of spectroscopic and analytical data.
2d: Oil, $C_{13}H_{17}NO_2$. IR: 3248, 1702. ^{1}H-NMR: 1.00 (3H, t, $J=7.7$ Hz), 1.40 (3H, s), 1.70—2.60 (2H, m), 3.17 (2H, t, $J=6.8$ Hz), 3.21 (2H, q, $J=7.7$ Hz), 9.25 (1H, br).
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