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C-13 NMR Spectra of Barbituric Acid Derivatives. II[1]

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Carbon-13 nuclear magnetic resonance spectra of thirty-two kinds of 5,5-disubstituted barbituric acid derivatives were measured. Two conclusions were obtained from analyses of these spectra. (1) The additive law is applicable to chemical shifts of sp^3-hybridized carbons. (2) Hammett's constant σ in Hansch analysis can be replaced by a quantity A expressed by the value related to chemical shifts of the 5-position carbon.

In the previous paper, the authors have considered C-13 nuclear magnetic resonance (NMR) spectra of 5-monosubstituted barbituric acid derivatives and have pointed out that the additive law is applicable to the carbon at 5-position and that there is a good correlation between chemical shifts of the carbon at 5-position and pK_a values.

In this paper, we discuss C-13 NMR spectra of 5,5-disubstituted barbituric acid derivatives.

Results and Discussion

Result of Measurement

C-13 chemical shifts of 5,5-disubstituted barbituric acid derivatives are shown in Table I. Table II shows chemical shifts of substituent carbons of 5-monosubstituted barbituric acid derivatives, whose chemical shifts of ring carbons have been shown in the previous paper.

Chemical shifts in Tables I and II are the values in ppm upfield from CS_2. As an example of spectra, the chart of 5-ethyl-5-allylbarbituric acid, for which 16 scans were accumulated, is shown in Fig. 1.

Assignments of Chemical Shifts

Comparing the original charts, we assigned the chemical shifts of the substituent carbons as follows.

(1) The methyl carbons of isopropyl-, isobutyl- and isoamyl-groups show the signals which are twice as strong as the signals of the other carbons (Table III).

These signals are easily assigned. Therefore, we estimate that the terminal methyl carbons in isoalkyl groups show chemical shifts at 174.5 (at 2′), 169.1 (at 3′) and 169.8 (at 4′) respectively.…………(Estimation 1)

(2) In general, the terminal methyl carbons in *n*-alkyl groups show the signals in higher field compared with the middle methylen carbons. Now, about the ethyl group of **15**, we assigned 182.4 to the terminal methyl carbon, and 163.3 to the methylen carbon. These estimations coincide with the results of K. Rehse.[3]…………(Estimation 2)

Using Estimation 2, we assigned the ethyl group of compound No. **8** (182.5 to CH_3, 160.3 to CH_2) and those from **9** to **15** similarly.

(3) Comparing the signals of **1** and **8**, we assigned the signal at 169.7 to the carbon of methyl group.…………(Estimation 3)

Using Estimation 3, we assigned the carbons of methyl groups in **2**—**6**.

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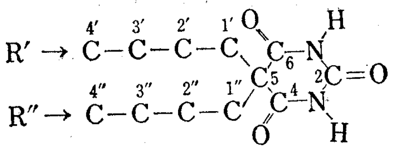
[1] Part I: J. Okada and T. Esaki, *Yakugaku Zasshi*, 93, 1014 (1973).

[2] Location: *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*

[3] K. Rehse, *Deut. Apotheker Zeitung*, 112, 1194 (1972).

Table I. C–13 Chemical Shifts of 5,5-Disubstituted Barbituric Acid Derivatives



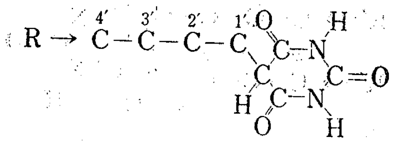
No.	R′	R″	Ring				Side chain R′				Side chain R″			
			C–2	C–4	C–5	C–6	C–1′	C–2′	C–3′	C–4′	C–1″	C–2″	C–3″	C–4″ (ppm)
1	methyl	ethyl	41.9	18.3	140.8	18.3	169.7				159.6	182.7		
2	methyl	propyl	43.1	18.4	141.7	18.4	169.0				(152.3)[a]	173.9	178.1	
3	methyl	isopropyl	41.7	18.7	138.3	18.7	173.9				154.7	174.3 ×2[b]		
4	methyl	butyl	42.3	18.8	142.0	18.8	169.1				153.4	165.2	169.9	178.3
5	methyl	isobutyl	42.3	18.5	143.0	18.5	167.0				145.7	167.2	169.4 ×2	
6	methyl	*sec*-butyl	41.8	18.6	138.1	18.9	173.0				148.0	167.8 178.1	179.4	
7	methyl	1-cyclohexenyl	41.9	20.0	136.0	20.0	—				—	—	—	—
8	ethyl	ethyl	42.3	19.2	135.5	19.2	160.3	182.5			160.3	182.5		
9	ethyl	propyl	42.4	19.3	136.1	19.3	160.6	183.5			152.4	174.5	178.7	
10	ethyl	isopropyl	42.2	19.7	132.9	19.7	165.1	183.1			155.5	174.8 ×2		
11	ethyl	butyl	42.0	18.7	135.9	18.7	159.9	182.7			153.8	165.0	169.5	178.4
12	ethyl	isobutyl	42.7	19.2	137.5	19.2	157.9	183.3			149.5	166.8	168.9 ×2	
13	ethyl	isoamyl	42.7	19.5	136.2	19.5	(160.4)	183.0			157.1	158.3	164.1	169.6
14	ethyl	allyl	42.6	20.0	134.1	20.0	159.4	181.8			148.5	60.8	72.9	
15[c]	ethyl	phenyl	42.3	20.8	131.9	20.8	163.3	182.4			53.8	63.3 ×2	66.2 ×2	64.2
16	propyl	propyl	42.4	19.1	137.2	19.1	151.7	174.6	178.6		151.7	174.6	178.6	
17	propyl	isopropyl	42.2	19.6	133.9	19.6	155.6	173.8	178.2		155.0	174.7 ×2		
18	propyl	butyl	42.4	19.1	136.8	19.1	(152.1)	173.9	178.4		153.6	165.2	169.8	178.4
19	propyl	isobutyl	42.5	19.2	138.0	19.2	149.1	174.4	178.2		145.5	166.8	168.8 ×2	
20	propyl	isoamyl	42.1	18.7	136.8	18.7	(151.8)	174.1	178.4		155.7	158.5	164.4	169.9 ×2
21	propyl	allyl	42.8	19.9	136.6	19.9	(152.4)	174.4	178.5		152.1	61.1	72.9	
22	isopropyl	butyl	41.9	19.3	133.5	19.3	154.4	174.0 ×2			157.6	164.4	169.1	178.0
23	isopropyl	allyl	42.3	20.2	133.7	20.2	155.0	174.5 ×2			153.7	60.0	72.6	
24	butyl	butyl	42.5	19.3	137.0	19.3	153.8	165.2	169.9	178.6	153.8	165.2	169.9	178.6
25	butyl	isobutyl	42.4	19.0	137.9	19.0	(152.5)	165.6	169.5	178.2	145.2	166.5	168.6 ×2	
26	butyl	isoamyl	42.5	19.1	137.0	19.1	153.6	165.2	169.8	178.3	155.2	158.3	164.2	169.8 ×2
27	butyl	allyl	42.4	19.6	136.5	19.6	153.6	164.9	169.3	178.0	149.4	60.8	72.4	
28	isobutyl	isobutyl	42.4	18.9	139.2	18.9	143.6	167.6	169.3 ×2		143.6	167.6	169.3 ×2	
29	isobutyl	allyl	42.9	19.7	138.2	19.7	146.5	167.4	169.5 ×2		148.1	61.4	72.4	
30	isoamyl	isoamyl	42.5	19.1	136.9	19.1	155.2	158.3	164.2	169.7 ×2	155.2	158.3	164.2	169.7 ×2
31	isoamyl	allyl	42.5	19.7	136.8	19.7	156.0	158.3	164.3	169.7 ×2	149.6	60.8	72.4	
32	allyl	allyl	42.6	20.4	136.8	20.4	150.3	61.1	72.3		150.3	61.1	72.3	

[a] The parenthesized numbers are not detected, but estimated.

[b] Symbol "×2" means double intensity.

[c] Our data coincide with that of K. Rehse, *Deut. Apotheker Zeitung*, **112**, 1194 (1972).

Table II. C-13 Chemical Shifts of 5-Monosubstituted Barbituric Acid Derivatives



No.	R	Side chain C-1′	C-2′	C-3′	C-4′ (ppm)
33	methyl	180.7			
34	ethyl	170.3	181.9		
35	propyl	161.4	172.7	178.2	
36	isopropyl	159.9	172.5 ×2[a)]		
37	butyl	(162.5)[b)]	163.7	169.5	178.2
38	isobutyl	(152.3)	166.3	169.7 ×2	
39	*sec*-butyl	153.4	165.3 175.7	180.0	
40	isoamyl	164.3	157.1	165.6	169.6 ×2
41	allyl	159.9	59.1	73.9	

a) Symbol "×2" means double intensity.
b) The parenthesized numbers are not detected, but estimated.

Table III. Assignment of Double Intensity Signals

Deriv. No.	$-CH\langle^{\underline{C}H_3}_{\underline{C}H_3}$	Deriv. No.	$-CH_2-CH\langle^{\underline{C}H_3}_{\underline{C}H_3}$	Deriv. No.	$-CH_2-CH_2-CH\langle^{\underline{C}H_3}_{\underline{C}H_3}$
3	174.3	**5**	169.4	**13**	169.6
10	174.8	**12**	168.9	**20**	169.9
17	174.7	**19**	168.8	**26**	169.8
22	174.0	**25**	168.6	**30**	169.7
23	174.5	**28**	169.3	**31**	169.7
		29	169.5		
Mean	174.5	Mean	169.1	Mean	169.8 (ppm)

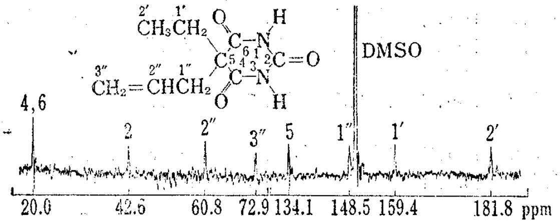


Fig. 1. Spectrum of 5-Ethyl-5-allylbarbituric Acid (3м DMSO, 16 Scans)

(4) Using Estimation 1, 2 and 3, we assigned the signals of **2** as follows.

$R' = -CH_3$ $R'' = -CH_2-CH_2-CH_3$
169.0 152.3 173.9 178.1

(5) Analyzing the signal pattern of **14** in the partial proton decoupled state, we assigned the signals of the double bond carbons in allyl group as follows.............(Estimation 4)

$R'' = -CH_2-CH=CH_2$
doublet triplet
148.5 60.8 72.9

Using Estimation 4, we assigned the double bond carbons of allyl groups in **21**, **23**, **27**, **29**, **31**, **32** and **41**.

(6) Repeating the above mentioned estimations, we could assign all the signals, except **7**. The results are shown in Tables I and II.

Additive Law[4]

(1) Chemical Shifts of the Carbon at 5-Position——An additive equation was calculated on chemical shifts of the carbon at 5-position. Analysis was carried out according to the procedure described in the previous paper. The result is shown as an equation (1).

$$\delta_C(5) = 151.44 + \sum_l A_l n_l \qquad (1)$$

$\delta_C(5)$: chemical shift of the 5-position carbon (ppm)
A_l : additive parameter of the carbon at l-th position relative to the 5-position carbon (*cf.* Table IV)
n_l : number of carbon atoms at l-th position relative to the 5-position carbon

Table IV. Additive Parameter Values and 95% Confidence Limits of Equation (1)

	A_l (ppm)		A_l (ppm)
α	-2.97 ± 1.07	γ	0.47 ± 0.44
β	-4.50 ± 0.70	δ	-0.26 ± 0.40

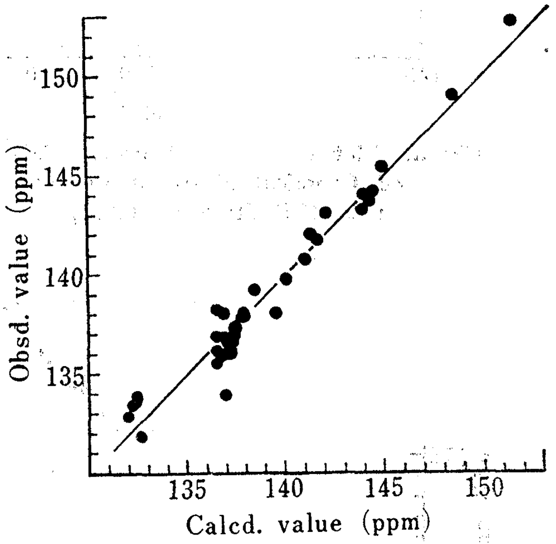


Fig. 2. Plot of Observed *versus* Calculated Chemical Shifts of the Carbon at 5-Position ($r=0.978$, $s=0.912$)

Table IV shows the A_l's values and their 95% confidence limits.

The values estimated by equation (1) are plotted against the observed values in Fig. 2.

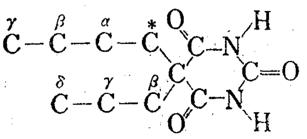
The correlation coefficient (r) is 0.978 and the standard deviation (s) is 0.912.

(2) Chemical Shifts of the Substituent sp^3-Carbons——Additive equations were calculated on chemical shifts of the substituent sp^3-carbons. The analyzing procedures were virtually identical with that used in the case of the carbon at 5-position. Table V shows additive parameters and 95% confidence limits of each position of substituent carbons, obtained as results of the least-squares analyses.

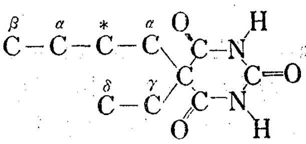
The values estimated using Table V are plotted against the observed values in Fig. 3—6.

Table V. Analyses of Chemical Shifts of Substituent sp^3-Carbons

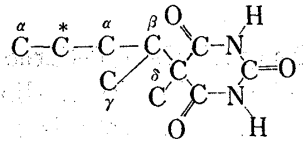
(1) 1′—Position



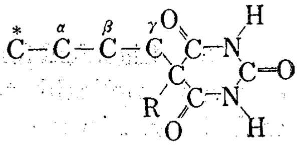
(2) 2′—Position



(3) 3′—Position



(4) 4′—Position



Position	Constant	α	β	γ	δ (ppm)
1′	177.14	-7.70 ± 1.22	-8.57 ± 0.85	1.60 ± 0.81	-1.51 ± 0.97
2′	189.21	-8.07 ± 0.36	-8.34 ± 0.37	2.02 ± 0.75	-0.61 ± 0.55
3′	194.14	-7.12 ± 0.51	-8.70 ± 0.82	1.58 ± 1.66	-0.38 ± 1.18
4′	186.78		-8.59 ± 0.17		

The skelton atoms, which are common to all the derivatives, are neglected in analyses.

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[4] The calculations were performed partly on Facom 230-60 and Facom 230-75 computers of Data Processing Center, Kyoto University.

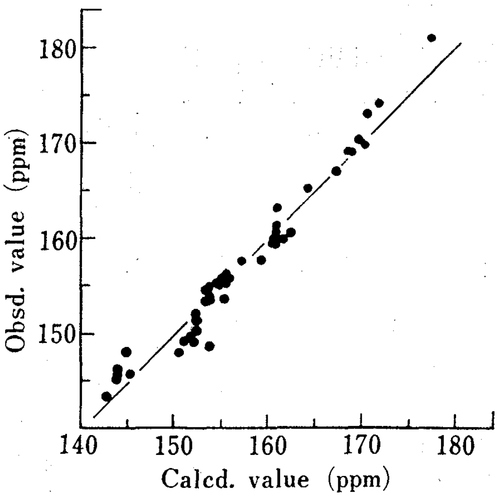

Fig. 3. Plot of Observed *versus* Calculated Chemical Shifts of the sp^3-Carbon at 1′-Position (r=0.977, s=1.727)

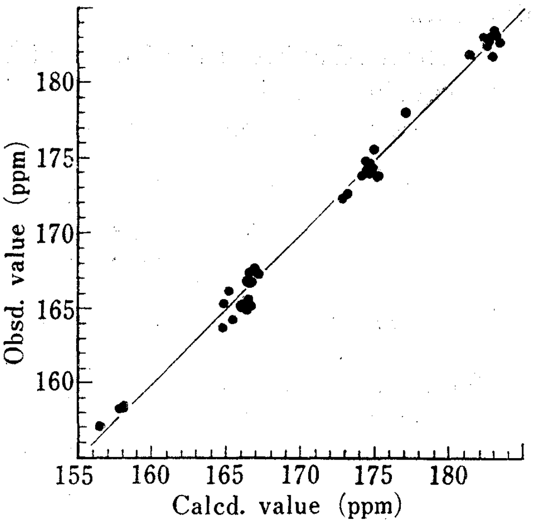

Fig. 4. Plot of Observed *versus* Calculated Chemical Shifts of the sp^3-Carbon at 2′-Position (r=0.996, s=0.715)

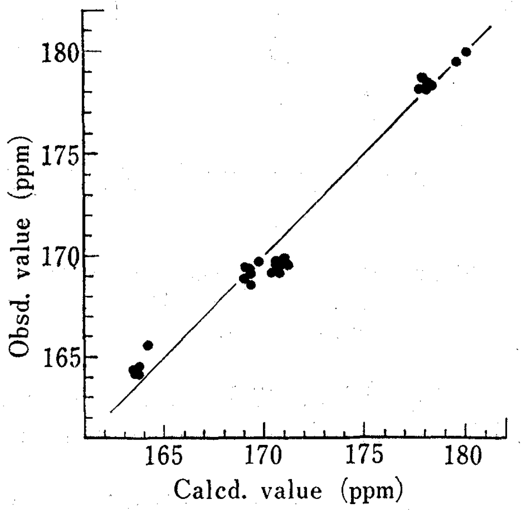

Fig. 5. Plot of Observed *versus* Calculated Chemical Shifts of the sp^3-Carbon at 3′-Position (r=0.989, s=0.744)

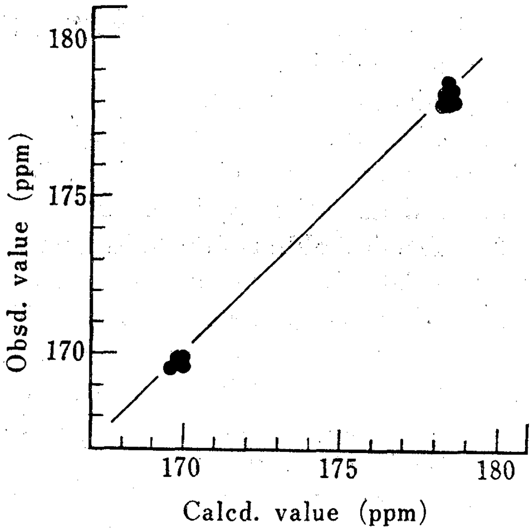

Fig. 6. Plot of Observed *versus* Calculated Chemical Shifts of the sp^3-Carvon at 4′-Position (r=0.9995, s=0.137)

(3) Chemical Shifts of All the sp^3-Carbons——The authors tried to calculate an additive equation applicable to chemical shifts of all the sp^3-carbons, that is, the carbon at 5-position and the substituent sp^3-carbons. In this case, it is satisfactory that an analysis should be

Table VI. Analysis of C-13 Chemical Shifts of the sp^3-Carbon (Example: 5-Ethyl-5-allylbarbituric Acid)

Position	α	β		γ		δ	Chemical shifts (ppm)
	C	C	N+O	C	N+O	C	
5	4	2	2	2	0	0	134.1
1′	2	3	0	1	2	1	159.4
2′	1	1	0	3	0	1	181.8
1″	2	4	0	1	2	1	148.5

carried out including not only carbon atoms but also nitrogen and oxygen atoms. The analyzing procedure in the case of 5-ethyl-5-allylbarbituric acid is shown in Table VI.

Other compounds were analyzed similarly and an additive equation was estimated by the least-squares method. The result is shown as an equation (2).

$$\delta_c(k) = 190.71 + \sum_i B_i n_{ki} \qquad (2)$$

$\delta_c(k)$: chemical shift of C-atom k (ppm)
B_i : additive parameter of the atom at i-th position relative to C-atom k (*cf.* Table VII)
n_{ki} : number of atoms at i-th position relative to C-atom k

Table VII shows the B_i's values and 95% confidence limits. The B_i's values owing to nitrogen and oxygen atoms could not be separated to each other in these cases of barbituric acid derivatives.

The values estimated by equation (2) are plotted against the observed values in Fig. 7. The correlation coefficient (r) is 0.990 and the standard deviation (s) is 2.003.

Now, we tried to examine the additive law considering the bond character of the carbon atom, that is, single bond or double bond. Table VIII shows correlation coefficients (r) and standard deviations (s) in both cases of considering and neglecting the bond character of the carbon atom.

But the differences of correlation coefficients in two cases could not be regarded as significant at 5% significant level.

Structure-Activity Relationship

Hansch and Fujita have proposed an equation (3) for the estimation of biological activities of drugs.[5] Their proposal is based on the assumption that the biological activities are shown by the product of transport facility and affinity to active sites.

$$\log(1/C) = a\pi^2 + b\pi + c\sigma + d \qquad (3)$$

C: calculated from ED_{50}, LD_{50} *etc.*
π: $\log P - \log P_0$ P : partition coefficient (octanol-water)
P_0: P of a standard substance (for example, barbituric acid)
σ : Hammett's σ-constant

In equation (3), log ($1/C$) represents relative biological activities of drugs, π^2 and π represents transport, serum-binding and receptor-binding factors, and σ represents changes in ionization, charge-charge or charge-dipole interaction with receptor, or hydrogen bonding.[6]

The authors think that σ in equation (3) may be replaced by a physical quantity related to electronic structures of drug molecules because the interactions between drugs and receptors will be electronic ones ultimately. We found that hypnotic activities of barbiturates could be estimated fairly well when σ was replaced by a quantity A expressed by the value related to the chemical shifts of the 5-position carbon, which Perkow has suggested as the biological

TABLE VII. Additive Parameter Values and 95% Confidence Limits of Equation (2)

	B_i (ppm)			B_i (ppm)	
	C	N+O		C	N+O
α	-6.56 ± 0.57		γ	1.54 ± 0.40	2.19 ± 0.74
β	-7.40 ± 0.53	-8.79 ± 0.79	δ	-0.46 ± 0.38	

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5) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
6) M.S. Tute, "Advances in Drug Research," Vol. 6, ed., by N.J. Harper and A.B. Simmonds, Academic Press, London, 1971, p. 47.

Table VIII. Comparison of Correlation Coefficients and Standard Deviations between Considering and Neglecting the Bond Character of Carbon Atoms

Position	Bond character			
	Consider		Neglect	
	r	s	r	s
5	0.980	0.856	0.978	0.912
1′	0.986	1.355	0.977	1.727
2′	0.996	0.716	0.996	0.715
3′	0.989	0.741	0.989	0.744
4′	0.9995	0.125	0.9995	0.137
All the sp^3-carbons	0.9905	1.950	0.9900	2.003

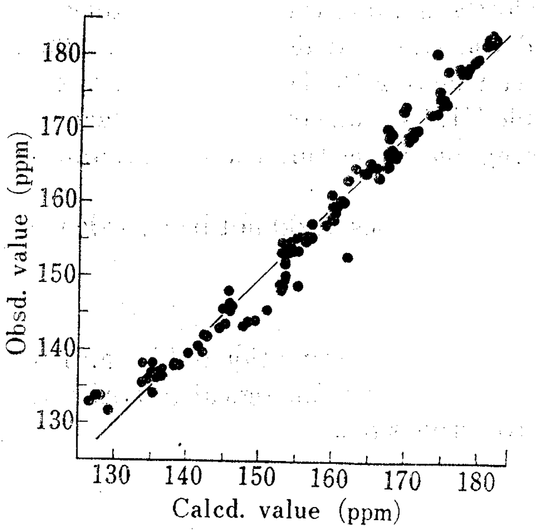

Fig. 7. Plot of Observed *versus* Calculated Chemical Shifts of the sp^3-Carbon ($r=0.990$, $s=2.003$)

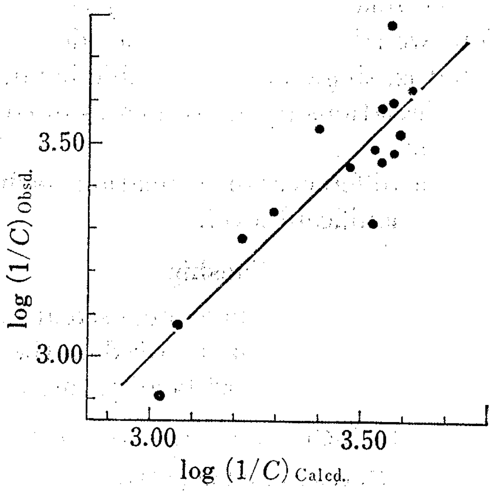

Fig. 8. Plot of Observed *versus* Calculated log ($1/C$) ($r=0.929$, $s=0.109$)

Table IX. Analysis of Hypnotic Action of Barbiturates

R′	R″	π[a]	A[b]	log ($1/C$)		
				Obsd.[c]	Calcd.	Δ log ($1/C$)
Allyl	allyl	2.40	1.20	3.54	3.395	0.145
Allyl	ethyl	2.20	1.27	3.28	3.214	0.066
Allyl	propyl	2.70	1.21	3.46	3.543	0.083
Allyl	isopropyl	3.00	1.28	3.60	3.569	0.031
Allyl	butyl	3.20	1.21	3.48	3.576	0.096
Allyl	isobutyl	3.00	1.16	3.63	3.614	0.016
Allyl	*sec*-butyl	3.00	1.30[d]	3.78	3.562	0.218
Allyl	isoamyl	3.50	1.20	3.45	3.468	0.018
Ethyl	ethyl	2.00	1.24	2.91	3.026	0.116
Ethyl	isopropyl	2.30	1.30	3.34	3.286	0.054
Ethyl	butyl	3.00	1.23	3.53	3.588	0.058
Ethyl	isoamyl	3.30	1.22	3.59	3.546	0.044
Ethyl	phenyl	2.77[e]	1.32	3.32	3.524	0.204
Butyl	isopropyl	3.30	1.28	3.49	3.523	0.033
Butyl	butyl	4.00	1.20	3.08	3.064	0.016

a) M. S. Tute, *Advances in Drug Research*, **6**, 35 (1971)

b) $A=\log[\delta_C(5)_{H,H}-\delta_C(5)_{R',R''}]$ $\delta_C(5)_{H,H}=152.7$ (ppm)

c) E. H. Volwiler, *J. Am. Chem. Soc.*, **47**, 2239 (1925); C (mole/kg): calculated from M. E. D.

d) calculated from equation (1)

e) C. Hansch and S.M. Anderson, *J. Med. Chem.*, **10**, 746 (1967) active center.[7] Table IX shows the analyzing procedure for the case of minimum effective dose (M.E.D.) in Volwiler's pharmacological data.[8]

In Table IX, all the π's values except phenobarbital are not observed but calculated ones using the additivity rules.[9] The result is shown as an equation (4).

$$\log(1/C) = -0.546\pi^2 + 3.289\pi - 0.375A - 0.903 \tag{4}$$

C: calculated from M.E.D. (mole/kg)

π: $\log P_{R',R''} - \log P_{H,H}$ $\left(\begin{array}{l}\text{Suffix "H,H" means "barbituric acid" as a standard,} \\ \text{"R',R''" means "disubstituted derivative".}\end{array}\right)$

A: $\log[\delta_c(5)_{H,H} - \delta_c(5)_{R',R''}]$ $\delta_c(5)_{H,H} = 152.7(\text{ppm})$

The values estimated by equation (4) are plotted against the observed values in Fig. 8. The correlation coefficient (r) is 0.929 and the standard deviations (s) is 0.109.

We also analyzed the data of minimum lethal dose (M.L.D.) in the above mentioned paper. The result is shown as an equation (5).

$$\log(1/C) = -0.487\pi^2 + 2.932\pi + 3.142A - 5.075 \tag{5}$$

C: calculated from M.L.D. (mole/kg)

π, A: same as π, A in equation(4)

The correlation coefficient (r) is 0.790 and the standard deviation (s) is 0.151.

Conclusion

Two conclusions were obtained from analyses of C-13 NMR spectra of barbituric acid derivatives.

(1) The additive law is applicable to chemical shifts of sp^3-hybridized carbons.

(2) Hammett's constant σ in Hansch analysis can be replaced by a quantity A expressed by the value related to chemical shifts of the 5-position carbon.

Experimental

Synthesis——5,5-Disubstituted barbituric acid derivatives, which were used for the measurement of C-13 NMR spectra, were synthesized by the usual methods,[10-13] but 5,5-diethylbarbituric acid (**8**), 5-ethyl-5-isoamylbarbituric acid (**13**) and 5-ethyl-5-phenylbarbituric acid (**15**) were obtained commercially.

Measurement of C-13 NMR Spectra——C-13 NMR spectra were measured in complete, partly partial, proton decoupled states on Hitachi R20B (15.085 MHz)and R-22 (22.63 MHz) spectrometers. All the samples except 5-methyl-5-(1-cyclohexenyl)barbituric acid (**7**) were prepared in concentration of 3 M dimethylsulfoxide (DMSO), but 5-methyl-5-(1-cyclohexenyl)barbituric acid (**7**) was in concentration of 2 M DMSO.

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7) V.W. Perkow, *Arzneim-Forsch.*, **10**, 284 (1960).

8) E.H. Volwiler, *J. Am. Chem. Soc.*, **47**, 2239 (1925).

9) M.S. Tute, *Advances in Drug Research*, **6**, 35 (1971).

10) O. Kamm and C.S. Marvel, "Organic Syntheses," Coll. Vol. I, ed, by H. Gilman, John Wiley and Sons, Inc., New York, N.Y., 1932, p. 23.

11) *a*) N. Weiner, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, N.Y., 1943, p. 279; *b*) P.A. Levene and G.M. Meyer, *ibid.*, p. 288; *c*) C.R. Noller and R. Dinsmore, *ibid.*, p. 358.

12) *a*) K. Nakajima, "Yuki Kagobutsu Goseiho," Vol. 11, ed. by Yuki Gosei Kagaku Kyokai, Gihodo, Tokyo, 1966, p. 45; *b*) Y. Kamata, *ibid.*, p. 66; *c*) K. Nakajima, *ibid.*, p. 85.

13) W. Kropp and L. Taub, U.S. Patent 1947944 (1934).