fractions. The components of both fractions were identified by VPC as described in the previous section. The results are given in the earlier section.

A 2.6 g. portion of the distillation residue (62.0 g.) was redistilled at 0.5 mm. Hg through a short column until a bath temperature of 180° was reached. The distillate, after acetylation with Ac_2O and pyridine, and chromatography on alumina, afforded the following crystalline compounds. Cadinol, m.p. 77~77.5°, $[\alpha]_D^{21}$ −40.2° (c=1.6, CCl_4). IR ν_{max}^{Nujol} cm^{-1}: 3259, 1140, 908, 932, 887, 832. α-Cadinol, m.p. 40~60°, $[\alpha]_D^{21}$ −8.2° (c=0.75, CCl_4). IR ν_{max}^{Nujol} cm^{-1}: 3361, 1124, 1042, 1010, 950, 932, 895, 812. Both compounds were identified by comparison of their IR spectra with those of authentic specimens.

Authors are deeply indebted to Takasago Perfumery Industry Co., Ltd. for the assistance in many respects of the present research.

Summary

The constituents of the essential oil from the leaf and wood of *Chamaecyparis obtusa* (Sieb. et Zucc.) have been investigated; a sample of the commercial leaf oil was also examined. Elemol and eight monoterpenes were found in the leaf oil. This is the first recorded isolation of elemol from this species. The wood oil was found to contain γ-cadinene, calamenene, two cadinols, and seven monoterpenes. *d*-Longifolene, *d*-γ-cadinene, calamenene, and thunbergene were identified in the commercial leaf oil.

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137. **Keiji Sekiguchi, Toshihisa Yotsuyanagi,**[*1] **and Soichi Mikami**[*2] :

Studies on the Method of Thermal Analysis of Organic Medicinals. V.[*3,*4] Semi-micro Apparatus for the Differential Thermal Analysis Permitting Direct Observation.

(*Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University*[*1] *and Hospital Pharmacy, University of Tokyo*[*2])

Although differential thermal analysis (DTA) has been developed since the end of the last century, applications were mainly limited to inorganic materials, such as ceramics, minerals and alloys, and rather few investigations concerning the thermal behaviors of organic materials were performed except those of natural and synthetic polymers. The reason why the method has been rarely applied to organic substances of low and medium molecular weight will be ascribed to the followings : 1. Because the apparatus is mostly designed for the metallurgical studies operating at higher temperatures, it does not fit well for use at lower range of temperature. 2. The sample size is usually about several hundred miligrams or more which will often be an extravagant requirement for organic chemists.

Since DTA is not applied so frequently as certain other kinds of measurement, such as spectrophotometry or pH determination significance will at present be attached to the mere collection of experimental data concerning thermal behaviors of organic materials.

[*1] Kita-12-Jo, Nishi-5-chome, Sapporo, Hokkaido (関口慶二, 四柳智久).

[*2] Hongo, Tokyo (三上総一).

[*3] Part Ⅳ. K. Sekiguchi, K. Ito, Y. Nakamori : This Bulletin, **11**, 1123 (1963).

[*4] Partly presented at the Hokkaido Branch Meeting of Pharmaceutical Society of Japan, August, 19th, 1962.

In the present study, the authors designed a semi-micro DTA apparatus using a couple of thermistors as the detector of temperature difference. It could be constructed easily and inexpensively. Moreover, the apparatus has a peculiarity to permit simultaneous visual observation of the sample during the course of measurement. Tests concerning both reliability and applicability gave results sufficient enough to prove the fact that the apparatus was suitable for the analysis of organic materials and the requirements stated above were largely satisfied. Also, they tried to find some effective applications of DTA to chemical and pharmaceutical investigations.

Experimental and Results

Apparatus

Electrical Circuit——The circuit diagram of the amplifier modified the one reported by Inoue[1] is shown in Fig. 1 in which a switch for phase inversion is omitted. To the bridge consisting of each two thermistors and resistances, a voltage of 1.3 V. is applied. The drift of the scale of the micro-ammeter is prevented by connecting the input to a stabilizer. (Toshiba Photoelectric Voltage Stabilizer, Type PS-1A, 100±0.1 V.). For the amplifier, thermistors having internal resistance of 3~50 Kohm at 25° will be suitable, but those of lesser resistance (about 100 ohm) may be adopted for analysis at lower range of temperature. Couples of matched thermistors were supplied by Nihon Electric Co., Ltd. (Type BT-14, 10 Kohm at 25°) and by TOA Electronics Ltd. (Glass thermistor, Type 302 J, 3 Kohm at 25°, max. temp. 300°, $R_{25}/R_{80}=2.4$).

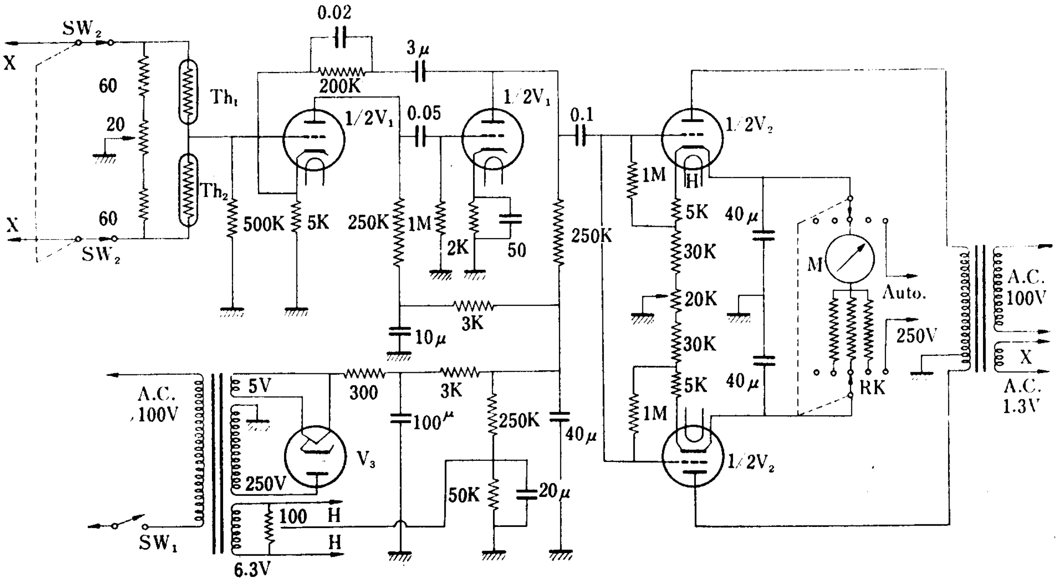

Fig. 1. Circuit Diagram of Amplifier

V_1: 12AX7-HiFi, V_2: 6SN7, V_3: 5MK9 M: 100 μA Ampermeter
RK: These resisters are so adjusted as the scale of M becomes integral ratio.

Heating Bath and Cells——The heating bath is so constructed that both the sample and the reference cell may be heated equally by the bath liquid which is circulated with air bubbles from the inlet tube. Suction is done through the outlet tube connected to a water aspirator or preferably to a small electric vacuum pump *via* a large glass bottle for the ballast. The bath liquid tested were H_2O, H_2SO_4, Hg, glycerol, liquid paraffin and silicon oil, among which the latter three were found unsuitable because of high viscosity, fuming or deterioration by repeated heating. In the case of Hg, suction was not applied, so the fluctuation of the base line became large. For analysis up to about 80°, H_2O could be used; however, regulation of the rate of heating became the more difficult, the higher the temperature rose. Only H_2SO_4 gave excellent results from room temperature up to about 270° and were adopted for the bath liquid.

The temperature of the bath is directly read with a mercury thermometer located in the middle and in the same depth of both cells. An electric furnace is used as heater and the heating rate is controlled

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1) M. Inoue, T. Saito: Yakugaku Zasshi, 80, 693 (1960).

manually by a variable transformer. Once the manner of voltage elevation is established, linear rise of temperature will be easily and reproducibly obtained, if suction is maintained constant and the change of heat capacity of the bath liquid due to evaporation or absorption of moisture is prevented.

The most unique part of the apparatus is the double cell, consisting of an inner tube for sample or inert material and a jacket which is in contact with the bath liquid. (Fig. 2). The temperature becomes almost equal throughout the liquid by suction stirring; however, if the sample and the reference substance are heated directly, appreciable fluctuation of the base line will not be avoided because of high sensitivity of thermistors. Moreover, peaks in the DTA curves will become less pronounced due to increased heat transmission. In the case of the double cell, the air layer exerts a buffering action against incidental temperature difference between both jackets by which the base line is made nicely flatten. Also, decreased heat transmission of this type of cell is effective for reducing the sample amount. Another factor affecting on sample size is the heat capacity of the inner tube. The smaller it is, the greater becomes the net increase of temperature difference between the sample and the reference; thus, the peaks in the curve due to phase reaction will be more strongly marked. Several kinds of cells, shown in Figs. 3 and 4 were used according to the amount of sample available.

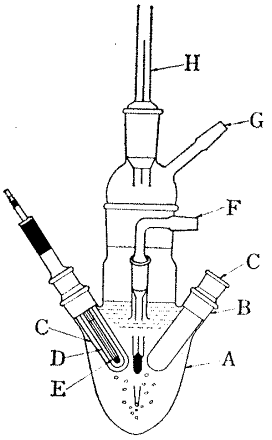
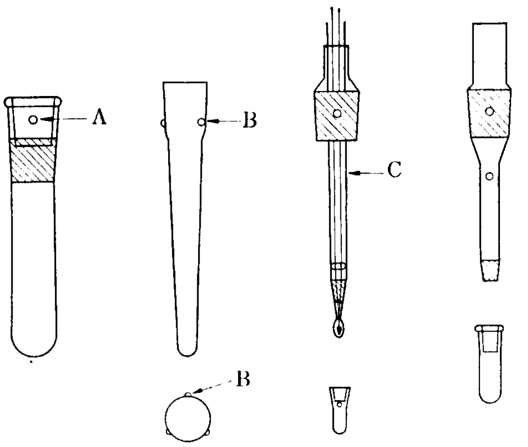


Fig. 2. Heating Bath

A : Bath
B : Side tube
C : Jacket
D : Inner cell
E : Thermistor
F : Inlet tube
G : Outlet tube
H : Thermometer



Jacket

Inner Cell (Type I) Sample size : 30~100 mg.

Inner Cell (Type Ⅱ) 3~15 mg.

Inner Cell (Type Ⅲ) 20~50 mg. for glass thermistor

Fig. 3. Several Types of Double Cells

A: Small vent B: Small knob C: Thermistor

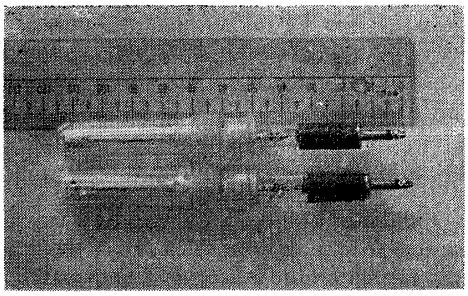


Fig. 4. Photograph of Assembled Double Cell and Thermistor

Inner cell : Type Ⅳ
Sample size : 30~100 mg.

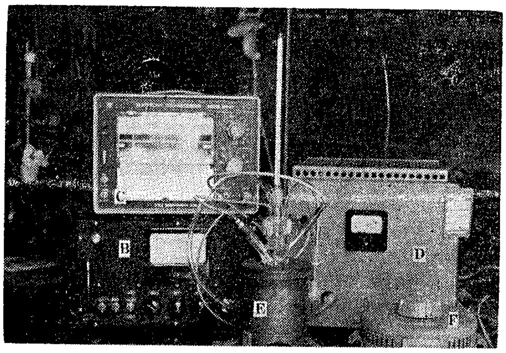


Fig. 5. Whole Assembly of Differential Thermal Analysis Apparatus

A : Heating bath
B : Amplifier
C : Recorder
D : Voltage stabilizer
E : Electric furnace
F : Transformer

Recordinng——When measurement is done manually, deflection of the pointer of the microammeter and time in minute and second are checked at every degree of temperature. In the semi-automatic procedure, the output is fed into a recorder. For the present investigation, a recorder of TOA Electronics, Type EPR-2T (14 ranges from 5 mV. to 100 V; chart speed=20, 60, 180 mm./hr. and mm./min.) was used. By turning and then returning back immeadiately the sensitivity dial or the zero-adjuster, temperature of the bath is easily checked and the relation of differential temperature to both temperature and time is recorded simultaneously on one chart. Such a recording system is more convenient than the one often adopted in commercial analyzers using two recorders for representing separately the change of temperature and differential temperature as function of time. The whole assembly of the apparatus is shown in Fig. 5.

Reference Substance——Among commonly used substances, such as powdered silica, α-alumina or NaCl, the best one for analysis of organic materials was found to be KCl powder obtained by lyophylizing its dilute solution. The specific surface of the powder was measured to be 2.5~2.8 m^2/g. (1.1~1.2 μ in size) by gas adsorption analysis. The powder has an apparent volume nearly similar to those of organic materials. In each practice, the amount of reference KCl is taken approximately equal to that of the sample.

Effect of Operating Conditions

Direct and Indirect Heating——As is seen in Fig. 6, fluctuation of the base line becomes larger when the sample is heated directly with liquid. Although in this case, the line can be more flattened by increased suction, vigorous circulation of air bubbles makes it difficult to observe visual change of the sample.[*5] On the other hand, the base line obtained with the double cell is found to be almost a straight line. It must be taken in mind that unless both cells are kept in the bath for some time to attain heat equilibrium, a continuous drift of the base line will occur at the beginning of measurement.

Heating Rate——Heating rate exerts a great influence upon the depth and the position of maximum deflection in the DTA curve. (Fig. 7). Deviation of the peak temperature from the ordinary melting point

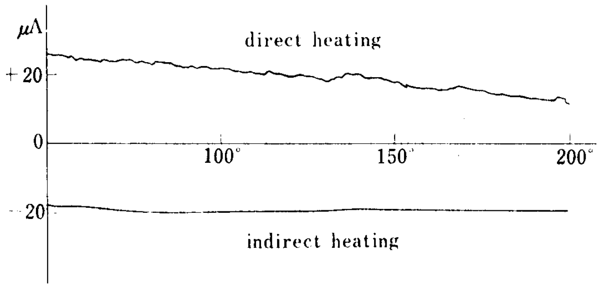


Fig. 6. Fluctuation of Base Line by Direct and Indirect Heating

Freeze-dried KCl, 75 mg. for each cell (Type I);
Recording: manual Sensitivity=50
Heating rate=1.5±0.2°/min.

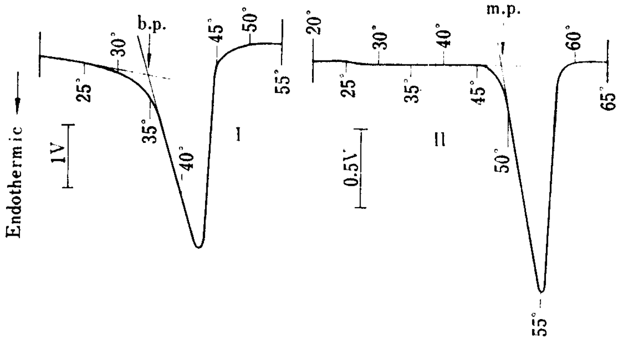


Fig. 8. DTA Curves of Ethyl Ether and Urethane; Test on Deviation of Boiling and Melting Point at Lower Temperatures

Sample: I KCl 51.0 mg.+Et_2O 3 drops; II recryst. urethane 62.7 mg.
Reference: freeze-dried KCl 62.6 mg.
Cell: type IV Recording: semi-automatic
Sensitivity: I 2.5 V; II 1 V
Heating rate: I 0.8°/min.; II 0.9°/min.
Chart speed=180 mm./hr.

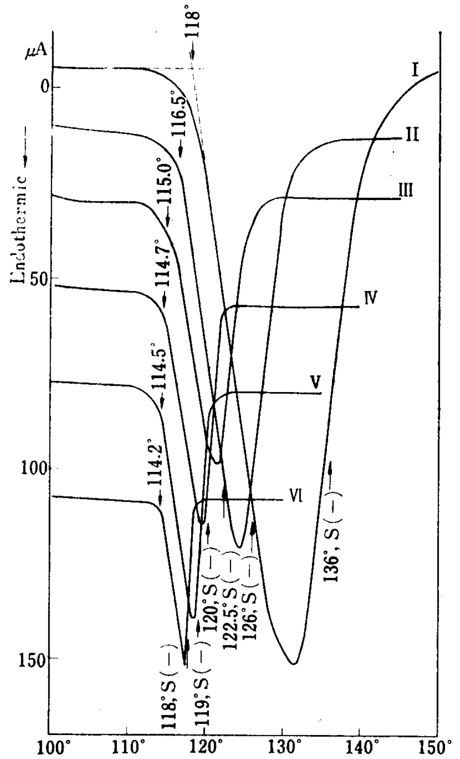


Fig. 7. DTA Curves of Acetanilide; Effect of Heating Rate

Sample: twice recryst., fused in cell, each 49.3 mg.
Reference: freeze-dried KCl, 70.6 mg.
Cell: type I; Recording: manual;
Sensitivity=50
Heating rate: I 8±1°/min.,
II 5±0.5°/min., III 2.7±0.2°/min.,
IV 1.0±0.2°/min., V 0.67±0.03°/min.,
VI 0.25±0.03°/min.

[*5] Similarly, when a cell of large size is used and the sample amount is increased to more than 500 mg., the base line becomes smoother, even by direct heating; however, the height of the peak associated with phase reaction decreases to about one twentieth or less.

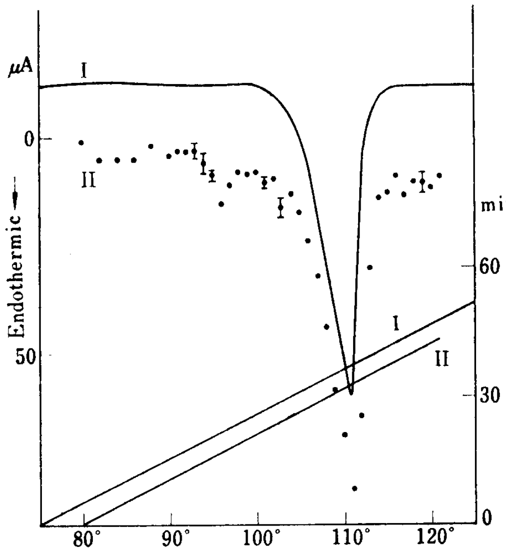


Fig. 9. DTA Curves of Eutectic Mixture of Chloramphenicol and Urea; Effect of Suction Stirring of Bath Liquid

Sample: Prepared by fusion in a Pt crucible, powder; I 59.2 mg.; II 64.5 mg.
Reference: freeze-dried KCl, 70.6 mg.
Cell: type I; Recording: manual
Sensitivity=50; Heating rate: I 1.0±0.1°/min.. II 1.0±0.2°/min.
Suction stirring: I applied, II not applied.

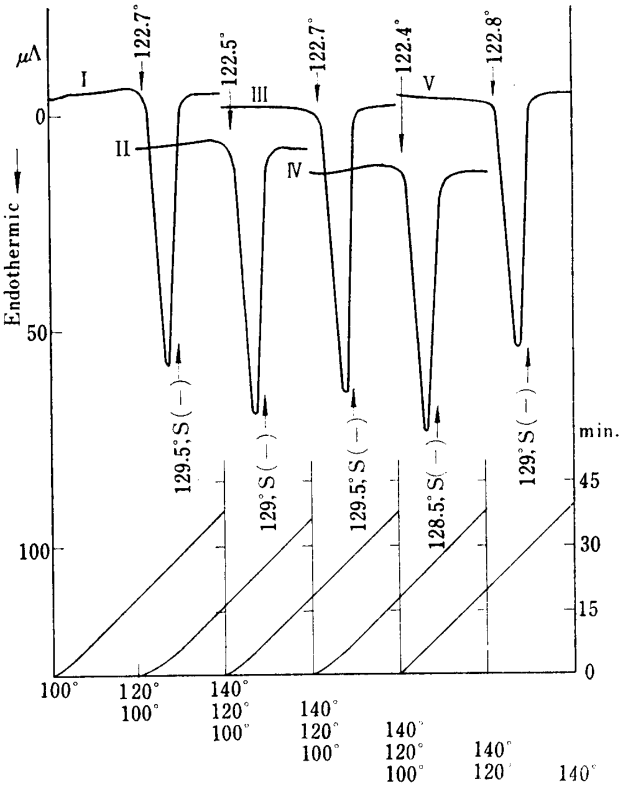


Fig. 10. DTA Curves of Benzoic Acid; Test on Reproducibility

Sample: twice recryst.; I, III, V powder; II, IV fused mass, 54∼56 mg.
Reference: freeze-dried KCl, 70.6 mg.; Cell: type I
Recording: manual; Sensitivity=50;
Heating rate=1.0±0.1∼0.2°/min.
S(−): point of disappearance of solid phase

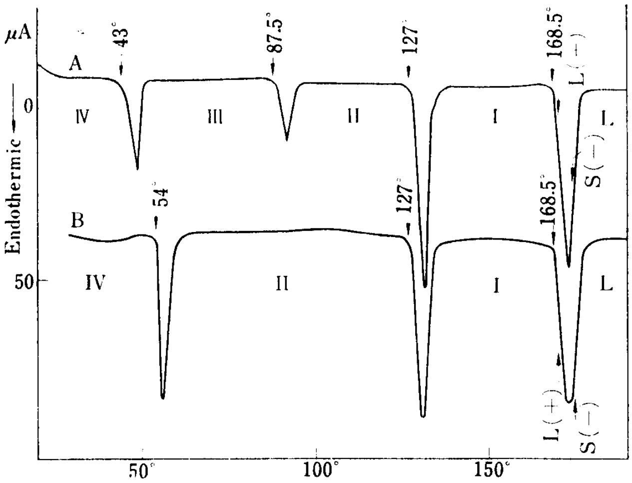


Fig. 11. DTA Curves of Ammonium Nitrate

Sample: A. recryst. from EtOH, powder, 71.8 mg.; B. fused in the cell and allowed to stand at room temperature for 2 days, 72.0 mg.
Reference: freeze-dried KCl, 70.6 mg. Cell: type I
Recording: manual Sensitivity=50
Heating rate: A. 1.4±0.1°/min.; B. 1.5±0.1°/min.
Ratio of peak area: A. 0.49:0.38:1.00:0.97; B. 0.72:1.00:0.98
L(+): point of appearance of liquid phase;
S(−): point of disappearance of solid phase

becomes larger by increasing the rate. The point where the last trace of solid disappears (represented in figures as S (−)) is always found at a temperature a few degrees higher than the peak temperature. However, the point at which the solid begins to melt is not appreciably affected by the rate of heating and is nearly equal to the value obtained with the ordinary melting point apparatus. Even when phase transition, such as boiling and melting, occurs at lower temperatures, the point of fall in the curve agrees fairly well with the value in table, unless the rate is too rapid. (Fig. 8). Although the rate can be varied from 0.1° to about 15° per minute, it is advisable to adopt a rate between 0.3° and 5° in order to obtain linear rise of temperature by manual control.

Suction Stirring——The results in Fig. 9 indicate that a well defined DTA curve will be obtained only when the bath is adequately stirred.

Reproducibility——As shown in Fig. 10 almost the same results will be obtained with a given amount of the sample, if in each run, suction maintained constant and the manner of dial setting of the transformer is fixed.

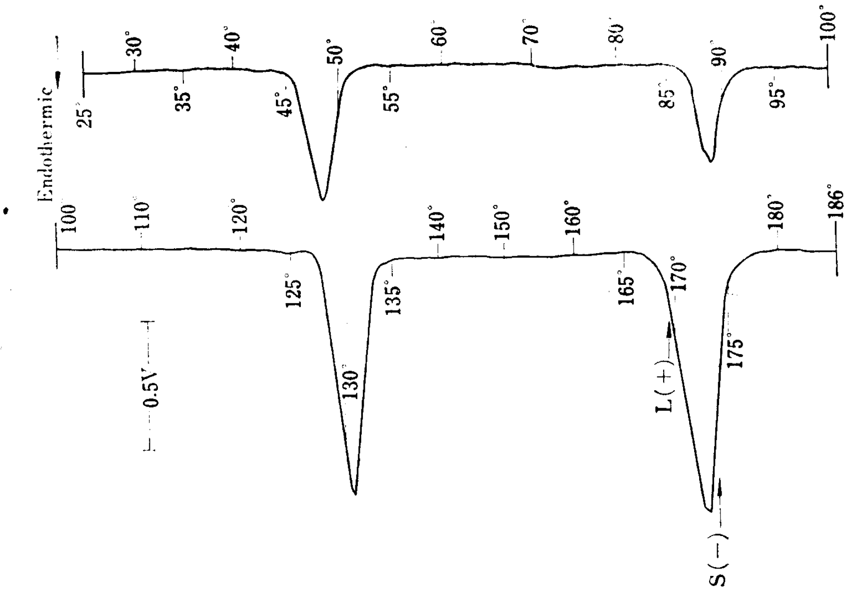


Fig. 12. DTA Curves of Ammonium Nitrate

Sample: JIS analytical grade, powder, 78.0 mg. Reference: freeze-dried KCl 75.5 mg.
Cell: type I Recording: semi-automatic Sensitivity=1V
Heating rate=1.0±0.1°/min. (about 10° before and after each transition)
Chart speed=180 mm./hr. Ratio of peak area: 0.47:0.33:1.00:1.23

Examples of Application

Polymorphic Transition of Ammonium Nitrate——DTA curves by manual and automatic recording are shown in Figs. 11 and 12. It is observed that the temperature of the first transition varies from 38° to 50°, whereas, other transitions occurs at nearly constant temperatures. (87.5±1.5°, 127±0.5° for the second and the third transition; 169±0.5° for fusion). In some sample, especially in a fused one, the second peak occasionally disappears, (five times in twenty experiments) while the first transition takes place at a temperature of 54° with an increase of peak area, nearly amounted to the sum of those for both transitions. When the ratio of each peak area is calculated by taking the one for the third transition as unity, and is compared to the values for reference (0.38:0.32:1.00:1.3),[*6] somewhat higher value is found with transitions at lower temperatures, while lower one for fusion. It is considered that the temperature difference between the bottom and the upper part of the cell which is not heated with bath liquid will produce these discrepancy. When glass wool is wrapped from the side tube of the bath to the terminal of the thermistor in order to prevent the upward heat conductance in some degree, the peak ratios approach to the value for reference.

Polymorphic Transition of Bromo-diethylacetylurea and α-Bromoisovalerylurea——Res-

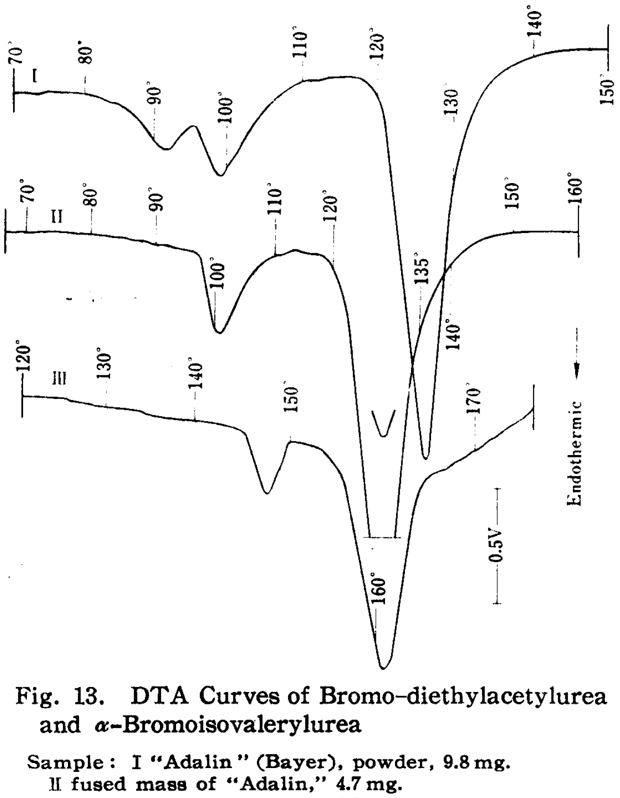


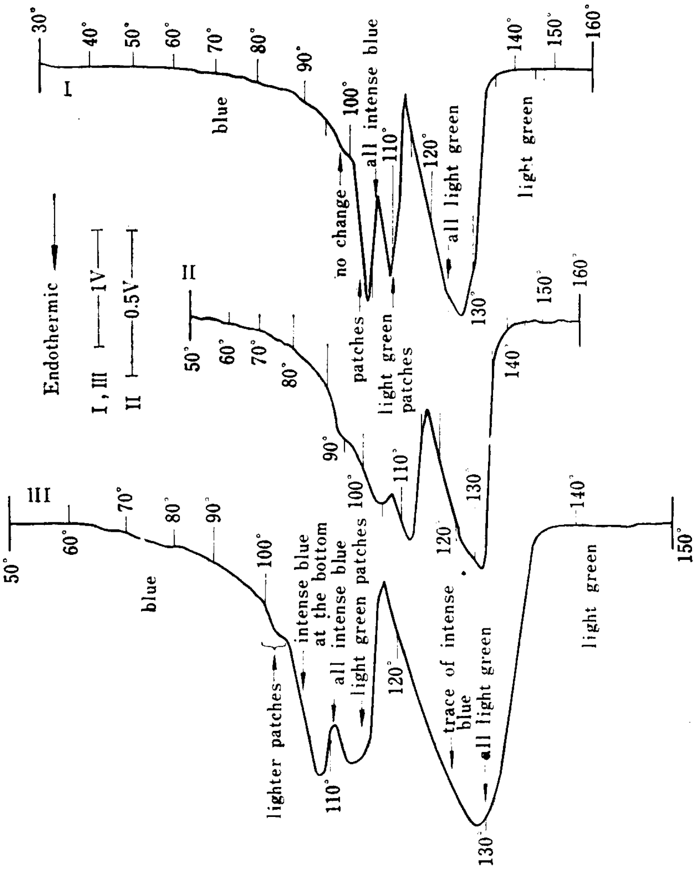
Fig. 13. DTA Curves of Bromo-diethylacetylurea and α-Bromoisovalerylurea

Sample: I "Adalin" (Bayer), powder, 9.8 mg.
Ⅱ fused mass of "Adalin," 4.7 mg.
Ⅲ bromovalerylurea (from MtOH), powder, 11.9 mg.
Reference: I, Ⅱ freeze-dried KCl, 10.0, 5.2 mg.
Ⅲ no reference material
Cell: type Ⅱ; Recording: semi-automatic; Sensivitity=1 VHeating rate: I 9°/min., Ⅱ 10~11°/min., Ⅲ 7°/min.
Chart speed=20 mm./min.

[*6] Heats of transitions and fusion of NH_4NO_3 reported in literature vary considerably. The above ratios were calculated by using the following values cited from "Kagakubinran" (ed. by Chem. Soc. of Japan, 1958); 0.38 kcal./mol. at 305.3°K (Ⅳ-Ⅲ), 0.32 kcal./mol. at 357.4°K (Ⅲ-Ⅱ), 1.01 kcal./mol at 398.4°K (Ⅱ-I), and 1.3 kcal./mol. at 442.8°K (fusion).

ults shown in Fig. 13 indicate the effect of heat capacity of the sample holder on the size of sample. By using a cell of small heat capacity, the sample amount required is much reduced to a degree of several milligrams. Although resolution of peaks for the first and the second transition of bromo-diethylacetylurea is somewhat incomplete, the curve will be sufficient for practical purpose. The fact that the peak for the first transition disappears completely when the compound is once fused and allowed to solidify suggests practical stability of the metastable form at room temperature. The gradual fall of the curve of α-bromoisovalerylurea before melting may be due to sublimation, and the rise after melting will be attributed to thermal decomposition, which is also detected by the smell of valeric acid.

Dehydration of Copper Sulfate Pentahydrate——Since dehydration is a composite of several elementary reactions, such as departure of water molecules from the parent hydrate, recrystallization of the lower ones or the anhydrous compound, formation of liquid water, and the subsequent evaporation or boiling, the DTA curve of this hydrate should have complex features. As is expected, results obtained with this apparatus are somewhat more complicated than those that have been reported in literatures. Also, it is found that color changes of the sample during heating correspond to the rise and fall in the DTA curve. (Fig. 14). One shoulder and three peaks are found between 90° and 140°; however, their positions are affected by experimental conditions. Almost all results done semiautomatically or manually confirm the presence of a shoulder. Although it is said that two water molecules came off simultaneously from the pentahydrate, curves and visual notes in the figure will not deny the possibility of stepwise dehydration. The color change to intense blue suggests the presence of condensed H_2O, nevertheless, exothermic reaction due to condensation of H_2O does not appear in the DTA curve. It is thought that the process in the hydrate will be different from usual condensation of vapor and for this reason, the heat required will become smaller. The second peak will be assigned to vaporization of the condensed H_2O, since fading in color is noticed when temperature is raised beyond this peak. The last peak in the curve will be attributed to the change from the trihydrate to the monohydrate. Complex features of this reaction are represented by several knicks in the corresponding peak.



[I]
Sample: Kahlbaum A.R., powder, 97.0 mg.
Reference: freeze-dried KCl, 75.5 mg.
Cell: type I Recording: semi-automatic
Sensitivity=2.5V
Heating rate=0.9~1.0°/min.
Chart speed=60 mm./hr.

[II]
Sample: mechanical mixt. of 17.0 mg. of $CuSO_4 \cdot 5H_2O$ and 43.0 mg. of freeze-dried KCl
Sensitivity=1V
Heating rate=3.5±0.2°/min.
Chart speed=180 mm./hr.

[III]
Sample: powder, 57.2 mg.
Sensitivity=2.5V
Heating rate: not controlled
Chart speed=180 mm./hr.

Fig. 14. DTA Curves of Copper Sulfate Pentahydrate

Determination of the Heat of Transition of Potassium Nitrate Using Benzoic Acid as an Internal Reference Substance——If a substance of known heat of transition or fusion does not react with a sample material both in solid and liquid state, it can be chosen as an internal reference for the evaluation of the heat of phase reaction of the sample. Since the differential temperature can be regarded as proportional to the change of voltage or current of the meter within a small range of temperature, the nearer are the peaks for the sample and the internal reference, the more precise determination of the heat will be accomplished, though, however, peak overlapping is not preferable. The new method was tested to find the heat of transition of KNO_3 from the aragonite to the calcite structure by conducting DTA of its intimate mixture with a given amount of benzoic acid which is taken as a heat standard. (4.14 kcal./mol. for fusion).[*7] Conduction of heat was prevented by wrapping the necks of both cells with cotton gauze and with separable jackets of foamed polystylol. Heating rate was maintained as constant as possible. The equation for calculating the heat of transition of $KNO_3(\Delta H_t)$ is as follows :

$$\Delta H_t = \Delta H_m \times \frac{\text{moles of benzoic acid}}{\text{moles of } KNO_3} \times \frac{S_{KNO_3}}{S_{B.A.}},$$

where ΔH_m is the heat of fusion of benzoic acid, and S_{KNO_3} and $S_{B.A.}$ represent areas for the endothermic peaks of KNO_3 and benzoic acid, respectively. Reproducible results as shown in Fig. 15 and Table I were obtained with mechanical and partly fused mixture of different proportion. Calculated values of ΔH_t show small variation and the mean well agrees with the value in literature. (1.218±0.005 kcal./mol.).2)

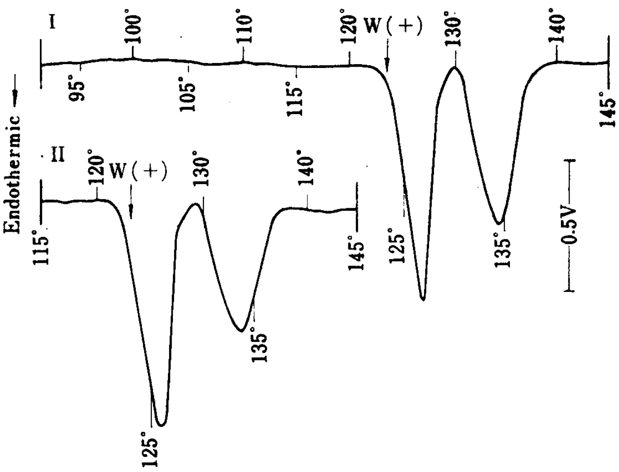


Fig. 15. DTA Curves of the Mixture of Benzoic Acid and Potassium Nitrate; Estimation of the Heat of Transition of Potassium Nitrate

Sample : I. mol. ratio of KNO_3/B. A.=3.388, mechanical mixt., 85.5 mg. II. mol. ratio of KNO_3/B. A.=2.417, mechanical mixt., 104.5 mg.
Reference : freeze-dried KCl, 75.5 mg.
Cell : type I Recording : semi-automatic
Sensitivity=1 V Heating rate=1.00±0.05°/min.
Chart speed=180 mm./hr.
W(+) : temp. where the wall of sample cell becomes cloudy by the appearance of liquid phase.

Discrimination between Pyrabital and the Physical Mixture of Aminopyrine and Barbital——In J. P. VII, it is stated that pyrabital is consisted of two moles of aminopyrine and one mole of barbital,

Table I. Determination of the Heat of Transition of Potassium Nitrate Using Benzoic Acid as Internal Reference

Sample state	B. A./KNO_3 a) (mol./mol.)	Total sample amount (mg.)	Heating rate b) (°C/min.)	Ratio of peak area (S-KNO_3/S-B. A.)	Heat of transition c) (kcal./mol.)
Phys. mixt. d)	0.414	100.4	0.95	0.70	1.20
Phys. mixt.	0.414	104.5	1.00	0.71	1.22
〃	0.414	103.8	1.00	0.73	1.26
〃	0.295	85.5	1.00	0.97	1.19
Fused mass e)	0.295	85.5	0.97	1.04	1.27
Phys. mixt.	0.295	74.5	1.00	0.91	1.12
〃	0.295	70.1	1.05	0.99	1.21
Fused mass	0.295	70.1	1.10	0.97	1.18
Phys. mixt.	0.295	101.9	1.00	1.02	1.24
〃	0.209	93.6	0.93	1.34	1.17
〃	0.209	87.0	1.10	1.34	1.16
				mean	1.20

a) Benzoic acid of A. R. ("Kahlbaum") was twice recrystallized from H_2O. KNO_3 of JIS A. R. was recrystallized from EtOH-H_2O mixture.
b) maintained constant within ±10%.
c) calculated by taking the heat of fusion of benzoic acid as 4.14 kcal./mol. (I. C. T.).
d) intimately mixed by trituration in an agate mortar.
e) Benzoic acid in the mixt. was fused below 145° and allowed to solidify at room temperature.

[*7] International Critical Tables; converted in kcal./mol.

2) V. Sokolov, N. Shmidt : Izvest. Sektora Fiz-Khim., 27, 217 (1956) (C. A. 50, 15200).

becomes partly soft over 90° and melts completely at about 113°. Although the expression is somewhat vague, it will implies that the J.P. preparation contains one-to-one molecular compound of both components along with excess aminopyrine. Since by chemical method, it is difficult to determine whether a given preparation contains barbital in the form of molecular compound or not, other method will be required. In the preceeding paper of this series, one of the authors pointed out that a physical mixture has a tendency to exhibit metastable eutectic liquefaction when both components form a molecular compound. However, the phenomenon is frequently overlooked by visual observation. Since DTA is much more sensitive than the thaw-melt method for the detection of small heat effect, it will effectively applied in order to make discrimination between a stable and a metastable mixture of equal composition.

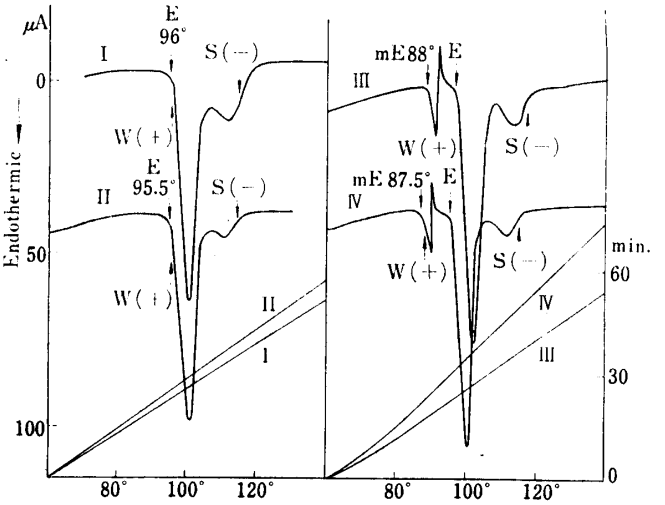


Fig. 16. DTA Curves of Aminopyrine and Barbital System

Sample: I. phys. mixt. of aminopyrine and the molecular compound of aminopyrine and barbital, mol. ratio=1:1, powder, 56.0 mg.; II. commercial product of J.P. VII, powder, 67.5 mg.; III, IV. phys. mixt. of aminopyrine and barbital, mol. ratio=2:1, powder, 55.7, 64.1 mg.
Reference: freeze-dried KCl, 70.6 mg. Cell: type I
Recording: manual Sensitivity=50
Heating rate: I 1.5°/min.; II 1.4°/min.; III 1.5°/min.; IV 1.0°/min.
E: stable eutectic point; mE: metastable eutectic point;
W(+): temp. where the wall of sample cell becomes cloudy by the appearance of liquid phase.

In Fig. 16, DTA curves of the equimolar mixture of aminopyrine and the molecular compound, the one having two-to-one molar ratio of aminopyrine and barbital, and a commercial preparation are shown. The mixture containing the molecular compound exhibits two endothermic peaks; the first one is attributed to stable eutectic fusion, and the second to complete melting. No liquefaction was observed visually until the curve reached just above the temperature of fall at 95~96°, which is well agreed with the eutectic point measured by the thaw-melt method. In the case of the mere physical mixture of amionpyrine and barbital, there appears one pair of additional endothermic and exothermic peaks below the temperature of the stable eutectic point. This endothermic fall beginning at about 88° is caused by the metastable eutectic liquefaction. The fact that an exothermic peak of characteristic shape occurs immeadiately after the first fall must be attributed to both or either of the heat of molecular compound formation and/or that of solidification of the metastable liquid. Rapid rise of the curve from the bottom to the summit will indicate that overlapping of opposite heat effects occurs simultaneously at this range of temperature. Validity of the assignment of these peaks was confirmed by visual observation concerning the appearance and disappeaeance of solid and liquid phase. DTA curves obtained with several commercial products were quite similar to that of the stable mixture. More detailed study on this system will be given later on.

Discussion

Differential thermal analysis is generally accepted as a powerful means for the study of phase changes, such as polymorphic transition, fusion, desolvation, and decomposition. However, since thermal effects due to these reactions are merely registered on the DTA curves by producing similar endothermic or exothermic peaks, it is often difficult to determine to what kinds of reaction they are attributed. For this reason, the device permitting visual observation of the sample will be effective for the investigation of phase reactions accompanying changes in state or decompositions involving color change. Though not a few types of DTA apparatus are now in practical use, there are few that is possible to make direct observation.[3] The one presented here is not only simple and easy to handle, but also suffices nearly all the requirements for the

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3) V. Hogan, S. Gordon: Anal. Chem,, **32**, 573 (1960); J. Chin: *Ibid.*, **35**, 933 (1963).

study of organic materials of low and medium molecular weight. Although the temperature range of the apparatus is limited by the use of thermistors from room temperature to about 250°, this will not offer significant weakness, since characteristic portions of the DTA curves for most organic compounds and their mixtures mainly lie in this range. During the course of measurement, appearance and disappearance of liquid or solid phase, desolvation process, and in some cases, even polymorphic transition can be observed directly. The detecting power of coupled thermistors for temperature difference is so sensitive that the apparatus can catch a small heat effect which is often missed by an analyzer using thermocouples. Also, it is durable and has been used for three years without trouble.

It is said that DTA can be applied both qualitatively and quantitatively; however, factors that intervene in the procedure are so complicated that it will not be adopted for quantitative purposes without difficulty. At the same time, the result will accompany comparatively large experimental error. In the method proposed here for determining the heat of phase reaction, some of the factors influencing on the result are excluded or simplified by making direct comparison between the peak area of the sample and that of the reference in the same thermogram; thus, the precision will be improved and the time for operation will become short. Since reactions between inorganic and organic materials occur infrequently, it is not difficult to select a substance for the internal reference, which has a temperature and a known heat of transition suitable for the sample. Also, the selection itself is done easily by DTA. For this reason, the authors believe that the method proposed here will have practical application, especially to organic materials.

The fact that completely different DTA curves were obtained with pyrabital and the corresponding mixture of aminopyrine and barbital will afford a general criterion for the distinction of a molecular compound from its component mixture. In other words, the same result will serve as an illustrative example that DTA can be applied to find whether a given pair of components can form a molecular compound or not.

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Summary

A convenient DTA apparatus using two matched thermistors was designed and was easily and inexpensively constructed. Because of sensitivity of the thermistors for detecting temperature difference and of the advantage of the double cell consisting of a inner tube and a jacket, the sample size is much reduced even to a few milligrams. The arrangement of the cell is also effective for making the base line flatten. Another characteristic point of the apparatus is that it permits direct viewing of the sample during the course of measurement. Since it is often desirable to compare peaks in the DTA curve with visual changes, the arrangement is found very useful for the study of phase reactions of organic materials. Tests concerning the experimental conditions show that analysis can be performed with accuracy and reproducibility. Applications were done for the studies of thermal behaviors of ammonium nitrate, bromo-diethylacetylurea and α-bromoisovalerylurea. Direct transformation of ammonium nitrate from the modification of IV to II was occasionally noticed. It was also confirmed that there was clear correspondence between the fall and rise of the DTA curve of copper sulfate pentahydrate and the changes in color observed with eye.

As a general application of DTA, a simple method for evaluating the heat of transition was proposed. It is based on direct comparison of two peaks by conducting DTA

with a mixture of the sample and the inert substance of known heat of transition. The heat of polymorphic transition of potassium nitrate at 128～129° was found to be 1.20 kcal./mol. by using benzoic acid as an internal standard. It is thought that the method will have wide application, especially to organic materials. Also, discrimination of pyrabital from the corresponding mixture of aminopyrine and barbital was successfully done by DTA. The curve of the former shows two peaks which is due to the stable eutectic liquefaction and to melting, while that of the latter exhibits in addition to these peaks, one pair of endothermic and exothermic ones which is attributed to the metastable eutectic liquefaction and to the molecular compound formation, respectively. These results will suggest that DTA is generally applicable to the detection of molecular compound between organic medicinals.

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138. Haruki Nishimura, Osamu Yamauchi, and Hideji Takamatsu :
Studies on Phenylalkanethiolamine. VI.[*1] Synthesis and Configuration of 2-Phenyl-3,4-dimethylthiomorpholine.

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In the previous papers of this series the authors reported studies on synthesis of various derivatives of 1-phenyl-2-aminoethanethiol[1] and the configuration of 1-phenyl-2-dimethylaminopropanethiol.[2] The present paper deals with synthesis of N-(2-mercaptoethyl)ephedrines and *erythro*- and *threo*-2-phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazines, which appear to be of interest from a pharmacological point of view.

In an attempt to obtain N-(2-mercaptoethyl)-*l*-ephedrine (Ⅲ), N-chloroacetyl-*l*-ephedrine (I), prepared by the reaction of *l*-ephedrine (L-*erythro*-series) with chloroacetyl chloride in benzene, was converted to N-thioglycoloyl-*l*-ephedrine (Ⅱ) by potassium hydrosulfide in ethanol. On reduction with lithium aluminum hydride Ⅱ gave a crude product (Ⅲ), but the infrared spectrum showed no clear SH absorption band. Since it was difficult to purify the crude product as will be mentioned, other synthetic methods were investigated.

When *l*-ephedrine was caused to react with ethylene sulfide, *l*-ephedrine was recovered unchanged, and no product was obtained.

However, when N,N'-dithiodiacetyl-bis-*l*-ephedrine (Ⅳ), obtained by the reaction of *l*-ephedrine with dithiodiacetyl chloride in chloroform, was reduced with lithium aluminum hydride, Ⅲ was obtained in a nearly pure state. The N-(2-mercaptoethyl) derivatives (Ⅶ) and (Ⅷ) were analogously prepared from *d*-*ψ*-ephedrine (L-*threo*-series) and *dl*-ephedrine(DL-*erythro*-series) through the corresponding intermediates (V) and (Ⅵ). In their infrared spectra all these compounds showed the SH absorption band near 2550 cm^{-1} and no amide I band that was present in the spectra of the amides (Ⅳ), (V), and (Ⅵ).

[*1] Part V : Yakugaku Zasshi, 84, 824 (1964).

[*2] Ebie-kami-2-chome, Fukushima-ku, Osaka (西村温樹, 山内 脩, 高松秀二).

1) Part I : Yakugaku Zasshi, 84, 797 (1964).

2) *a*) Part Ⅱ : *Ibid.*, 84, 806 (1964). *b*) Part Ⅲ : *Ibid.*, 84, 811 (1964).