A SIMPLE SYNTHESIS OF 2-SUBSTITUTED 4-OXAZOLIDINONES AND 1,3-OXAZIN-4-ONES FROM AMIDE-ALCOHOLS (STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS 748[1])

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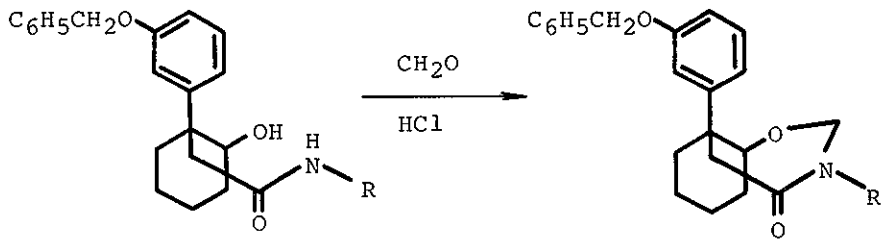
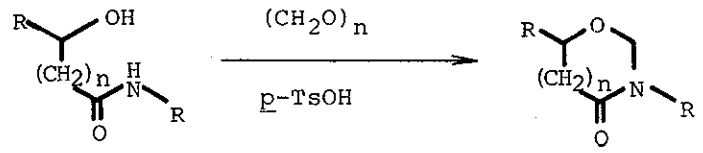
Acid-catalyzed cyclisation of the secondary amides (7~10) possessing a hydroxyl group at α- or β-position with various carbonyl compounds gave the novel 2-substituted 4-oxazolidinones (11~15) and tetrahydro-1,3-oxazin-4-ones (16~24).

In preceeding papers[2,3], we have reported that a reaction of the secondary amides (1), possessing a hydroxyl group at γ-position, with formalin and hydrochloric acid gave the seven-membered ring compound, 1,3-oxazepin-4-ones (2), which formed a methylene bridge between hydroxyl and amide functions, and the application of this reaction on the simple secondary amides (3) (n=0,1,2) having a hydroxyl group at α-, β- or γ-position with paraformaldehyde in

the presence of p-toluenesulphonic acid provided oxazolidinones (4), oxazinones (5), and oxazepinones (6), respectively.



1 R=CH_3, $CH_2C_6H_5$, $(CH_2)_2C_6H_5$ 2 R=CH_3, $CH_2C_6H_5$, $(CH_2)_2C_6H_5$



3

4 n=0
5 n=1
6 n=2

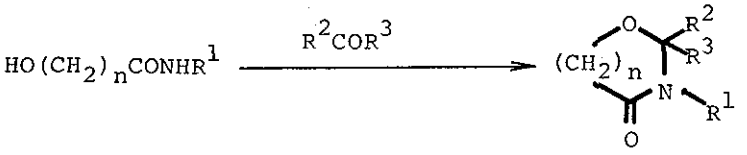
As the continuation of our study searching for the general applicability of this reaction, a cyclisation reaction of the secondary amides (7~10) with various carbonyl compounds was investigated. The present paper describes the facile formation of some novel 2-substituted oxazolidinones (11~15) and oxazinones (16~36).

At first the N-benzylhydracrylamide (10), which was cyclised in the best yield with formaldehyde, was used as the starting material of this reaction. When aliphatic aldehydes (C_2-C_{10}), benzaldehyde,

and phenylacetaldehyde were adopted as carbonyl compounds, the corresponding oxazine derivatives (24~36) were obtained in good yields, but the reaction with ketones such as cyclohexanone, acetophenone or 3-hexanone gave a trace amount of the expected products. While the reaction of the N-methylhydracrylamide (9) with the aldehydes and ketones gave the 2-monosubstituted oxazines (16~20) and 2,2-disubstituted oxazines (21~23), respectively. The bulkiness of the benzyl group comparing with methyl function seems to cause the difference of the reactivity between N-benzylamides and N-methyl ones. Furthermore, the oxazolidinones (11~15) were obtained in the same way from N-methylglycolamide (7) and N-benzylglycolamide (8) by using the corresponding aldehydes or ketones.

These results were summarized in Table I. The structures of these compounds were verified by spectral data and elemental analyses as shown in Table I and II.

Namely 4-oxazolidinones showed amide carbonyl absorption at 1700 cm^{-1} in i.r. spectrum and the n.m.r. spectrum revealed methine proton at 2-position having a long range coupling $J_{2,5}$ 1-2 Hz at δ 4.2 - 5.0 p.p.m. with the exception of 13 which has no proton at 2-position. Similarly, oxazinones indicated the presence of carbonyl group at 1640 - 1655 cm^{-1} in i.r. spectrum and methine proton of 2-monosubstituted compounds at δ 4.46 - 5.64 p.p.m. All spectral data were in agreement with their assigned structures.



7 n=1, $R^1=CH_3$

8 n=1, $R^1=CH_2C_6H_5$

9 n=2, $R^1=CH_3$

10 n=2, $R^2=CH_2C_6H_5$

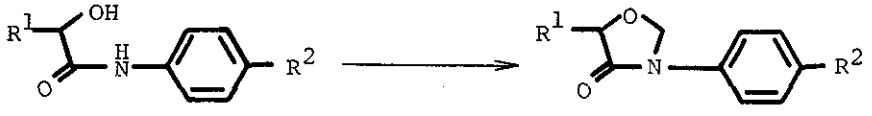
11~13 n=1, $R^1=CH_3$

14, 15 n=1, $R^1=CH_2C_6H_5$

16~23 n=2, $R^1=CH_3$

24~36 n=2, $R^1=CH_2C_6H_5$

On the other hand, similar reaction of the N-phenylhydracrylamide, γ-hydroxy-N-methylbutyramide, and N-benzyl-γ-hydroxybutyramide were unsuccessful. The low reactivity of the N-phenylamide-alcohol seems mainly due to the electron-withdrawing effect of phenyl group on the amide nitrogen atom. A reaction of the substituted phenyl amide-alcohols (37,38), having an electron-releasing group on benzene ring, with formaldehyde gave the cyclisation products (39,40), but the amide having p-nitrophenyl group recovered the starting material. These facts also suggest that the electronic effect of phenyl group on the amide nitrogen plays an important role in a cyclisation reaction.



37 $R^1=H$, $R^2=OCH_3$

38 $R^1=C_6H_5$, $R^2=OCH_3$

39 $R^1=H$, $R^2=OCH_3$

40 $R^1=C_6H_5$, $R^2=OCH_3$

EXPERIMENTAL

M.p.s were determined on a Yanagimoto hot-stage apparatus. I.R. and n.m.r. spectra were recorded with Hitachi-215 spectrophotometer and JNM-PMX-60 spectrometer (tetramethylsilane as internal standard), respectively.

3-Benzyl-3,4,5,6-tetrahydro-2-methyl-2H-1,3-oxazin-4-one (24). A mixture of N-benzylhydracrylamide (10) (5.0 g), paraldehyde (10 ml), p-toluenesulphonic acid (0.8 g), and xylene (150 ml) was refluxed for 5 h with stirring under the azeotropic removal of the water formed by using the water-separator. After removal of the solvent, the residue was dissolved in chloroform (100 ml) and the extract was washed with aqueous sodium hydrogen carbonate, water, aqueous hydrochloric acid (1 N), and water. The organic layer was dried over magnesium sulphate and filtered. After evaporation of the solvent, distillation of the residue gave a pale yellow oil (143-144°/1mmHg) which was purified by silica gel column chromatography by using chloroform as an eluent, and redistillation of the product gave the oxazinone (24).

All the cyclisation products listed in Table I were obtained in a similar way as mentioned above by using the appropriate carbonyl compounds (1.5-2 molar equiv.) instead of paraldehyde with the modification of the reaction solvent to benzene in the case of 16, 20, and 32. The phenylacetaldehyde was used as a 40-50 % solution in diethyl phthalate.

3-(4-Methoxyphenyl)-4-oxazolidinone (39). A mixture of N-p-methoxyphenylglycolamide (2.0 g), paraformaldehyde (1.2 g), p-toluenesulphonic acid (0.3 g), and xylene (40 ml) was refluxed

for 30 h with stirring under the azeotropic removal of the water formed by using the water-separator. After removal of the solvent, the residue was dissolved in chloroform (50 ml) and the extract was washed with aqueous sodium hydrogen carbonate, water, aqueous hydrochloric acid (1 N), and water. The organic layer was dried over magnesium sulphate and filtered. Evaporation of the solvent gave a brownish oil which was purified by silica gel column chromatography by using chloroform as an eluent. Recrystallisation of the residue from ether gave the oxazolidinone (39) (0.45 g, 21.1 %) as colourless scales, m.p. 82-84° (Found: C, 62.38; H, 5.70; N, 7.32. $C_{10}H_{11}NO_3$ requires C, 62.16; H, 5.74; N, 7.25 %), $\nu_{max.}$ (KBr) 1695 cm^{-1} (C=O), δ ($CDCl_3$) 3.80 (3H, s, OCH_3), 4.40 (2H, t, J 1 Hz, 5-H), 5.46 (2H, t, J 1 Hz, 2-H), 6.94, 7.45 (4H, each d, J 9.5 Hz, aromatic protons).

3-(4-Methoxyphenyl)-5-phenyl-4-oxazolidinone (40). A mixture of N-p-methoxyphenylmandelamide (1.0 g), p-toluenesulphonic acid (0.16 g), paraformaldehyde (0.6 g), and xylene (40 ml) was treated in the same way as the synthesis of 39 to give the oxazolidinone (40) (0.19 g, 18.2 %) as colourless prisms, m.p. 116-118° (Found: C, 71.09; H, 5.52; N, 4.97. $C_{16}H_{15}NO_3$ requires C, 71.36; H, 5.61; N, 5.20 %), $\nu_{max.}$ (KBr) 1690 cm^{-1} (C=O), δ ($CDCl_3$) 3.76 (3H, s, OCH_3), 5.40 (1H, t, J 1 Hz, 5-H), 5.56 (2H, d, J 1 Hz, 2-H), 6.7-7.7 (9H, m, aromatic protons).

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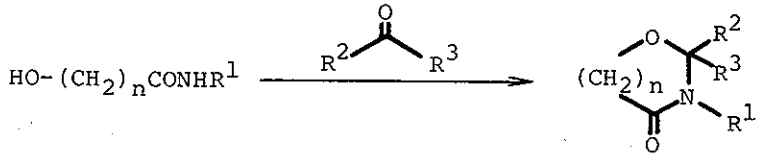
Table I. The Cyclisation Reaction of the Secondary Amides Possessing a Hydroxyl Group at α- or β-Position with Carbonyl Compounds



Compd. No.	n	R^1	R^2	R^3	Reaction Time (h)	Yield(%)	b.p.(mmHg) or m.p./Recryst. Solvent	Formula	Anal. Calcd. (Found) C	H	N
11	1	CH_3	H	CH_3	8	13.9	39-40 (0.9)	$C_5H_9NO_2$	52.16 (51.93)	7.88 (8.03)	12.17 (11.97)
12	1	CH_3	H	C_6H_5	8	80.5	126-128 (0.5)	$C_{10}H_{11}NO_2$	67.78 (67.32)	6.26 (6.56)	7.91 (7.79)
13	1	CH_3	$-(CH_2)_5-$		8	19.7	78-79 (0.4)	$C_9H_{15}NO_2$	63.88 (63.43)	8.94 (9.04)	8.28 (8.17)
14	1	$CH_2C_6H_5$	H	CH_3	16	34.6	108-109 (0.42)	$C_{11}H_{13}NO_2$	69.09 (68.76)	6.85 (7.07)	7.33 (7.25)
15	1	$CH_2C_6H_5$	H	C_6H_5	9	66.5	163-164 (0.6)	$C_{16}H_{15}NO_2$	75.87 (75.93)	5.97 (5.92)	5.53 (5.61)
16	2	CH_3	H	CH_3	8	24.8	72-73 (0.9)	$C_6H_{11}NO_2$			
17	2	CH_3	H	C_2H_5	6.5	67.0	72-73 (0.5)	$C_7H_{13}NO_2$			9.78 (9.61)
18	2	CH_3	H	$(CH_2)_4CH_3$	8	37.0	105-106 (0.5)	$C_{10}H_{19}NO_2$	64.83 (64.86)	10.34 (10.37)	7.56 (7.54)
19	2	CH_3	H	C_6H_5	8	70.3	147 (0.8)	$C_{11}H_{13}NO_2$	69.09 (69.16)	6.85 (6.98)	7.33 (7.23)

20	2	CH_3	H	$CH_2C_6H_5$	8	30.1	149-150 (1.0)	$C_{12}H_{15}NO_2$	70.22 (70.32)	7.37 (7.32)	6.82 (6.77)
21	2	CH_3	$-(CH_2)_5-$		8	47.3	108-110 (0.6)	$C_{10}H_{17}NO_2$	65.54 (65.28)	9.35 (9.39)	7.64 (7.46)
22	2	CH_3	CH_3	C_6H_5	10	16.1	115 (0.5)	$C_{12}H_{15}NO_2$	70.22 (70.37)	7.37 (7.52)	6.82 (6.81)
23	2	CH_3	C_2H_5	$(CH_2)_2CH_3$	8	7.9	84-85 (0.6)	$C_{10}H_{19}NO_2$	64.83 (65.21)	10.34 (10.55)	7.56 (7.56)
24	2	$CH_2C_6H_5$	H	CH_3	5	61.1	142-143 (0.8)	$C_{12}H_{15}NO_2$	70.22 (69.94)	7.37 (7.37)	6.82 (6.61)
25	2	$CH_2C_6H_5$	H	C_2H_5	6	52.3	133 (0.7)	$C_{13}H_{17}NO_2$			6.39 (6.09)
26	2	$CH_2C_6H_5$	H	$(CH_2)_2CH_3$	7	55.3	133 (0.5)	$C_{14}H_{19}NO_2$	72.07 (71.99)	8.21 (7.96)	6.00 (6.02)
27	2	$CH_2C_6H_5$	H	$CH(CH_3)_2$	6.5	57.3	142-143 (1.3)	$C_{14}H_{19}NO_2$	72.07 (72.08)	8.21 (8.03)	6.00 (5.94)
28	2	$CH_2C_6H_5$	H	$(CH_2)_3CH_3$	6	43.5	141-142 (0.5)	$C_{15}H_{21}NO_2$	72.84 (73.13)	8.56 (8.79)	5.66 (5.74)
29	2	$CH_2C_6H_5$	H	$CH_2CH(CH_3)_2$	7.5	64.4	147 (1.0)	$C_{15}H_{21}NO_2$	72.84 (72.83)	8.56 (8.54)	5.66 (5.63)
30	2	$CH_2C_6H_5$	H	$(CH_2)_4CH_3$	8.5	55.4	145-146 (0.6)	$C_{16}H_{23}NO_2$	73.53 (73.56)	8.87 (9.05)	5.36 (5.27)
31	2	$CH_2C_6H_5$	H	$(CH_2)_5CH_3$	8	44.9	151-152 (0.5)	$C_{17}H_{25}NO_2$	74.14 (74.35)	9.15 (9.24)	5.09 (5.04)
32	2	$CH_2C_6H_5$	H	$(CH_2)_6CH_3$	8	48.2	168-169 (0.7)	$C_{18}H_{27}NO_2$	74.70 (75.08)	9.40 (9.43)	4.84 (4.88)
33	2	$CH_2C_6H_5$	H	$(CH_2)_7CH_3$	8.5	24.0	165-166 (0.4)	$C_{19}H_{29}NO_2$	75.20 (75.07)	9.63 (9.88)	4.62 (4.46)
34	2	$CH_2C_6H_5$	H	$(CH_2)_8CH_3$	9	23.7	172-174 (0.4)	$C_{20}H_{31}NO_2$	75.67 (75.65)	9.84 (9.80)	4.41 (4.42)
35	2	$CH_2C_6H_5$	H	C_6H_5	5	53.0	168-170 (0.6)	$C_{17}H_{17}NO_2$	76.38 (76.08)	6.41 (6.48)	5.24 (5.36)
36	2	$CH_2C_6H_5$	H	$CH_2C_6H_5$	10	70.1	72-73/ether	$C_{18}H_{19}NO_2$	76.84 (76.86)	6.81 (6.76)	4.98 (4.91)

Table II. Spectral Data of the Cyclisation Products

Compd. No.	IR $\nu_{max.}^{neat}$ cm^{-1} (C=O)	NMR ($CDCl_3$) δ
11	1700	1.41 (3H, d, J 5.5 Hz, $CHCH_3$), 2.81 (3H, s, N-CH_3), 4.23 (2H, t, J 1 Hz, 5-H), 4.9-5.4 (1H, m, 2-H)
12	1700	2.64 (3H, s, N-CH_3), 4.38, 4.42 (2H, dd, J 15 Hz, 1.5 Hz, 5-H), 5.84 (1H, t, J 1.5 Hz, 2H), 7.41 (5H, s, aromatic protons)
13	1700	1.3-2.2 (10H, m, -$(CH_2)_5$-), 2.82 (3H, s, N-CH_3), 4.23 (2H, s, 5-H)
14	1700	1.30 (3H, d, J 5 Hz, $CHCH_3$), 4.27, 4.33 (2H, dd, J 15 Hz, 1.5 Hz, 5-H), 4.14, 4.83 (2H, each d, J 16 Hz, N-$CH_2C_6H_5$), 4.9-5.3 (1H, m, 2-H), 7.25 (5H, s, aromatic protons)
15	1700	3.55, 4.99 (2H, each d, J 15 Hz, N-$CH_2C_6H_5$), 4.41, 4.50 (2H, dd, J 14 Hz, 2 Hz, 5-H), 5.73 (1H, t, J 2 Hz, 2-H), 6.9-7.7 (10H, m, aromatic protons)
16	1650	1.45 (3H, d, J 6 Hz, $CHCH_3$), 2.33-2.75 (2H, m, 5-H), 2.87 (3H, s, N-CH_3), 3.47-4.40 (2H, m, 6-H), 4.87 (1H, q, J 6 Hz, 2-H)
17	1650	0.93 (3H, t, J 7.5 Hz, CH_2CH_3), 1.5-2.1 (2H, m, CH_2CH_3), 2.3-2.7 (2H, m, 5-H), 2.86 (3H, s, N-CH_3), 3.5-4.4 (2H, m, 6-H), 4.68 (1H, dd, J 5 Hz, 4 Hz, 2-H)
18	1650	0.6-2.0 (11H, m, $(CH_2)_4CH_3$), 2.3-2.7 (2H, m, 5-H), 2.87 (3H, s, N-CH_3), 3.5-4.4 (2H, m, 6-H), 4.73 (1H, t, J 5 Hz, 2-H)
19	1640	2.4-3.0 (5H, m, N-CH_3, 5-H), 3.7-4.3 (2H, m, 6-H), 5.64 (1H, s, 2-H), 7.37 (5H, aromatic protons)
20	1655	2.2-2.6 (2H, m, 5-H), 2.6-3.4 (5H, m, $CHCH_2C_6H_5$, N-CH_3), 3.45-4.3 (2H, m, 6-H), 4.9 (1H, dd, J 7 Hz, 3.5 Hz, 2-H), 7.25 (5H, s, aromatic protons)

21	1640	0.6-2.1 (10H, m, $-(CH_2)_5-$), 2.47 (2H, t, J 6 Hz, 5-H), 2.86 (3H, s, $N-CH_3$), 3.88 (2H, t, J 6 Hz, 6-H)
22	1650	1.88 (3H, s, $C-CH_3$), 2.3-2.8 (2H, m, 5-H), 2.90 (3H, s, $N-CH_3$), 3.23-3.96 (2H, m, 6-H), 7.33 (5H, s, aromatic protons)
23	1650	0.6-2.1 (12H, m, $C-C_2H_5$, $C-C_3H_7$), 2.46 (2H, t, J 6 Hz, 5-H), 2.84 (3H, s, $N-CH_3$), 3.90 (2H, t, J 6 Hz, 6-H)
24	1650	1.34 (3H, d, J 6 Hz, $CHCH_3$), 2.2-2.8 (2H, m, 5-H), 3.5-4.3 (2H, m, 6-H), 4.32, 4.94 (2H, each d, J 16 Hz, $N-CH_2C_6H_5$), 4.83 (1H, q, J 6 Hz, 2-H), 7.26 (5H, s, aromatic protons)
25	1650	0.84 (3H, t, J 7 Hz, CH_2CH_3), 1.4-2.0 (2H, m, CH_2CH_3), 2.4-2.8 (2H, m, 5-H), 3.5-4.2 (2H, m, 6-H), 4.19, 5.08 (2H, each d, J 15.5 Hz, $N-CH_2C_6H_5$), 4.64 (1H, t, J 5 Hz, 2-H), 7.27 (5H, s, aromatic protons)
26	1650	0.6-1.9 (7H, m, $(CH_2)_2CH_3$), 2.4-2.8 (2H, m, 5-H), 3.5-4.2 (2H, m, 6-H), 4.23, 5.01 (2H, each d, J 15.5 Hz, $N-CH_2C_6H_5$), 4.67 (1H, t, J 5 Hz, 2-H), 7.24 (5H, aromatic protons)
27	1655	0.76, 0.91 (6H, each d, J 7 Hz, $CH(CH_3)_2$), 1.6-3.1 (3H, m, $CH(CH_3)_2$, 5-H), 3.4-4.3 (2H, m, 6-H), 4.06, 5.19 (2H, each d, J 15.5 Hz, $N-CH_2C_6H_5$), 4.46 (1H, d, J 3 Hz, 2-H), 7.23 (5H, s, aromatic protons)
28	1650	0.5-2.0 (9H, m, $(CH_2)_3CH_3$), 2.4-2.8 (2H, m, 5-H), 3.5-4.5 (2H, m, 6-H), 4.21, 5.06 (2H, each d, J 15.5 Hz, $N-CH_2C_6H_5$), 4.70 (1H, t, J 5 Hz, 2-H), 7.28 (5H, s, aroamtic protons)
29	1650	0.82, 0.89 (6H, each d, J 7 Hz, $CH(CH_3)_2$, 1.3-2.1 (3H, m, $C-CH_2-CH<$), 2.60 (2H, t, J 6 Hz, 5-H), 3.5-4.3 (2H, m, 6-H), 4.17, 5.12 (2H, each d, J 15.5 Hz, $N-CH_2C_6H_5$), 4.73 (1H, dd, J 4 Hz, 8 Hz, 2-H), 7.28 (5H, s, aromatic protons)
30	1655	0.5-1.9 (11H, m, $(CH_2)_4CH_3$), 2.4-2.8 (2H, m, 5-H), 3.5-4.3 (2H, m, 6-H), 4.20, 5.04 (2H, each d, J 15.5 Hz, $N-CH_2C_6H_5$), 4.67 (1H, t, J 5 Hz, 2-H), 7.23 (5H, s, aromatic protons)

31	1655	0.5-2.0 (13H, m, $(CH_2)_5CH_3$), 2.3-2.8 (2H, m, 5-H), 3.5-4.3 (2H, m, 6-H), 4.24, 5.04 (2H, each d, J 15.5 Hz, $N\text{-}CH_2C_6H_5$), 4.70 (1H, t, J 5 Hz, 2-H), 7.26 (5H, s, aromatic protons)
32	1650	0.6-2.1 (15H, m, $(CH_2)_6CH_3$), 2.3-2.9 (2H, m, 5-H), 3.5-4.3 (2H, m, 6-H), 4.19, 5.03 (2H, each d, J 15.5 Hz, $N\text{-}CH_2C_6H_5$), 4.66 (1H, t, J 5 Hz, 2-H), 7.23 (5H, s, aromatic protons)
33	1650	0.6-2.0 (17H, m, $(CH_2)_7CH_3$), 2.5-2.8 (2H, m, 5-H), 3.5-4.3 (2H, m, 6-H), 4.26, 5.09 (2H, each d, J 15.5 Hz, $N\text{-}CH_2C_6H_5$), 4.72 (1H, t, J 5 Hz, 2-H), 7.30 (5H, s, aromatic protons)
34	1650	0.5-2.0 (19H, m, $(CH_2)_8CH_3$), 2.5-2.8 (2H, m, 5-H), 3.5-4.4 (2H, m, 6-H), 4.24, 5.11 (2H, each d, J 15.5 Hz, $N\text{-}CH_2C_6H_5$), 4.72 (1H, t, J 5 Hz, 2-H), 7.30 (5H, s, aromatic protons)
35	1650	2.69 (2H, t, J 6 Hz, 5-H), 3.47, 5.43 (2H, each d, J 15 Hz, $N\text{-}CH_2C_6H_5$), 3.86, 3.92 (2H, each t, J 6 Hz, 6-H), 5.63 (1H, s, 2-H), 6.9-7.6 (10H, m, aromatic protons)
36	1640	2.43-2.80 (2H, m, 5-H), 2.85-3.13 (2H, m, $C\text{-}CH_2C_6H_5$), 3.46-4.34 (2H, m, 6-H), 4.28, 5.15 (2H, each d, J 15.5 Hz, $N\text{-}CH_2C_6H_5$), 4.89 (1H, dd, J 7 Hz, 4 Hz, 2-H), 6.9-7.7 (10H, m, aromatic protons)

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