The trends of NE level after the continuation of oscillation for more than one hr with or without αMMT treatment are difficult to interpret.

Brain dopamine levels were not decreased by oscillation (Table II). However, there were consistent slight increases of DA in every oscillated groups. This is in a good agreement with the report of Goldberg and Salama.[6] The mechanisms of these changes are open to question.

Material and Method

Female ddy-strain mice (20—24 g) were used throughout the study. One week prior to each study, the thirteen animals were housed in a light-tight room maintained at 23+1°. The room was illuminated artificially from 7:00 am to 7:00 pm and darkened from 7:00 pm to 7:00 am. Commercial rat chow (CH-2, Clea Japan Inc.) and water were available ad libitum. On the day the animals were sacrificed, they were brought into the laboratory at 7: 30 am and food was removed. Great care was taken during the transfer.

α-Methyl-*meta*-tyrosine (αMMT, Mann Research Laboratories) was dissolved in a small amount of 4 N NaOH, and the solution was adjusted to a pH of 7 with 4 N HCl and diluted with saline to form an 10 mg/ml solution. The αMMT or vehicle solutions were intraperitoneally administered immediately before the oscillation began.

Oscillation-stress was conducted at 20+1° in a stainless cage previously spread with 7 g polyethylene chips, as previously reported.[11] The system permitted a to- and fro operation at 129 excursions per minute. Mice were stressed in groups of 12 animals, for 1/2, 1, 2, or 4 hr. All the animals were killed by decapitation at 11: 30 am, when all the oscillations were scheduled to end. The brain was rapidly exposed and removed, following the guidelines given by Welch and Welch,[12] and assayed on the same day. Three brains were pooled together for each measurement. Brain NE and dopamine (DA) were analyzed fluorometrically according to the method of Shellenberger and Gordon.[13] Vehicle administered groups served as controls in relating to the αMMT administered ones.

Acknowledgement We wish to thank Prof. Y. Kasuya and Dr. K. Imai, Faculty of Pharmaceutical Sciences, University of Tokyo for their advice and encouragement.

12) M.K. Shellenberger and J.H. Gordon, *Analytical Biochem.*, 39, 356 (1971).
13) A.S. Welch and B.L. Welch, *Analytical Biochem.*, 30, 161 (1969).

[Chem. Pharm. Bull. 21(12)2770—2775(1973)]

UDC 547.751.04 : 547.462.8'261.04

Studies on Indole Derivatives. XXIII.[1] Diels-Alder Reaction of 3-Indoledithiocarboxylic Acid Derivatives and Dimethyl Acetylenedicarboxylate and Reactions of Their Products

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(Received April 2, 1973)

We reported previously that the reaction of indoles with carbon disulfide in tetrahydrofuran, using sodium hydride, and methylation of its products with dimethyl sulfate afforded methyl 3-indoledithiocarboxylates, which were derivatives of an enamino dithiocarboxylate, and the replacement reaction of these dithiocarboxylates with nucleophilic reagents gave the

1) Part XXII: G. Kobayashi, Y. Tominaga, S. Kisaki, M. Sone, and S. Ueno, *Chem. Pharm. Bull.* (Tokyo), 21, 2344 (1973).
2) Location: *1-14, Bunkyo-machi, Nagasaki.*

corresponding indole derivatives.[3] The present paper describes the Diels–Alder reaction of dimethyl acetylenedicarboxylate and 3-indoledithiocarboxylic acid derivatives, which have a diene system in the thiocarbonyl group of its dithiocarboxylic and a double bond between α- and β-positions of indole. This paper also describes the reaction of Diels–Alder reaction products with amines and its treatment with hydrochloric acid.

Diels-Alder Reaction

When methyl 1,2-dimethylindole-3-dithiocarboxylate (Ia) was allowed to react with one mole of dimethyl acetylenedicarboxylate in dioxane or dimethylformamide on a steam bath for 5—10 min, yellow crystals of mp 105° were obtained in 90% yield. Elemental analysis of the compound agreed with $C_{18}H_{19}O_4NS_2$ and the molecular formula was also supported by mass spectrum (*m/e*: 377 (M^+)). The ultraviolet (UV) spectrum of this compound was not similar to that of the parent compound (Ia) and its infrared (IR) spectrum exhibited an absorption of the carbonyl group at 1720 cm^{-1}. The nuclear magnetic reasonance (NMR) spectrum of this compound is shown in Table I. This NMR spectrum gave useful information in the structure analysis. These data indicated that the Diels–Alder reaction product had the structure of 4*a*, 5-dimethyl-1-methylthio-3,4-bis(methoxycarbonyl)-4*aH*-thiopyrano[4,3-*b*]indole (IIa).

In a similar manner as above, the reaction of other compounds, methyl 2-methyl- (Ib), methyl 1-methyl-2-phenyl- (Ic), methyl 2-phenyl- (Id), and cyanomethyl 2-methyl- (Ie) 3-indoledithiocarboxylates with dimethyl acetylenedicarboxylate afforded the Diels–Alder reaction products (IIb—e) in good yield. The Diels–Alder reaction product could not be obtained in the case of methyl 1-methyl-3-indoledithiocarboxylate.

The reaction of 3-morpholino- (If) or 3-piperidino- (Ig) 1,2-dimethyl thiocarbonylindoles, which were obtained by the replacement reaction of Ia with secondary amines, with dimethyl acetylenedicarboxylate also gave the Diels–Alder reaction products in good yield.

Recently, Smutny and others[4] have reported the Diels–Alder reaction between 3-dialkylaminodithioacrylates and maleic anhydride. Our results were ascribed to belong to the same category with their experiment.

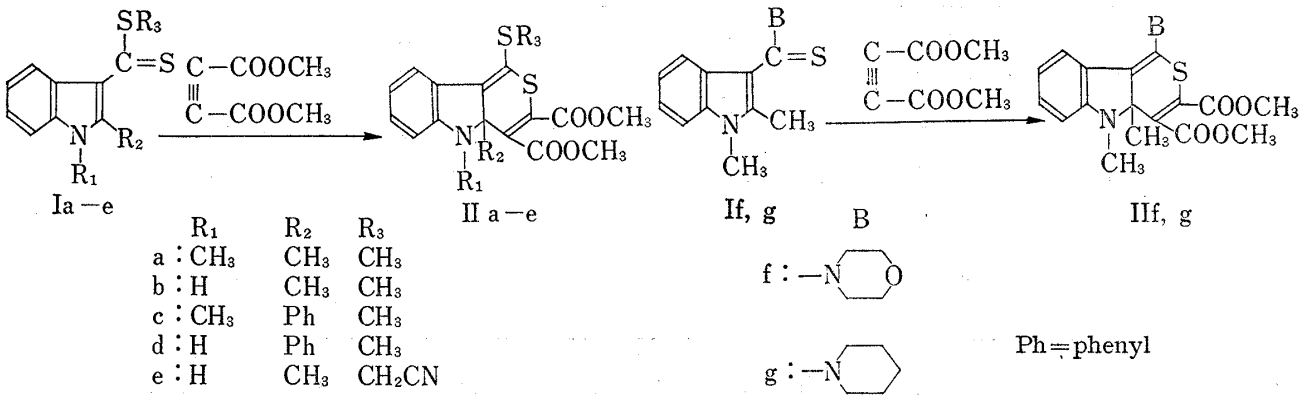


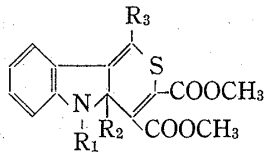
Chart 1

Reaction of Diels-Alder Product with Amines

Ketenethioacetals are attacked by nucleophilic reagents with replacement of either one methylthio group or two methylthio groups attached to the same carbon atom by such groups

3) *a*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **90**, 132 (1970); *b*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **91**, 1164 (1971); *c*) Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **93**, 1433 (1973).
4) R. Kalis, A.E. Smith, and E.J. Smutny, *Tetrahedron Letters*, **1971**, 2241.

TABLE I.



No.	mp (°C)	Yield (%)	R_1	R_2	R_3	Formula	Analysis (%) Calcd. (Found) C	H	N	NMR_{ppm} in pyridine	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)
IIa	105	95	CH_3	CH_3	SCH_3	$C_{18}H_{19}O_4NS_2$	57.29 (57.10)	5.08 (5.02)	3.71 (3.70)	NCH_3 3.02 SCH_3 2.40 CCH_3 1.35	CO 1720	258(4.30) 380(3.88)
IIb	122	85	H	CH_3	SCH_3	$C_{17}H_{17}O_4NS_2$	56.20 (56.02)	4.72 (4.71)	3.86 (3.63)	SCH_3 2.40 C-CH_3 1.52	NH 3390 CO 1705 1720	256(4.17) 364(3.79)
IIc	131	70	CH_3	ph	SCH_3	$C_{23}H_{21}O_4NS_2$	62.86 (62.68)	4.82 (4.83)	3.19 (3.11)	NCH_3 2.65 SCH_3 2.30	CO 1710 1720	236(4.15) 260(4.03) 388(3.72)
IId	160	65	H	ph	SCH_3	$C_{22}H_{19}O_4NS_2$	62.11 (61.67)	4.50 (4.86)	3.29 (3.36)	—	NH 3420 CO 1710	260(4.23) 370(3.88)
IIe	118	80	H	CH_3	SCH_2CN	$C_{18}H_{16}O_4N_2S_2$	55.67 (55.85)	4.15 (4.05)	7.21 (7.43)	SCH_2 4.18 C-CH_3 1.52	NH 3410 CN 2220 CO 1700 1720	257(4.23) 380(3.85)
IIf	170	70	CH_3	CH_3		$C_{21}H_{24}O_5N_2S$	60.56 (60.80)	5.81 (6.00)	6.73 (6.69)	C-CH_3 1.34	CO 1725	225(4.17) 255(4.16) 366(3.83)
IIg	120	70	CH_3	CH_3		$C_{22}H_{26}O_4N_2S$	63.75 (63.39)	6.32 (6.32)	6.76 (6.53)	—	CO 1724 1735	225(4.27) 252(4.24) 366(3.92)

TABLE II. The NMR Data (ppm)

	Solvent	OCH_3	NCH_3	SCH_3	CCH_3
Ia	pyridine	—	3.45	2.90	2.71
IIa	pyridine	3.75 3.92	3.02	2.40	1.35
IIa	TFAA	4.25 (6H)	3.30	3.20	2.50
IIb	pyridine	3.78 3.76	—	2.40	1.52
IIb	TFAA	4.30 (6H)	—	3.20	2.56
VIII	TFAA	4.21 4.24	—	—	3.23

as amine or active methylene.[5,6] The most versatile derivatives of ketenethioacetal are obtained by reaction with amines.

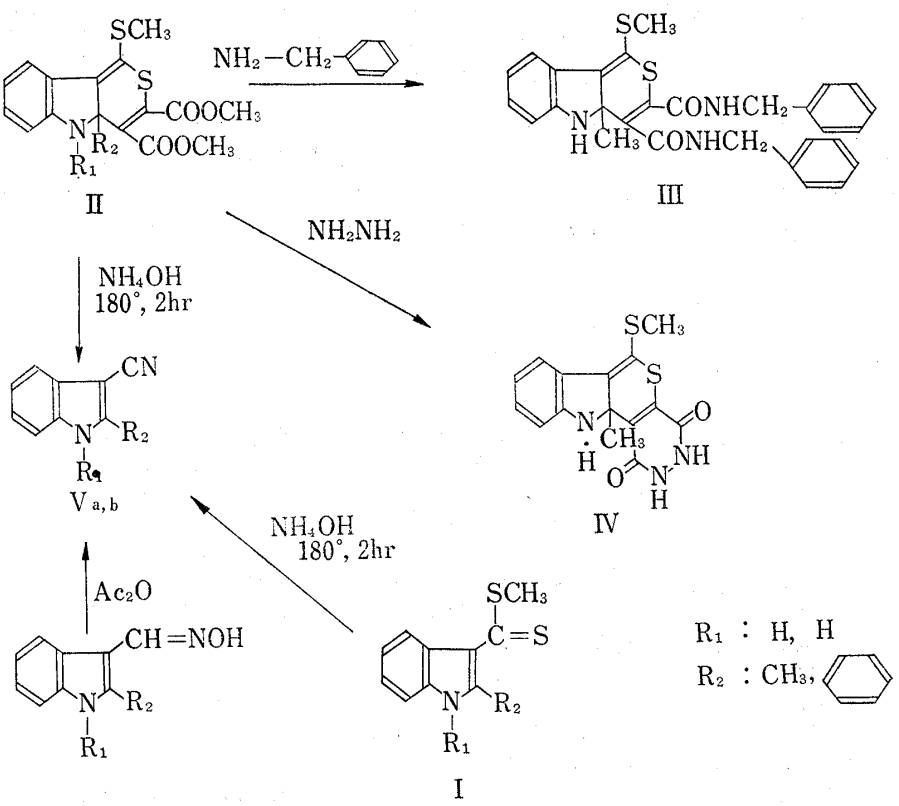
Since Diels–Alder product is a cyclic ketenethioactal,[7] the reaction of II with amines was attempted. The reaction of IIb with benzylamine gave the replaced product by methoxyl

5) *a*) R. Gompper and W. Topfel, *Chem. Ber.*, **95**, 2871, 2881 (1962); *b*) R. Gompper and W. Hagele, *Chem. Ber.*, **99**, 2885 (1966).

6) *a*) G. Kobayashi, S. Furukawa, Y. Matsuda, and Y. Washida, *Chem. Pharm. Bull.* (Tokyo), **15**, 187 (1967); *b*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **92**, 713, 1468 (1972).

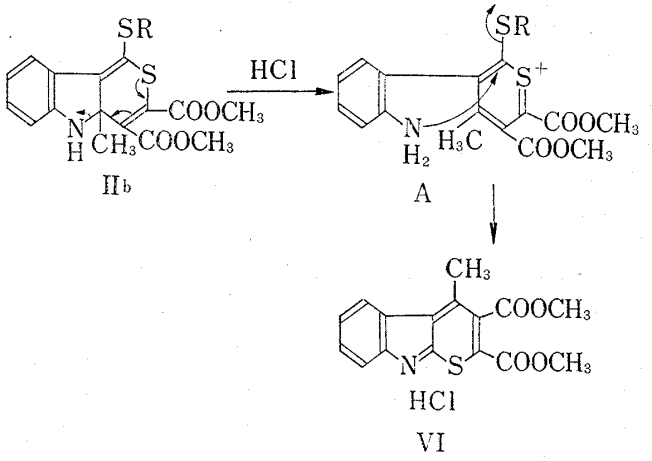
7) *a*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **91**, 203 (1971); *b*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **92**, 449 (1972).

groups instead of methylthio group. By the similar reaction of IIb with hydrazine hydrate, a pyridazinone derivative (IV) was obtained. However, the reaction of IIb or IId with 40% ammonia at 180° for 2 hr in a sealed tube gave 3-cyanoindoles (Va,b) obtained through the occurred Retro Diels–Alder reaction. These products were identified with the samples[3c,8] reported previously.



II III IV Va,b I

Chart 2



IIb A VI

Chart 3

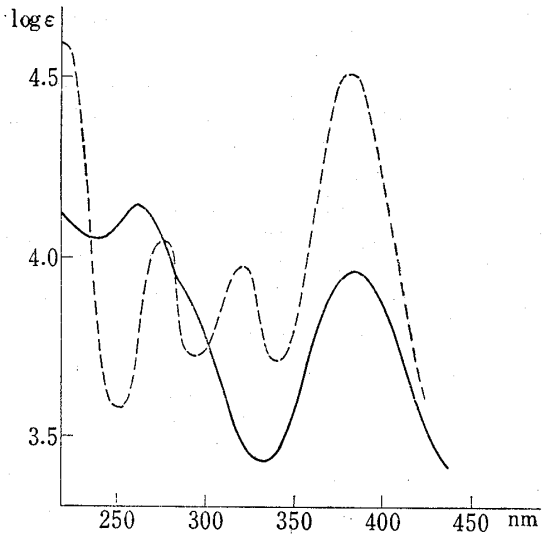


Fig. 1. Ultraviolet Spectra of Ia and IIa

------: Ia ——: IIa

8) R.C. Blume and H.G. Lindwall, *J. Org. Chem.*, **10**, 255 (1945).

Treatment of IIb with Hydrochloric Acid

Most ring opening reactions of indoles are initiated by protonation or other electrophilic attack at α-position generating a 3H-indolinium ion.[9] If the conversion of IIb into a ring opened compound intermediate in acidic solution easily occured, the treatment with the acidic solution would give an intermediate cation (A) (Chart 3) having an amino group which might attack to the carbon atom bearing a methylthio function. Treatment of IIb with methanolic acid gave red needles (VI), mp 190°, in a good yield. Elemental analysis of VI supported a molecular formula of $C_{16}H_{13}O_4NS \cdot HCl$. Its mass spectrum of free base showed the molecular ion peak at *m/e* 315. The IR spectrum of VI showed no absorption band dueto NH or NH_2 but due to carbonyl groups at 1720 and 1732 cm^{-1}. The NMR spectrum (in TFAA) of VI showed the signals due to methoxyl protons as singlets at 4.21 (3H) and 4.24 ppm (3H) and aryl methyl protons as a singlet at 3.23 ppm (3H). From these data, this compound should be given as the structure of 1-methyl-2,3-bis(methoxycarbonyl)thiopyrano[2,3-*b*]indole hydrochloride (VI).

Experimental

Reaction of 3-Indoledithiocarboxylates (Ia—e) and Dimethyl Acetylenedicarboxylate——To a solution of 0.01 mole of Ia—e in 50 ml of dioxan or dimethylformamide, 1.4 g of dimethyl acetylenedicarboxylate was added at room temperature and the mixture was heated on a steam bath for 10 min to 4 hr. The reaction mixture was diluted with H_2O and extracted with benzene. The extract was dried over Na_2SO_4 and evaporated to leave crude crystals which were recrystallized from MeOH to give the Diels–Alder products. In the case of 2-phenylindole derivatives, the reaction time was about 4 hr longer than those of other compounds. These results are shown in Table I. Mass Spectrum (IIa) *m/e*: 377 (M^+), 362, 347, 330, 318, 303, 288, 273.

Reaction of 3-Indolecarbothioamide (If, g) and Dimethyl Acetylenedicarboxylate——To a solution of 0.01 mole of If or Ig in 50 ml of dioxan, 1.4 g of dimethyl acetylenedicarboxylate was added at room temperature and the mixture was heated on a steam bath for 8 hr. The reaction mixture was poured into 200 ml of H_2O, the yellow precipitated solid was collected on a filter, and recrystallized from MeOH to give the Diels–Alder products. These results are shown in Table II.

Reaction of IIb with Benzylamine——To a solution of 1 g of IIb in 20 ml of MeOH, 0.5 g of benzylamine was added and the mixture was allowed to stand at room temperature for 24 hr. The precipitated yellow needles were collected on a filter and recrystallized from MeOH to the dibenzylamide (III) of mp 245°, in 80% yield. *Anal.* Calcd. for $C_{29}H_{27}O_2N_3S_2$: C, 67.82; H, 5.30; N, 8.18. Found: C, 67.70; H, 5.21; N, 8.37. IR(KBr) cm^{-1}: 3450, 3320 (NH), 1640 (C=O). UV λ_{max}^{EtOH} nm (log ε): 259 (4.85), 315 (4.59).

Reaction of IIb with Hydrazine Hydrate——To a solution of 1 g of IIb in 30 ml of MeOH, 0.5 ml of hydrazine hydrate was added at room temperature, the mixture was refluxed for 6 hr, and the solvent was evaporated under a reduced pressure. The residue was recrystallized from MeOH to pyridazinone derivative (IV) of mp 250° in 60% yield. *Anal.* Calcd. for $C_{15}H_{13}O_2N_3S_2$: C, 54.38; H, 3.96; N, 12.69. Found: C, 54.26; H, 4.05; N, 12.49. IR (KBr) cm^{-1}: 3440 (NH), 3200—2840 (NH or OH), 1640 (C=O). UV λ_{max}^{EtOH} nm (log ε): 258 (4.26), 330 (3.95).

Synthesis of 3-Cyanoindole Derivatives——a) A solution of 0.5 g of IIb or IId and 10 ml of 40% NH_3 in 20 ml of MeOH was heated at 180° for 2 hr in a sealed tube. Removal of the solvent gave 0.32 g of a crude product. This was recrystallized from -MeOH to 3cyanoindole derivatives as white needles. These melting points agreed with those of the known compounds.[3c]

b) The reaction of I and NH_3 was carried out in a similar manner. The yield was 60—80%.

c) 2-Phenyl-3-cyanoindole, mp 243° (decomp.), was obtained by heating the oxime of 2-phenylindole-3-aldehyde with acetic anhydride.

Treatment of IIb with Hydrochloric Acid——To a solution of 1 g of IIb in 50 ml of MeOH, 5 ml of 20% HCl was added, the mixture was refluxed for 1 hr, and then the solvent was evaporated until 15 ml remained. The concentrated solution was allowed to stand at room temperature for 4 hr and then the precipitated red needles were collected on a filter and recrystallized from MeOH and 10% HCl to 0.72 g of 1-methyl-2,3-bis(methoxycarbonyl)thiopyrano[2,3-*b*]indole hydrochloride as red needles of mp 190°. *Anal.* Calcd. for $C_{16}H_{14}O_4NSCl$: C, 54.18; H, 3.99; N, 3.99. Found: C, 54.43; H, 4.03; N, 4.28. IR (KBr) cm^{-1}: 1720, 1732

9) R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York and London, 1970, pp. 331—337.

($COOCH_3$). UV λ_{max}^{EtOH} nm (log ε): 249 (4.20), 284 (4.43), 382 (4.04). NMR (in TFAA) ppm: 4.21 (3H, s, OCH_3), 4.24 (3H, s, OCH_3). Mass Spectrum *m/e*: 315 (M^+), 283, 272, 258.

Acknowledgement The authors are very grateful to Mrs. H. Mazume for microanalytical data, to Mr. S. Owatari for measurement of IR and UV spectra, to Mr. H. Inata for the measurement of NMR spectra, and to Mr. N. Yamaguchi for the measurement of mass spectra, all of this University.

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Synthesis of N-(Alkylaminomethyl)amides

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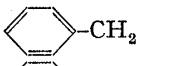
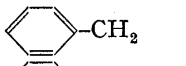
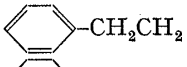
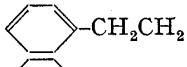
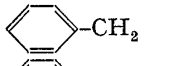
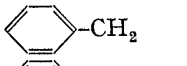
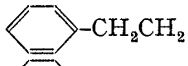
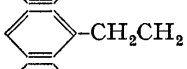
(Received April 7, 1973)

Up to the present there has been known an abundance of the methylene compounds bound to both amine nitrogen (N^I) and amide or imide nitrogen (N^{II}), simply expressed by a general formula, $>N^I-CH_2-N^{II}<$. As well known they are easily prepared by heating formaldehyde, amine and amide (or imide) together in solution. Neverthless, the usual method is unsatisfactory in obtaining the compound, of which N^I is grouped in the type of –NHR (R=alkyl), although by the use of amphoteric α-amino acid as the amine reactant the compound, $RCONHCH_2NHCH(R')CO_2H$, has been reported[2)] to be obtained.

TABLE I. Formation of N-(Alkylaminomethyl)amide Hydrochlorides

$$RCONH_2 + CH_2O + R'\overset{+}{N}H_3\overset{-}{Cl} \longrightarrow RCONHCH_2\overset{+}{N}H_2R' + H_2O \quad (Cl^-)$$

R	R′	Yield (%)	R	R′	Yield (%)
		80	C_2H_5		72
		93	C_2H_5		75
		71	C_2H_5		86
	n-C_4H_9	90	C_2H_5	n-C_4H_9	83
	C_2H_5	85	C_2H_5	C_2H_5	72
	iso-C_4H_9	83	H		85
CH_3		82	H		75
CH_3		82	H		93
CH_3		77	H	n-C_4H_9	87
CH_3	n-C_4H_9	76	H	C_2H_5	73
CH_3	C_2H_5	81			

1) Location: *2-2-1, Oshika, Shizuoka.*
2) H. Fraenkel-Conrat and H.S. Oleott, *J. Am. Chem. Soc.*, **70**, 2673 (1948); F. Lauria, C. Bernardelli, G. Tosolini and W. Logemann, *Ann.*, **706**, 233 (1967); *idem, ibid.*, **706**, 237 (1967); C, Bernardelli, G. Bucher, F. Lauria, W. Logemann, G. Tosolini, and G. Vita, *ibid.*, **706**, 243 (1967).