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Synthesis of Pyrazolone Derivatives. XXIX.[1] Synthesis of 1,3-Dioxolane-indazole Derivatives

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Several 2′-phenyl-spiro[1,3-dioxolane-2,5′-indazoles] having alkyl or alkoxy side chains at 1′(III), 3′a(IV) and 3′(V) were prepared as analgesic agents. III and IV were derived to oxo-indazoles (VII, VIII), which were hydrogenated to give the corresponding hydroxy indazoles (IX, X). Some of these compounds showed slight analgesic activity.

Keywords——pyrazolone; indazole; dioxaspiro-decane; alkylation; keto-enol tautomer; analgesic

In our study concerning the structure-activity relationships of the series of pyrazolone derivatives, it seems to be interest to synthesize and test the pharmacological activities of indazole derivatives having some alkyl groups on their 1′-N, 3′a-C or 3′-O position. This paper describes the synthesis and analgesic activity test of such indazole derivatives.

Starting material 7-ethoxycarbonyl-8-oxo-1,4-dioxaspiro [4,5] decane (II) was obtained from diethyl γ,γ-ethylenedioxypimelate by the method of Gardner, *et al.*[3] The compound (II) was allowed to react with phenylhydrazine or *p*-nitrophenylhydrazine to give 4′,6′, 7′-trihydro-3′-hydroxy-2′-phenyl-spiro[1,3-dioxolane-2,5′-[2H]indazole] (Ia) and 4′,6′,7′-trihydro-3′-hydroxy-2′-*p*-nitrophenyl-spiro[1,3-dioxolane-2,5′-[2H]indazole] (Ib) respectively, Theoretically, Ia,b may exist in tautomeric forms. The infrared (IR) spectra of Ia,b in KBr disks showed absorptions at 3460 and 3450 cm^{-1} respectively for the OH group, and no carbonyl absorption was observed. On the contrary, in chloroform solution they showed characteristic amide carbonyl absorptions 1710 cm^{-1}. In the nuclear magnetic resonance (NMR) spectra, no hydroxy proton was observed, and cyclic 7 protons were observed at 1.9—2.7 ppm. These facts supported that Ia,b exist as keto-enol tautomers.

Alkylation of Ia,b was then carried out. The compounds (Ia,b) were allowed to react with alkyl halide in the presence of potassium carbonate or sodium alkoxide to give a mixture of 1′N-alkyl (III) and angular 3′aC-alkyl (IV) derivatives, which were separated and purified through chromatography on silica gel.

The structure of IV was confirmed by an alternative synthesis. A facile alkylation of ethyl oxocyclopentane carboxylate in acetone was reported lately by Barco, *et al.*[4] Using their method, II was allowed to react with alkyl halide to give 7-alkyl-7-ethoxycarbonyl-8-oxo-1,4-dioxaspiro[4,5]decanes (VI). Compounds (VIa—c) were then condensed with phenylhydrazines to give IVa,c,d which were found to be identical with the compounds (IVa,c,d) obtained from I.

The structure of III was supported by analytical and spectral data. Although alkylation of I under the condition described above did not give 3′-alkoxy derivatives (V),

1) Part XXVIII: I. Ito, N. Oda, and S. Nagai, *Ann. Rept. Pharm. Nagoya City Univ.*, 23, 44 (1975).
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3) P.D. Gardner, L. Rand, and G.R. Haynes, *J. Am. Chem. Soc.*, **78**, 3425 (1956).
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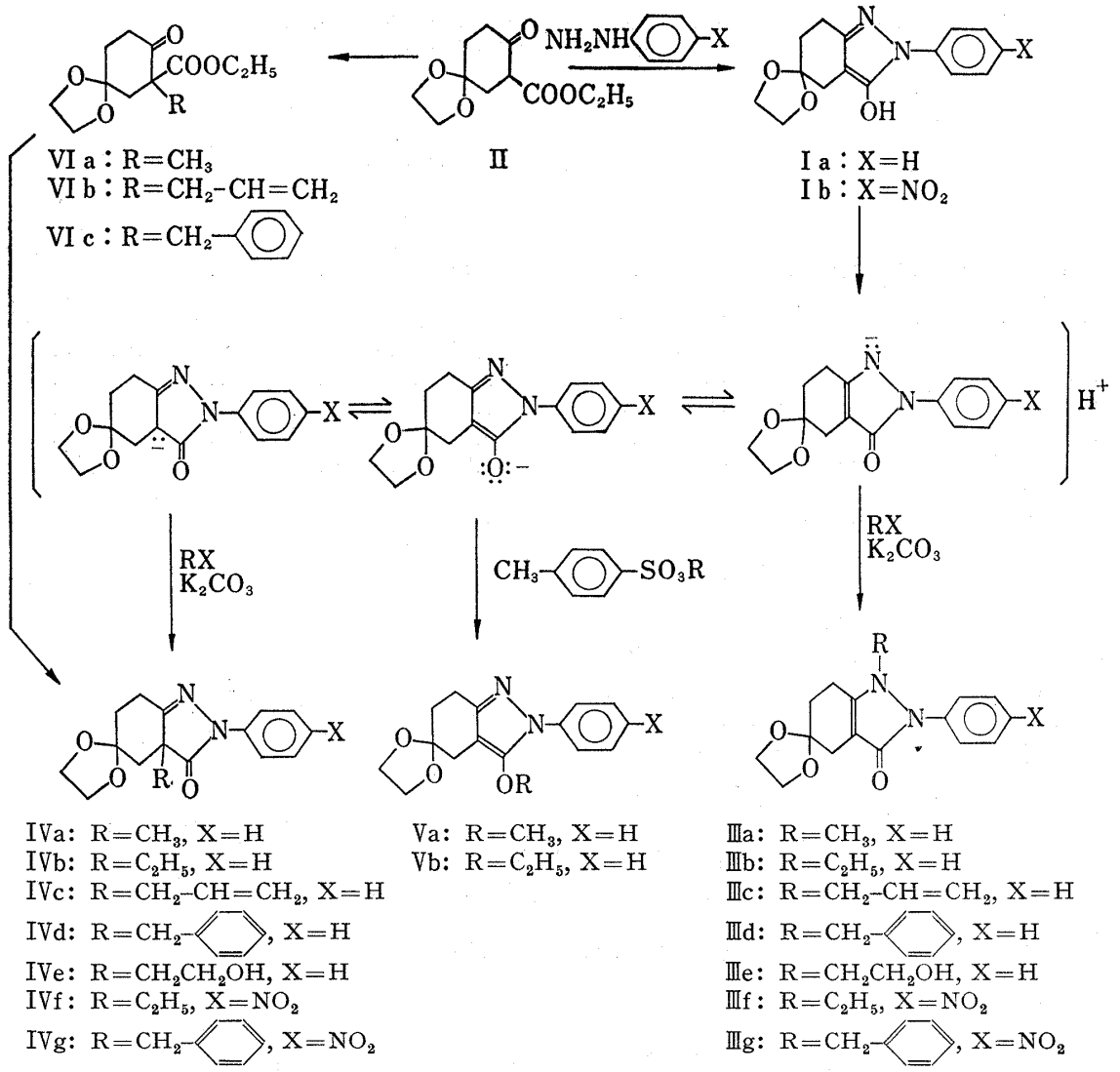


Chart 1

treatment of I with alkyl *p*-toluenesulfonate and sodium hydride in an aprotic solvent, dimethylformamide (DMF) gave Va,b. Va,b exhibited no carbonyl absorptions in the IR spectra. The analytical data and the melting points of IIIa—g and IVa—g were shown in Table I and II.

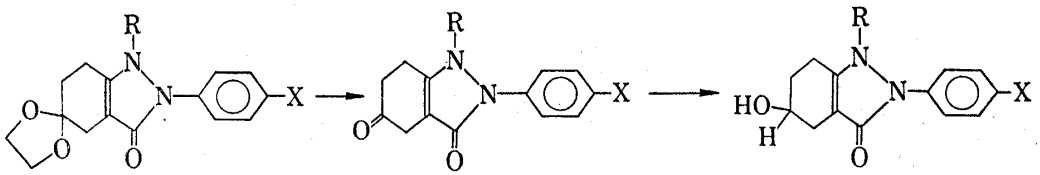
TABLE I. 1′-Alkyl-2′,3′,4′,6′,7′-pentahydro-3′-oxo-2′-phenyl-spiro[1,3-dioxolane-2,5′-[1H]indazoles] (III)

No.	mp(°C)	Formula	Analysis (%)					
			Calcd.			Found		
			C	H	N	C	H	N
IIIa	131—132	$C_{16}H_{18}O_3N_2$	67.12	6.34	9.78	67.27	6.35	9.97
IIIb	141—142	$C_{17}H_{20}O_3N_2$	67.98	6.71	9.33	67.72	6.71	9.26
IIIc	96— 97	$C_{18}H_{20}O_3N_2$	69.21	6.45	8.97	69.27	6.34	8.95
IIId	193—194	$C_{22}H_{22}O_3N_2$	72.91	6.12	7.73	73.08	5.87	7.64
IIIe	193—194	$C_{17}H_{20}O_4N_2$	64.54	6.37	8.86	64.57	6.37	8.62
IIIf	165—166	$C_{17}H_{19}O_5N_3$	59.12	5.55	12.17	59.10	5.61	12.25
IIIg	121—123	$C_{22}H_{21}O_5N_3$	64.86	5.20	10.31	64.77	5.20	10.34

Table II. 3′a-Alkyl-3′,3′a,4′,6′,7′-pentahydro-3′-oxo-2′-phenyl-spiro[1,3-dioxolane-2,5′-[2H]indazoles] (IV)

No.	mp(°C) bp(°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVa	bp 168—170 (0.5 mmHg)	$C_{16}H_{18}O_3N_2$	67.12	6.34	9.78	67.39	6.59	9.82
IVb	*a*)	$C_{17}H_{20}O_3N_2$	67.98	6.71	9.33	67.90	6.51	9.35
IVc	*a*)	$C_{18}H_{20}O_3N_2$	69.21	6.45	8.97	69.18	6.35	8.71
IVd	mp 124—126	$C_{22}H_{22}O_3N_2$	72.91	6.21	7.73	73.20	5.92	7.81
IVe	*a*)	$C_{17}H_{20}O_4N_2$	64.54	6.37	8.86	64.35	6.93	8.86
IVf	mp 165—166	$C_{17}H_{19}O_5N_3$	59.12	5.55	12.17	58.91	5.36	12.10
IVg	mp 238—239	$C_{22}H_{21}O_5N_3$	64.86	5.20	10.31	64.91	5.05	10.07

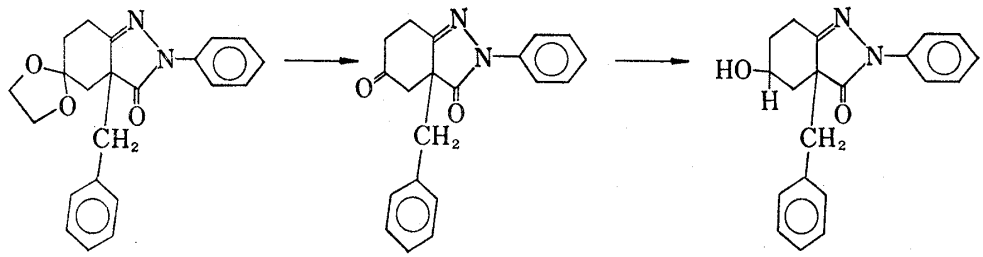
a) refined through a column chromatography (Wakogel C-200)



III

VII a : R=CH_3, X=H
VII b : R=C_2H_5, X=H
VII c : R=CH_2—⬡ , X=H
VII d : R=C_2H_5, X=NO_2

IX : R=C_2H_5, X=H



IVd VIII X

Chart 2

Table III. 1-Alkyl-2,3,4,5,6,7-hexahydro-3,5-dioxo-2-phenyl-1H-indazoles (VII)

No.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIa	149—150	$C_{14}H_{14}O_2N_2$	69.41	5.82	11.56	69.38	5.76	11.57
VIIb	143—144	$C_{15}H_{16}O_2N_2$	70.25	6.29	10.93	70.27	6.47	10.85
VIIc	186—187	$C_{20}H_{18}O_2N_2$	75.45	5.70	8.80	75.51	5.82	8.58
VIId	223—224	$C_{15}H_{15}O_3N_3$	59.79	5.02	13.95	60.05	5.22	13.75

The ketal compounds (IIIa,b,d,f and IVd) were treated with diluted hydrochloric acid to give the corresponding oxo-compounds (VIIa—d and VIII). Compounds (VIIa—d and VIII) showed characteristic 6-membered cyclic carbonyl absorptions at about 1710 cm^{-1}. The analytical data and the melting points of VIIa—d were shown in Table III.

The oxo-compounds (VIIb and VIII) were reduced with sodium borohydride to give hydroxy indazoles (IX and X).

Analgesic Activity

The analgesic activity of these compounds was determined by the acetic acid writhing method. Writhing was induced in mice by an intraperitoneal injection of 0.6% acetic acid (10 ml/kg). Occurrence of writhes in the subsequent period of 10—15, 25—30, 40—45 and 55—60 min was observed. As shown in Table IV, compounds, IIId, VIIb and VIIc showed slight analgesic activity, but others did not have any effect. The effects of the compounds were weaker than that of aminopyrine.

Table IV. Analgesic Effects on Mice

Compd. 100 mg/kg *p.o.*	Number of mice used	Times				Total		Inhibitory %
		1	2	3	4	ratio	%	
Control	10	10	10	10	9	39/40	98	—
Aminopyrine	10	2	3	3	3	11/40	28	71
IIIb	10	9	9	9	8	35/40	88	10
IIId	9	6	7	5	5	23/36	64	35
IVd	10	9	9	8	8	34/40	85	13
Vb	10	10	10	10	8	38/40	95	3
VIIa	10	10	10	9	9	38/40	95	3
VIIb	8	7	7	6	5	25/32	78	20
VIIc	10	8	9	8	7	32/40	80	18
VIII	10	9	9	9	9	36/40	90	8

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and uncorrected. IR spectra were taken on a Nihon Bunko IR-G spectrophotometer. UV spectra were measured on a Hitachi EPS-3T spectrophotometer. NMR spectra were measured on a Jeol JNM-NH-100 spectrometer using tetramethylsilane as an internal standard.

4′,6′,7′-Trihydro-3′-hydroxy-2′-phenyl-spiro[1,3-dioxolane-2,5′-[2H]indazoles] (Ia, b)——A solution of 0.1 mol of II[3] and 0.1 mol of phenylhydrazines in 50 ml of EtOH was refluxed for 12 hr. After evaporation of the solvent, the crystals which appeared were recrystallized from AcOEt. 4′,6′,7′-Trihydro-3′-hydroxy-2′-phenyl-spiro[1,3-dioxolane-2,5′-[2H]indazole] (Ia): Colorless prisms, mp 190—191°. Yield, 22.6 g (83.1%). *Anal.* Calcd. for $C_{15}H_{16}O_3N_2$: C, 66.16; H, 5.92; N, 10.30. Found: C, 66.13; H, 5.94; N, 10.39. IR ν_{max}^{KBr} cm^{-1}: 3460 (OH), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (–C–N). NMR ($CDCl_3$: DMSO-d_6=1: 1) δ: 2.0—2.7 (7H, cyclic H), 4.0 (4H, singlet, ). 4′,6′,7′-Trihydro-3′-hydroxy-2′-*p*-nitrophenyl-spiro[1,3-dioxolane-2,5′-[2H]indazole] (Ib): Yellow needles, mp 235—236°. Yield, 21.8 g (68.8%). *Anal.* Calcd. for $C_{15}H_{15}O_5N_3$: C, 56.78; H, 4.78; N, 13.24. Found: C, 56.46; H, 4.63; N, 13.13. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (–C–N). NMR ($CDCl_3$: DMSO-d_6=1: 1) δ: 1.9—2.7 (7H, cyclic H), 4.0 (4H, singlet, ).

1′-Alkyl-2′,3′,4′,6′,7′-pentahydro-3′-oxo-2′-phenyl-spiro[1,3-dioxolane-2,5′-[1H]indazoles] (IIIa—g) and 3′a-Alkyl-3′,3′a,4′,6′,7′-pentahydro-3′-oxo-2′-phenyl-spiro[1,3-dioxolane-2,5′-[2H] indazoles] (IVa—g)——a) A solution of 0.01 mol of I, 0.04 mol of K_2CO_3 and 0.02 mol of alkyl halide in 30 ml of acetone and 5 ml of MeOH was stirred for 24 hr at room temperature. The reaction mixture was then filtered. The filtrate was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (Wakogel

C-200). Elution with $CHCl_3$ gave IIIa—g, which was crystallized from AcOEt. The results are summarized in Table I. Elution with MeOH–$CHCl_3$ (2: 100) gave IVa—g. The results are summarized in Table II.

b) A solution of 0.01 mol of I and 0.01 mol of alkyl halide in 30 ml of anhydrous MeOH containing 0.01 atom of Na was refluxed for 12 hr. After evapolation of the solvent, the residue was neutralized with dilute AcOH. The mixture was extracted with $CHCl_3$, washed with water and evaporated. The residue was chromatographed on a column of silica gel (Wakogel C-200). Elution with $CHCl_3$ gave IIIa—g and elution with MeOH–$CHCl_3$ (2: 100) gave IVa—g. Their physical data were identical with these of the products obtained by the method a).

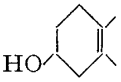
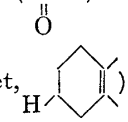
c) A solution of 0.01 mol of VIa—c and 0.01 mol of phenylhydrazine in 30 ml of anhydrous EtOH was refluxed for 10 hr. After evaporation of the solvent, the residue was crystallized from AcOEt to give IVa, c, d. Their physical data were identical with these of the products obtained by the method a) and b).

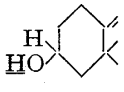
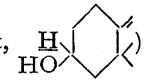
3′-Alkoxy-4′,6′,7′-trihydro-2′-phenyl-spiro[1,3-dioxolane-2,5′-[2H]indazoles] (Va, b)——A solution of 0.01 mol of I, 0.01 mol of NaH and 0.01 mol of alkyl *p*-toluenesulfonate in 100 ml of DMF was stirred at 120° for 2 hr. The mixture was poured onto 100 ml of water and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. The extract was evaporated under reduced pressure. The crude material was purified by chromatography on a column of silica gel (Wakogel C-200) with $CHCl_3$. 3′-Methoxy-4′,6′,7′-trihydro-2′-phenyl-spiro[1, 3-dioxolane-2,5′-[2H] indazole] (Va): Colorless oil. Yield, 1.86 g (65.0%). *Anal.* Calcd. for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.10; H, 6.30; N, 9.70. NMR ($CDCl_3$) δ: 3.90 (3H, singlet, OCH_3). UV λ_{max}^{EtOH} nm (log ε): 254 (4.38). 3′-Ethoxy-4′,6′,7′-trihydro-2′-phenyl-spiro[1,3-dioxolane-2,5′-[2H]indazole] (Vb): Colorless oil. Yield, 1.8 g (60.0%). *Anal.* Calcd. for $C_{17}H_{20}O_3N_2$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.81; H, 6.67; N, 9.31. NMR ($CDCl_3$) δ: 1.3 (3H, triplet, $OCH_2\underline{CH_3}$), 4.3 (2H, quartet, $OC\underline{H_2}CH_3$). UV λ_{max}^{EtOH} nm (log ε): 253 (4.24).

7-Alkyl-7-ethoxycarbonyl-8-oxo-1,4-dioxaspiro[4,5]decanes (VIa—c)——A solution of 0.01 mol of II, 5.5 g of K_2CO_3 and 0.02 mol of alkyl halide in 30 ml of acetone was refluxed for 5 hr. The mixture was filtered. After evaporation of the solvent, the residue was distilled. The product was used for the next step without further purification. bp: VIa, 132—133° (2 mmHg); VIb, 135—136° (3.5 mmHg); VIc, 180—181° (0.8 mmHg).

1-Alkyl-2,3,4,5,6,7-hexahydro-3,5-dioxo-2-phenyl-1H-indazoles (VIIa—d)——A mixture of 0.005 mol of III, 50 ml of 0.1N HCl and 10 ml of MeOH was refluxed for 3 hr. The mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was crystallized from benzene to give the oxo-compounds. The results are summarized in Table III.

3a-Benzyl-3,5-dioxo-2-phenyl-3,3a,4,5,6,7-hexahydro-2H-indazole (VIII)——A mixture of 1.81 g (0.005 mol) of IVd, 50 ml of 20% HCl and 10 ml of MeOH was refluxed for 5 hr. The mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was crystallized from AcOEt to colorless needles, mp 89—90°. Yield, 0.88 g (55.4%). *Anal.* Calcd. for $C_{20}H_{18}O_2N_2$: C, 75.54; H, 5.70; N, 8.80. Found: C, 75.53; H, 6.00; N, 8.72. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO). NMR ($CDCl_3$) δ: 2.5—3.3 (8H, multiplet, cyclic H and $-C\underline{H_2}$–Ph), 7.1 (5H, singlet, CH_2–Ph), 7.2—7.6 (5H, multiplet, –N–Ph).

1-Ethyl-2,3,4,5,6,7-hexahydro-5-hydroxy-3-oxo-2-phenyl-1H-indazole (IX)——To a solution of 1.78 g (0.005 mol) of VIIb in 50 ml of tetrahydrofuran (THF) was added 189 mg (0.005 mol) of $NaBH_4$ gradually, and then the mixture was heated to reflux for 2 hr. After evaporation of the solvent, water was added to the mixture and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was crystallized from EtOH to colorless prisms, mp 144°. Yield, 0.9 g (69.7%). *Anal.* Calcd. for $C_{15}H_{18}O_2N_2$: C, 69.84; H, 7.02; N, 10.84. Found: C, 69.68; H, 7.30; N, 10.56. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1650 (–C(=O)–N). NMR ($CDCl_3$) δ: 3.3 (1H, doublet,  exchanged with deuterium oxide), 4.1 (1H, triplet, ).

3a-Benzyl-3,3a,4,5,6,7-hexahydro-5-hydroxy-3-oxo-2-phenyl-2H-indazole (X)——To a solution of 1.59 g (0.005 mol) of VIII in 30 ml of THF was added 189 mg (0.005 mol) of $NaBH_4$ gradually. After completion of the addition, the mixture was heated to reflux for 2 hr. The mixture was concentrated, water was added and then extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was crystallized from EtOH to colorless prisms, mp 160—161°. Yield, 1.1 g (68.8%). *Anal.* Calcd. for $C_{20}H_{20}O_2N_2$: C, 74.98; H, 6.30; N, 8.74. Found: C, 74.88; H, 6.48; N, 8.48. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1685 (–C(=O)–N). NMR ($CDCl_3$) δ: 1.9 (1H, doublet,  exchanged with deuterium oxide), 2.3 (1H, multiplet, ).