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Ammonia Adducts of Barbiturates and Their Application to Particle Size Reduction[1,2]

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Ammonia adduct formation was confirmed with 9 barbiturates and ammonia interaction was felt with another 2. Thermal behaviors of the ammonia adducts were investigated by differential scanning calorimetry (DSC), thermogravimetry (TG), and others. Particle size of barbiturates was effectively reduced by formation of ammonia adducts and subsequent desorption of ammonia. Further, the effect of particle size on solubility and heat of fusion was investigated.

Keywords——barbiturates; particle size reduction; ammonia adduct; ammonia sorption and desorption; thermograms of ammonia adduct; particle size-solubility relationship; particle size-heat of fusion relationship; structure of ammonia adduct

Twelve barbiturates including allobarbital, amobarbital, barbital, barbituric acid, cyclobarbital, hexobarbital, mephobarbital, metharbital, pentobarbital, phenobarbital, propallylonal, and secobarbital were investigated as to whether they could form ammonia adducts, and whether ammonia desorption could influence particle size reduction. Thermal and other physico-chemical properties were determined by differential scanning calorimetry (DSC), infrared spectrophotometry (IR), X-ray powder diffraction analysis, and ordinary microscopy.

The conditions required for successful formation of ammonia adducts and of recovery of the parent barbiturates by desorption of ammonia were experimentally determined in this study.

Specific surface areas of the barbiturate powders recovered were measured by gas adsorption (BET) method and compared with those of mechanically pulverized particles of untreated commercial barbiturate powders.

Experimental

Materials——The barbiturates used in this study are listed in Table I. Pentobarbital and secobarbital were prepared by dissolving their sodium salts in a minimum amount of water, into which 1 N HCl solution was then added to precipitate crystals. The crystals were then washed several times with distilled water and dried at room temperature. Purity was checked by DSC measurements. Compressed liquid ammonia was employed as a source of ammonia.

Preparation of Ammonia Adducts of Barbiturates——Formation of ammonia adducts was as described in the previous paper, including both crystallization from liquid ammonia solution of the barbiturates and direct sorption of gaseous ammonia.[4] In addition, successful attempts were made to soak barbiturate powders directly with liquid ammonia.

Differential Scanning Calorimetry (DSC)——A Perkin-Elmer DSC-1B differential scanning calorimeter was used. The sample weight was determined to within 0.01 mg with a semimicrobalance, if needed for quantitative calorimetric analysis. The evolved gas was detected simultaneously in almost all cases, and dissociated ammonia gas was identified by Nessler's reagent solution.[4]

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1) Studies on Methods of Particle Size Reduction of Medicinal Compounds. VII. Part VI: K. Sekiguchi, K. Shirotani, M. Kanke, H. Furukawa, and M. Iwatsuru, *Chem. Pharm. Bull.* (Tokyo), **24**, 1621 (1976).

2) A part of this work was presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April 1975.

3) Location: *a*) *9-1 Shirokane 5-Chome, Minato-ku, Tokyo 108, Japan*; *b*) *Sagamiko, Kanagawa, 199-01, Japan.*

4) K. Sekiguchi, Y. Tsuda, and M. Kanke, *Chem. Pharm. Bull.* (Tokyo), **22**, 2972 (1974).

Table I. Barbiturates used in This Study

Common name	Substituents	Reagent source
Allobarbital	5,5-Diallyl	J.P. VIII grade
Amobarbital	5-Ethyl-5-isoamyl	J.P. VIII grade
Barbital	5,5-Diethyl	J.P. VIII grade
Barbituric acid	—	Reagent grade (Wako Pure Chem. Indust. Ltd.)
Cyclobarbital	5-(1-Cyclohexen-1-yl)-5-ethyl	J.P. VIII grade
Hexobarbital	5-(1-Cyclohexen-1-yl)1,5-dimethyl	J.P. VIII grade
Mephobarbital	5-Ethyl-1-methyl-5-phenyl	Prominal (Bayer Pharmaceutical Co,. Ltd.)
Metharbital	5,5-Diethyl-1-methyl	Gemonil (Dainippon Pharmaceutical Co., Ltd.)
Pentobarbital	5-Ethyl-5-(1-methylbutyl)	prepared from sodium pentobarbital, B.P. grade
Phenobarbital	5-Ethyl-5-phenyl	J.P. VIII grade
Propallylonal	5-(2-Bromoallyl)-5-isopropyl	Noctenal (Uji Pharmaceutical Co., Ltd.)
Secobarbital	5-Allyl–5-(1-methylbutyl)	prepared from sodium secobarbital (Yoshitomi Pharmaceutical Co., Ltd.)

Thermogravimetric Analysis (TG)——A Perkin-Elmer TGS-1 thermobalance was used. The sample weight was 1—6 mg, and a scanning speed from 4° to 16°/min was employed. The combining ratios of the ammonia adducts were determined by the mean values of 3—10 measurements.

Measurement of Specific Surface Area——A BET gas adsorption apparatus (Model P-600, Shibata Chemical Apparatus Mfg. Co., Ltd.) was used. Sample weights of 1.0—2.0 g were taken, with nitrogen gas as the adsorbant.

Infrared Spectroscopy (IR)——IR spectra by nujol mull method were determined with a Jasco IRA-1 Grating Infrared Spectrophotometer.

X-ray Powder Diffractometry——A JDX-7F X-ray Diffraction Analyzer made by Japan Electron Optics Laboratory Co., Ltd. was used (Ni filter, Cu-Kα ray $\lambda = 1.542$ Å). Sample powders were held at low temperature, if necessary, by cooling the sample chamber with dry ice.

Microscopic Observation——The thermal behavior of crystals obtained from ammonia-barbiturate solutions was observed on heating by hot-stage microscopy (Ernst Leitz Model 350). An ordinary microscope (Olympus Optical Co., Ltd. Model FHF-Tr-IV) was used to observe the effect of ammonia adduct formation on particle size reduction.

Solubility Measurements——Metharbital solubilities were measured, both for the commercial product and for desolvated products *via* ammonia interacted samples. About 1.5 g of sample powder was placed in 200 g of distilled water contained in the jacketed cell, and stirred at 600 rpm at temperatures of 20°, 30°, and 40°. Solution samples were taken by a glass syringe at intervals and filtered through a 0.22 μ membrane filter (Millipore GSWP 01300), and then aliquots of solutions were weighed and diluted for spectrophotometric assay at the wavelength of 255 nm.

Measurement of Heat of Fusion——A Perkin-Elmer DSC-1B Differential Scanning Calorimeter was used. Sample powders for both commercial barbiturates and barbiturates recovered by desorption of ammonia from their ammonia adducts were pulverized in an agate mortar. Areas under the melting peaks were measured with a planimeter.

Elemental Analysis——Barbituric Acid Ammonium Salt: *Anal.* Calcd. for $C_4H_4N_2O_3$–NH_3: C, 33.11; H, 4.86; N, 28.96. Found: C, 32.61; H, 4.68; N, 28.61.

Results and Discussion

It was found that 9 out of the 12 barbiturates investigated formed ammonia adducts, and 2 of the remaining 3 were felt to interact with ammonia, although formation of true adducts could not be proved. Barbiturates which formed ammonia adducts were allobarbital, amobarbital, barbital, barbituric acid, cyclobarbital, pentobarbital, phenobarbital, propallylonal, and secobarbital, and the barbiturates which were thought to interact with ammonia were metharbital and hexobarbital. On the other hand, mephobarbital neither formed adduct nor showed significant interaction with ammonia.

It is certain that phenobarbital formed at least one ammonia adduct; however, its thermal behaviors were so complicated and varied presumably because of participation of polymorphs that precise explanation of the thermograms is now difficult. For this reason, phenobarbital is omitted from the present study.

Concerning the other barbiturates which form adducts or interacted products with ammonia, their thermal behaviors were found to be as follows:

Thermograms of Ammonia Adducts of Barbiturates

1. Ammonia Adduct of Allobarbital——Eleven batches of allobarbital-ammonia adducts were obtained by recrystallization from liquid ammonia solution and 2 batches were obtained by wetting allobarbital powder with liquid ammonia. The ammonia adducts obtained by the above two methods showed identical characteristic patterns of DSC, EGD, and TG shown in Fig. 1 (b)—(d). The DSC pattern of pure allobarbital is also shown in Fig. 1 (a).

The endothermic peak on the DSC curve (b) which appeared between 40° and 90° is due to decomposition of the adduct and evolution of the ammonia, while the second peak appeared at about 175° is due to melting of pure allobarbital, judging from the corresponding EGD curve.

The combining ratio of the adduct was determined to be 1:2 (allobarbital:ammonia=1:1.95) from the weight decrease measured by TG with both adducts obtained by recrystallization and by wetting allobarbital powder. The adduct is decomposed easily on standing at room temperature, and also decomposes gradually in a refrigerator.

The allobarbital powder obtained by free dissociation of ammonia from the adduct at room temperature is difficult to handle or pulverize in a mortar with a pestle because of static electricity, while the allobarbital powder recovered by rapid desorption of ammonia, *i. e.*, placing the ammonia adduct at 50° under reduced pressure for one and a half hours, is easy to pulverize without interference from static electricity. Further, the specific surface area of the latter powder is comparatively larger than the former, as seen in Table II.

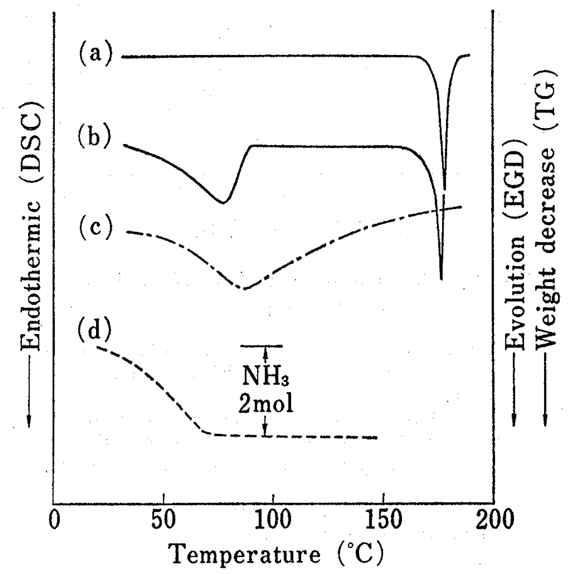

Fig. 1. Thermograms of Allobarbital and Its Ammonia Adduct

(a) DSC curve of commercial allobarbital under semi-closed oonditions: sample weight, 11.18mg; heating rate, 16°/min.
(b) and (c) Simultaneous DSC and EGD curves of the 1:2 (allobarbital:NH_3) adduct under semiclosed conditions: sample weight, 11.80 mg; heating rate, 16°/min.
(d) TG curve of the 1:2 adduct: sample weight, 1.97 mg; heating rate, 16°/min.

In the IR spectrum of the adduct, the new absorption bands arising from NH stretching vibration at the region around 3480 cm^{-1}, from C=N stretching vibration in the region of 1675—1635 cm^{-1}, and from NH_3 bending vibration in the region of 1610—1500 cm^{-1} appeared in comparison with the spectrum of allobarbital.

2. Ammonia Adduct of Amobarbital——Thermograms of amobarbital and of its ammonia adduct prepared from liquid ammonia solution are shown in Fig. 2. On the DSC pattern in Fig. 2 (b), in which the sample temperature was increased from room temperature, there are two endothermic peaks before melting at about 150°. The simultaneously obtained EGD curve shows ammonia elimination corresponding to the DSC curve, as seen in Fig. 2 (c).

The molecular ratio of the ammonia adduct was found to be approximately 1:2 (amobarbital: ammonia=1:1.88) from the weight decrease measured by TG, while the existence of a 1:1 adduct (amobarbital: ammonia=1:1.01) was indicated in the process of thermal decomposition, as shown in Fig. 2 (d). However, when the 1:2 adduct was kept at room temperature (25±3°), dissociation of combined ammonia was not stepwisely occurred and the presence of the 1:1 adduct could not be confirmed from the weight decrease curve by TG.

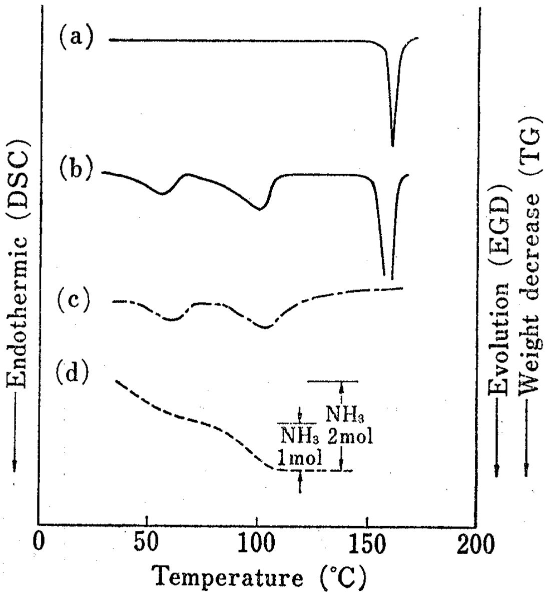

Fig. 2. Thermograms of Amobarbital and Its Ammonia Adduct

(a) DSC curve of commercial amobarbital under semiclosed conditions: sample weight, 8.71 mg; heating rate, 16°/min.
(b) and (c) Simultaneous DSC and EGD curves of the 1:2 (amobarbital: NH_3) adduct under semiclosed conditions: sample weight, 9.32 mg; heating rate, 16°/min.
(d) TG curve of the 1:2 adduct: sample weight, 3.20 mg; heating rate, 4°/min.

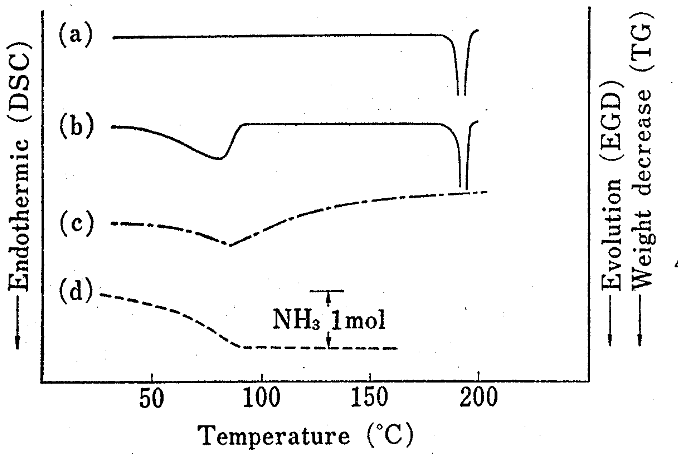

Fig. 4. Thermograms of Barbital and Its Ammonia Adduct

(a) DSC curve of commercial barbital under semiclosed conditions: sample weight, 11.70 mg; heating rate, 16°/min.
(b) and (c) Simultaneous DSC and EGD curves under semiclosed conditions of the 1:1 adduct obtained by recrystallization or by ammonia gas sorption: sample weight, 7.82 mg; heating rate, 16°/min.
(d) TG curve of the 1:1 adduct: sample weight, 5.84 mg; heating rate, 16°/min.

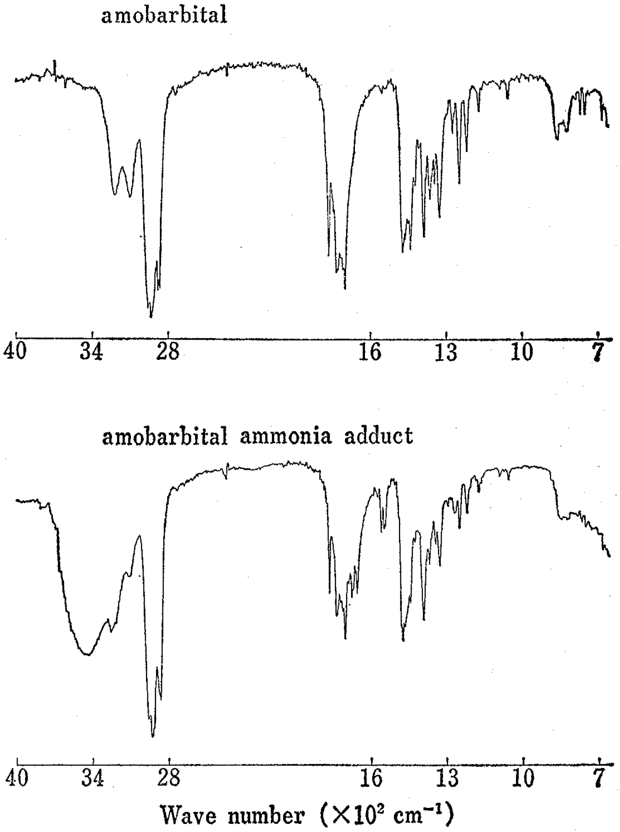

Fig. 3. Infrared Spectra of Amobarbital and Its Ammonia Adduct (Nujol mull)

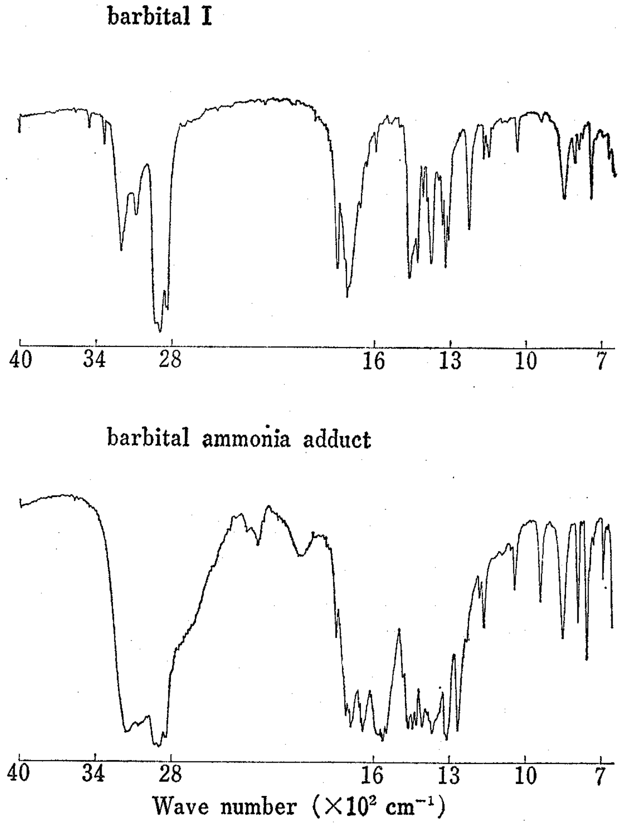

Fig. 5. Infrared Spectra of Barbital Form I and Its Ammonia Adduct (Nujol mull)

The IR spectra for amobarbital and its ammonia adduct are shown in Fig. 3. The new absorption bands in the region of 3720—3240 cm^{-1}, 1660—1635 cm^{-1}, and 1550—1520 cm^{-1} appeared in the spectrum of amobarbital ammonia adduct, which exhibited almost the same change as with allobarbital.

3. Ammonia Adduct of Barbital——Typical patterns of DSC and EGD curves of the crystals obtained from barbital-ammonia solution are shown in Fig. 4 (b) and (c) together with the thermogram of the original barbital (a). The endothermic peak on the DSC curve (b) which appeared between 50° and 100° is due to decomposition of the adduct and evolution of the ammonia, while the second peak appeared at about 190° is the melting of pure barbital, judging from the corresponding EGD curve (c). Although four polymorphic forms have been reported for barbital, ammonia-free barbital recovered from the adduct is identified from its melting point and characteristic X-ray pattern as the high temperature stable form.

In addition to the fact that an adduct is obtained by crystallization from liquid ammonia-barbital solution, it can also be obtained by introducing ammonia gas for about an hour into a flask which contains a thin layer of dry barbital powder. The DSC and EGD patterns of the latter adduct are identical to Fig. 4 (b) and (c), and its X-ray powder diffraction pattern is identical to that of the former.

The molecular ratio of the ammonia adduct was found to be 1:1 (barbital: ammonia= 1:0.95) by the weight decrease measured by TG, as shown in Fig. 4 (d).

The binding force between ammonia and barbital molecules is estimated to be 2.1 kcal/mol by subtracting the heat of ammonia evaporation, 5.6 kcal/mol,[5] from the heat of decomposition of the barbital ammonia adduct, about 7.7 kcal/mol, obtained by DSC measurements under semiclosed conditions.

The IR spectra for barbital I and its ammonia adduct are shown in Fig. 5. The adduct exhibited different pattern from ones for adducts of allobarbital and amobarbital which possess the combining ratio of 1:2 (barbiturate: ammonia). The new absorption bands arising from $C=\overset{+}{N}-H$ (immonium) in the region of 2200—1800 cm^{-1}, from C=N stretching vibration at the region around 1640 cm^{-1}, from NH_3 bending vibration in the region of 1590—1550 cm^{-1}, and mainly from C–N stretching and partly from NH bending vibration at 1265 cm^{-1} appeared in the spectrum of barbital ammonia adduct. Additionally, the bands at 1750 cm^{-1} and 1230 cm^{-1} weaken or disappear in the ammonia adduct and gradually become intense with the progression of the decomposition of the adduct into barbital I. This fact suggests that free $\rangle C=O$ disappeared by interaction with ammonia. These IR data suggest that immonium structure is, at least partly, involved in the adduct. In other words, the barbital molecule in the adduct may take polarized form, and may associate with ammonia by dipole-induced dipole interactions.

4. Ammonium Salt of Barbituric Acid——Different from other barbiturates, barbituric acid was insoluble in liquid ammonia but by soaking it in liquid ammonia for several hours, a compound with ammonia was separated. The compound is very stable at room temperature and the molecular ratio between barbituric acid and ammonia was found to be 1:1 (barbituric acid: ammonia) by elemental analysis. As is depicted in Fig. 6 (a) and (c), its DSC curve showed only one melting peak at a temperature considerably higher than the melting peak of free barbituric acid. Also, the IR spectrum of the compound in Fig. 7 is distinct from those of other substituted barbiturate adducts in that it lacks a peak at the region around 1560 cm^{-1} which is assigned to NH_3 bending vibration.

From the fact that barbituric acid is much stronger in acid strength than other barbiturates and from the above experimental results, it is thought that a salt is formed between barbituric acid and ammonia.

Incidentally, the appearance of a small endothermic peak below the melting peak in the DSC curve (a) will suggest that barbituric acid is a dimorphic substance.

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5) "Encyclopaedia Chimica I," Kyoritsu Shuppan, Tokyo, 1960.

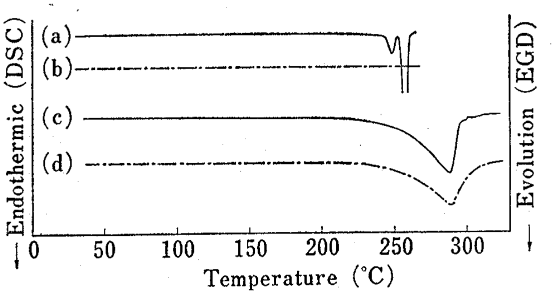
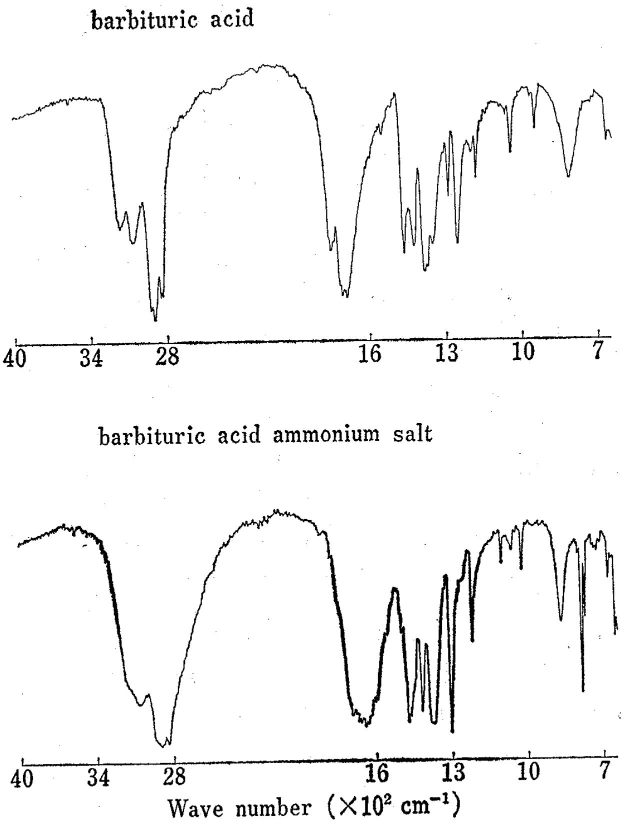


Fig. 6. Thermograms of Barbituric Acid and Its Ammonium Salt

(a) and (b) Simultaneous DSC and EGD curves of commercial barbituric acid under semiclosed conditions: sample weight, 6.55 mg; heating rate, 16°/min.
(c) and (d) Simultaneous DSC and EGD curves of the ammonium salt under semiclosed conditions: sample weight, 9.08 mg; heating rate, 16°/min.


barbituric acid

barbituric acid ammonium salt

Fig. 7. Infrared Spectra of Barbituric Acid and Its Ammonium Salt (Nujol mull)

5. Ammonia Adducts of Cyclobarbital——The curves (b), (c), and (d) in Fig. 8 are the results of DSC, EGD, and TG obtained with crystals immediately after preparation without pulverization. It is suggested that two kinds of ammonia adducts are formed. The combining ratio of the first adduct (the original crystals) could not be determined because of its instability; however, the ratio of the second one is found to be 1:1 (cyclobarbital: ammonia =1:1.05) from the weight decrease over 150° on the TG curve (d).

When the sample was triturated intimately in an agate mortar, the first adduct transformed completely to the second one as seen in the curves (e) and (f). The fact that the first peak appeared at much lower temperature range than the corresponding peak on the curve (b) will indicate that desorption of ammonia from the second adduct occurs more easily by the increase of surface area due to pulverization of the original sample.

Furthermore, areas under the endothermic peaks on the DSC curves (a), (b), and (e) were compared by measuring with a planimeter. From the results, it is supposed that the endothermic and the successive small and irregular exothermic peaks at about 140—170° on the DSC curve (b) are thought to be attributed to the combined heat effect of various phase reactions, such as the melting of the second adduct, ammonia desorption, and crystallization of free cyclobarbital.

The difference of the IR spectra between cyclobarbital and its ammonia adduct was almost the same as with barbital.

6. Ammonia Adduct of Pentobarbital——The characteristic thermograms of pentobarbital and its ammonia adduct prepared by crystallization from liquid ammonia are shown in Fig. 9 (a)—(d). The first endothermic peak in Fig. 9 (b) is attributed to decomposition of the adduct, judging from the corresponding EGD curve (c), while the second peak on the DSC curve is due to melting of free pentobarbital.

The combining ratio of the adduct is determined to be 1:1 (pentobarbital: ammonia= 1:1.02) from the weight decrease measured by TG, as shown in Fig. 9 (d). The pentobarbital-ammonia adduct is fairly stable at room temperature.

7. Ammonia Adducts of Propallylonal——Two types of adducts containing different ammonia contents were separated from propallylonal-ammonia solution by changing crystal-

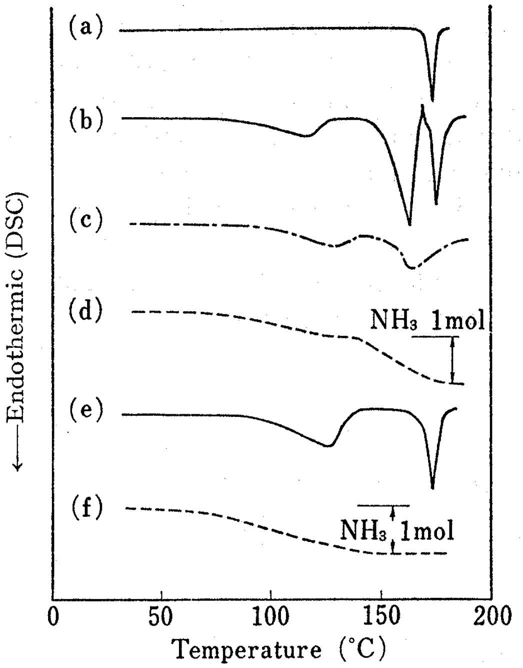


Fig. 8. Thermograms of Cyclobarbital and Its Ammonia Adduct

(a) DSC curve of commercial cyclobarbital under semiclosed conditions: sample weight, 5.83 mg; heating rate, 16°/min.
(b) and (c) Simultaneous DSC and EGD curves of the 1:1 ammonia adduct under semiclosed conditions: sample weight, 3.39 mg; heating rate, 16°/min.
(d) TG curve of the adduct: sample weight, 3.60 mg; heating rate, 16°/min.
(e) DSC curve of the adduct after intimate trituration: sample weight, 5.17 mg; heating rate, 16°/min.
(f) TG curve of the adduct after intimate trituration: sample weight, 2.42 mg; heating rate, 16°/min.

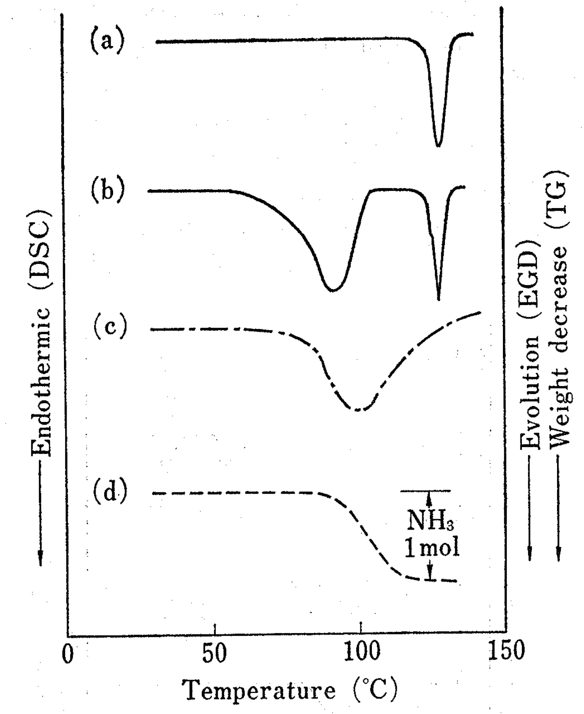


Fig. 9. Thermograms of Pentobarbital and Its Ammonia Adduct

(a) DSC curve of pentobarbital under semiclosed conditions: sample weight, 4.87 mg: heating rate, 16°/min.
(b) and (c) Simultaneous DSC and EGD curves of the 1:1 adduct under semiclosed conditions: sample weight, 12.36 mg; heating rate, 16°/min.
(d) TG curve of the 1:1 ammonia adduct: sample weight, 2.90 mg; heating rate, 16°/min.

lization conditions. Thermograms of them are shown in Fig. 10 (b)—(f). As depicted in the curves (g) and (h), another adduct was obtained as an intermediate product by heating or by mere triturating of the one that gave curve (b).

From weight decreases in the TG curves (d), (f), and (h), molecular ratios of these adducts were determined to be 1:2, 1:1, and 1:1 (propallylonal: ammonia=1:2.11, 1:1.03, and 1:1.09, respectively).

It is thought that the two 1:1 adducts belong to different chemical species because the intermediate adduct release ammonia at much higher temperature than the one from ammonia solution, in spite of the ease of desorption by triturating.

All of the three ammonia adducts thus confirmed are relatively unstable at room temperature, and lose ammonia gradually and completely. The ammonia-free propallylonal recovered from these adducts was found to be a mixture of two polymorphic forms, judging from two melting peaks, as seen in Fig. 10 (i). The lower melting peak appears at the same temperature as the melting of the commercial product (curve (a)), while the higher peak seems to correspond to the melting peak obtained on heating of freshly made adducts, as seen in Fig. 10 (b), (e), and (g). From these facts it is suggested that the polymorphic form stable at higher temperature is obtained by rapid elimination of ammonia from fresh adducts, but it readily converts into the more stable form as in the commercial product at room temperature.

The IR spectrum of the 1:2 adduct showed the new absorption bands in the region of 3680—3320 cm^{-1}, 2200—2020 cm^{-1}, 1970—1820 cm^{-1}, 1650—1620 cm^{-1}, and 1600—1530 cm^{-1} in comparison with one of propallylonal.

8. Ammonia Adduct of Secobarbital——Secobarbital-ammonia adduct crystallized from liquid ammonia solution showed quite different thermograms from the other barbiturates. It is said that secobarbital does not have polymorphic forms. The typical DSC pattern of the adduct is shown in Fig. 11 (b), along with the characteristic curve (a) of the pure secobarbital, for which the melting point agreed with the published value of 100°. The endothermic peak on the curve (b) is attributed to heat effect of ammonia elimination accompanied by melting of the adduct. This assignment was also supported by visual observation using a polarized hot-stage microscopy.

The combining ratio of the freshly made adduct could not be determined precisely. However, after trituration of the adduct in an agate mortar, the combining ratio became

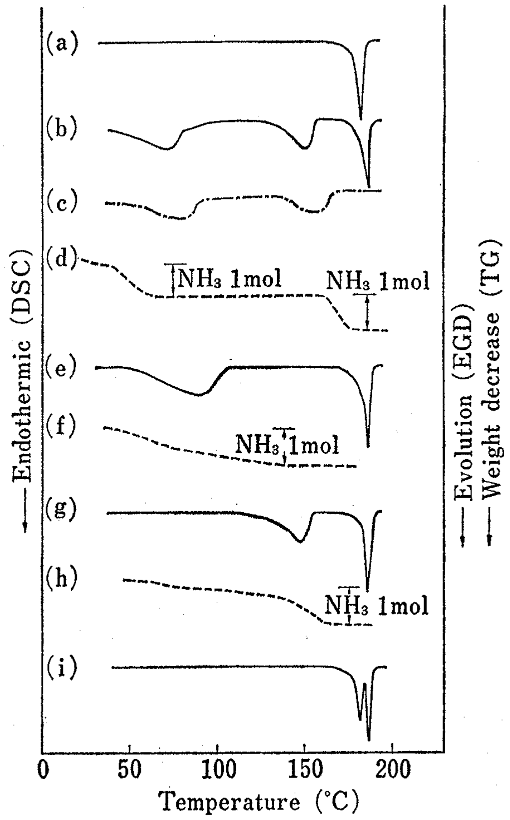


Fig. 10. Thermograms of Propallylonal and Its Ammonia Adducts

(a) DSC curve of commercial propallylonal under semiclosed conditions: sample weight, 7.53 mg; heating rate, 16°/min.
(b) and (c) Simultaneous DSC and EGD curves of the 1:2 adduct under semiclosed conditions: sample weight, 4.04 mg; heating rate, 16°/min.
(d) TG curve of the 1:2 adduct: sample weight, 3.47 mg; heating rate, 16°/min.
(e) DSC curve of the 1:1 adduct under semiclosed conditions: sample weight, 4.90 mg; heating rate, 16°/min.
(f) TG curve of the 1:1 adduct corresponding to the DSC curve (e): sample weight, 1.74 mg; heating rate, 16°/min.
(g) DSC curve of the 1:1 adduct under semiclosed conditions: sample weight, 5.25 mg; heating rate, 16°/min.
(h) TG curve of the 1:1 adduct corresponding to the DSC curve (g): sample weight, 3.04 mg; heating rate, 16°/min.
(i) DSC curve obtained after desorption of ammonia from all three types of ammonia adducts under reduced pressure: sample weight, 10.84 mg; heating rate, 16°/min.

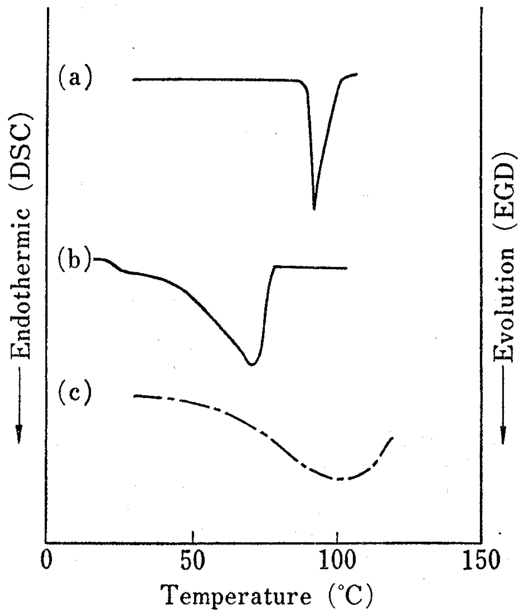


Fig. 11. Thermograms of Secobarbital and Its Ammonia Adduct

(a) DSC curve of commercial secobarbital under semiclosed conditions: sample weight, 5.12 mg; heating rate, 16°/min.
(b) DSC curve of the ammonia adduct: sample weight, 10.61 mg; heating rate, 16°/min.
(c) EGD curve of the adduct: sample weight, 8.17 mg; heating rate, 16°/min.

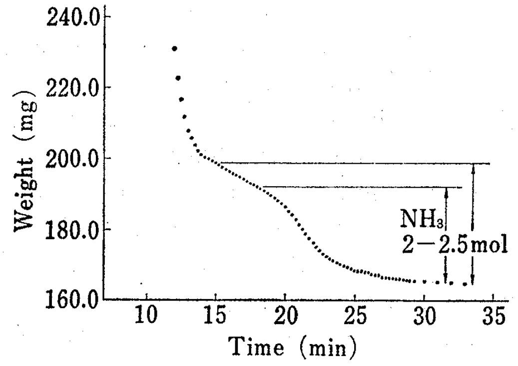


Fig. 12. Weight Decrease Curve of Metharbital- Ammonia Interacted Crystals obtained on a Semimicrobalance at Room Temperature (24±1)

constant and was determined to be 1:1 (secobarbital: ammonia=1:1.01), based on the weight balance before and after each DSC run.

The difference of the IR spectra between secobarbital and its ammonia adduct was similar to that for allobarbital.

9. Interaction of Ammonia with Metharbital——In the case of one particular batch of metharbital, fairly large transparent crystals were obtained by crystallization from metharbital-ammonia solution. However, when these crystals were removed from the solution to room temperature, they cracked and lost transparency immediately. Although DSC, TG, and X-ray powder diffractometry failed to confirm ammonia adduct formation in such fractured crystals, a weight decrease curve at nearly constant (room) temperature was successively obtained by placing the above freshly made crystals on a semimicrobalance, as shown in Fig. 12. From this curve, the formation of an adduct was recognized. Although its combining ratio can not be determined precisely, it is estimated to be 1:2—1:2.5 (metharbital: ammonia). Further, the particle size of the powder obtained by pulverizing such crystals in a mortar with 200 strokes is much smaller and more uniform than in the case of the commercial product pulverized by the same number of strokes, as shown by the microscopic photographs in Fig. 13.

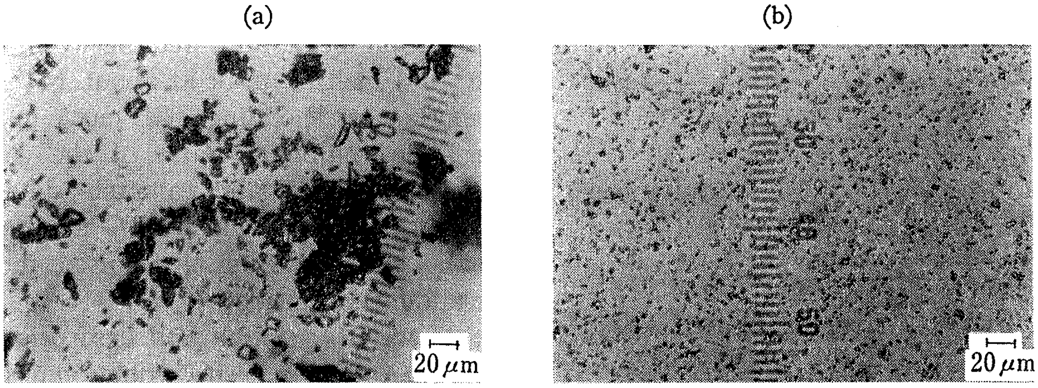


Fig. 13. Microscopic Photographs of Metharbital taken after Pulverizing in a Mortar with 50 Strokes

(a) Commercial metharbital, ×200.
(b) Size reduced particles *via* ammonia interaction, ×200.

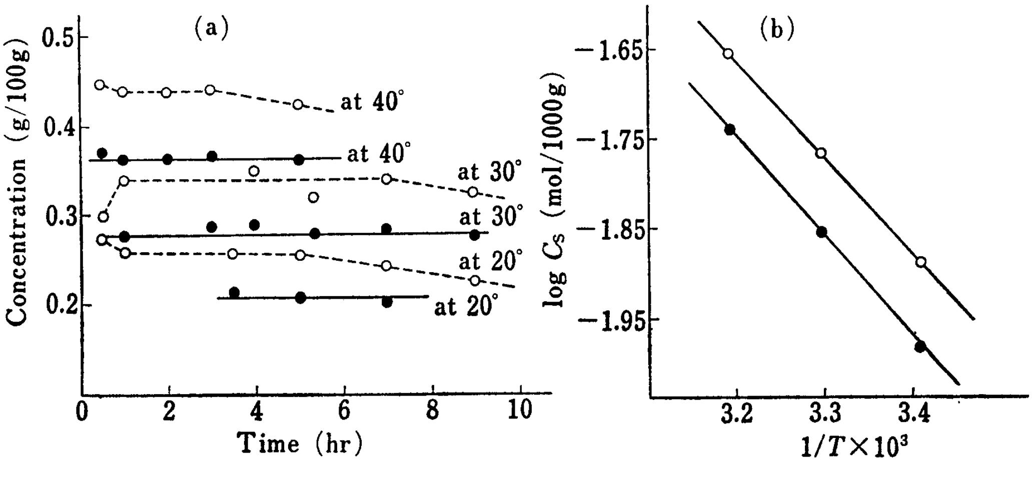


Fig. 14. (a) Dissolution Curves for Commercial Products and Size Reduced Particles *via* Ammonia Interaction of Metharbital, in Water at 20°, 30°, and 40°

---○---: size reduced particles, —●—: commercial product.

(b) The van't Hoff Plots of Solubility Values for Commercial Products and Size Reduced Particles of Metharbital

○: size reduced particles, ●: commercial product.

Moreover, the effect of particle size on solubility was investigated for both the powder obtained after treatment with ammonia and that of commercial product, as is depicted in Fig. 14 (a) and (b). The van't Hoff plots of these samples give two almost parallel lines. Since it is reported that metharbital exists in no more than one polymorphic form,[6,7] the higher solubility value at each temperature will be attributable to the smaller size of the reduced particles *via* ammonia interaction. Also, the parallelism of the lines will be explained by the fact there exists no transition temperature.

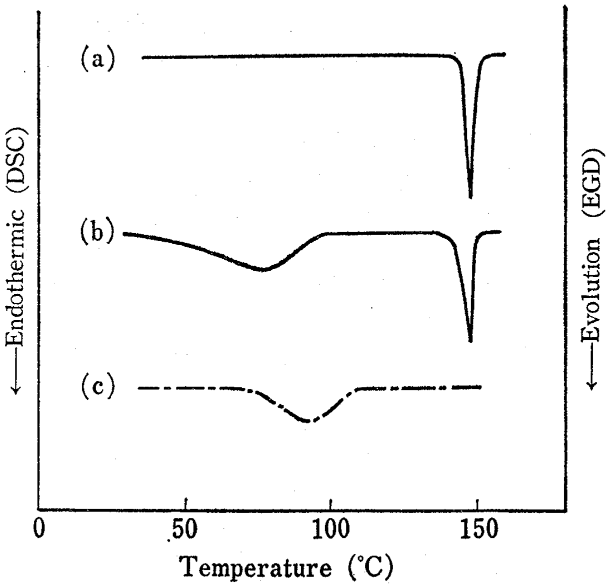


Fig. 15. Thermograms of Hexobarbital and Its Ammonia Interacted Compound

(a) DSC curve of commercial hexobarbital under semiclosed conditions: sample weight, 11.96 mg; heating rate, 16°/min.
(b) and (c) Simultaneous DSC and EGD curves of the hexobarbital ammonia interacted comp. under semiclosed conditions: sample weight, 12.43 mg; heating rate, 16°/min.

It is certain from these results that the adduct is formed between metharbital and ammonia, but the combining force is very weak as compared with one between other barbiturates and ammonia.

10. Interaction of Ammonia with Hexobarbital——Thermograms of hexobarbital and its ammonia interacted compound are shown in Fig. 15. On the DSC curve (b) ammonia elimination peak appeared between 30° and 100° and melting peak at about 147°, judging from the corresponding EGD curve (c). However, the combining ratio of the compound was differed from batch to batch and could not be determined precisely by TG measurements. Further investigation is required to confirm the adduct formation.

However, sorption and desorption of ammonia affect particle size reduction of hexobarbital, as shown in Table II.

Particle Size Reduction of Barbiturates by Ammonia Desorption from Their Ammonia Adducts

The effect of ammonia desorption conditions on the particle size of recovered barbiturates was investigated by BET measurements. These data are listed in Table II, together with reference data obtained from similar measurements of commercial products and sodium free forms. It is obvious from these data and also from particle size distribution data that the method of particle size reduction described in this paper is effective for all barbiturates investigated except for pentobarbital. Although barbiturate crystals, in general, are friable and easily pulverized mechanically, pentobarbital seems to have such a tendency strongly.

From the two cases shown in Table II (allobarbital and barbital), it is suggested that the particle size of barbiturate powders obtained by rapid desorption of ammonia from their ammonia adducts under reduced pressure and/or heat application is a little smaller than for powders obtained by desorption of ammonia from ammonia adducts under atmospheric pressure and room temperature.

Although the formation of hexobarbital-ammonia adduct was not detected completely, the particle size of hexobarbital crystals obtained from its ammonia solution was never-the-less effectively reduced, as is seen from the specific surface area data in Table II. This fact may indicate the formation of an ammonia adduct. Similarly, ammonia adduct formation of metharbital was not detected by DSC, TG, X-ray, and IR, but is suggested by particle size reduction.

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6) M. Brandstätter-Kuhnert and M. Aepkers, *Mikrochim. Acta*, **1962**, 1055.

7) R.J. Mesley, *Spectrochim. Acta*, **26A**, 1427 (1970).

TABLE II. Results of Particle Size Reduction of Barbiturates by Ammonia Desorption from Their Ammonia Adducts or Interacted Products under Several Conditions

Barbiturate	Source	Ammonia desorption conditions			No. of pulverizing strokes before BET	Specific surface area (m^2/g)
		Temp. (°C)	Time (hr)	Pressure (mmHg)		
Allobarbital	NH$_3$ adduct 1:2a)	room temp.		Atmospheric	300	2.7
	NH$_3$ adduct 1:2	50	1	1—3	300	3.5
	Commercial				300	0.8
Amobarbital	NH$_3$ adduct 1:2	75	1		130	2.6
	Commercial				130	1.4
Barbital	NH$_3$ adduct 1:1	room temp.		Atmospheric	200	2.3
	NH$_3$ adduct 1:1	50	1	1—3	200	2.6
	Commercial				200	1.2
Cyclobarbital	NH$_3$ adduct 1:1	80	3	1—3	300	2.2
	Commercial				300	1.8
Pentobarbital	NH$_3$ adduct 1:1	80	2b)	Atmospheric	200	2.1
	Na free form				200	2.1
Propallylonal	NH$_3$ adduct 1:2	120—130	2.5	1—3	200	6.7
	Commercial				200	4.4
Secobarbital	NH$_3$ adduct 1:1	room temp.	15	1—3	200	3.7
	Na free form				200	1.6
Metharbital	NH$_3$ interacted	room temp.		Atmospheric	200	1.6
	Commercial				200	0.6
Hexobarbital	NH$_3$ interacted	room temp.	15	1—3	200	2.1
	Commercial				200	0.9

a) Mole ratio of barbiturate to ammonia in ammonia adduct.
b) Ammonia was not completely removed at 60° and 75°.

Effect of Particle Size on Heat of Fusion

Heat of fusion was calculated both for commercial products of barbital, amobarbital, allobarbital, metharbital, and sodium free pentobarbital prepared from sodium pentobarbital and for ammonia free barbiturates recovered either *via* their ammonia adducts. The obtained values are listed in Table III together with the data of the specific surface area for the corresponding barbiturates quoted from Table II. It is obvious from the Table III, the smaller particles, *i.e.*, larger specific surface areas give somewhat smaller values of heat of fusion.

TABLE III. Effect of Particle Size on Heat of Fusion

	Heat of fusion,a) kcal/mol		Specific surface area, m^2/g	
	Commercialb)	*via* NH$_3$ adductc)	Commercialb)	*via* NH$_3$ adductc)
Allobarbital	7.58±0.05	7.25±0.12	0.8	3.5
Amobarbital	6.92±0.62	6.70±0.55	1.4	2.6
Barbital	6.74±0.08	6.37±0.86	1.2	2.6
Pentobarbital	5.14±0.09	5.16±0.05	2.1	2.1
Metharbital	7.19±0.10	6.91±0.09	0.6	1.6

a) Arithmetic mean of 2 to 6 samples.
b) Including sodium free form.
c) Including ammonia interacted comp.

Conclusion

1) It was confirmed that many kinds of barbiturates form one or two kinds of ammonia adducts. The barbiturates which were confirmed to form ammonia adducts easily have

pyrimidinetrione structures without any substitution of either of the two >NH groups in the pyrimidine ring.

2) Among barbiturates investigated, 1:2 adducts were formed between allobarbital, amobarbital, and propallylonal and ammonia. In addition, two kinds of 1:1 adducts having different thermal behaviors were confirmed with propallylonal. Although substituted barbiturates belong to monobasic acids, the above findings will suggest that at least one of the two ammonia molecules in the 1:2 adducts and the ammonia molecule in one of the two 1:1 adducts of propallylonal are combined by some secondary bonding force.

However, this supposition does not mean that neither the second ammonia molecule in the 1:2 adducts nor the ammonia molecule in another one of the 1:1 adducts of propallylonal are likely to be formed by an ionic bond of ammonium salt. On the contrary, it is supposed from the following reasons that secondary forces, such as dipole-induced dipole and dipole-dipole interactions and hydrogen bond will be involved in all of the bondings between ammonia and substituted barbiturates.

a. Substituted barbiturates are much weaker acids than barbituric acid that forms an ammonium salt.

b. Ammonia adducts of substituted barbiturates are all unstable and release ammonia easily.

c. Two patterns of IR spectra were obtained with adducts of substituted barbiturates; however, none of them shows evidence for salt formation observed in the spectrum of the ammonium salt of barbituric acid.

3) Particle size of barbiturates was effectively reduced by formation of ammonia adducts and subsequent desorption of ammonia. Small particle size distribution was also obtained.

4) A rapid ammonia desorption process under reduced pressure and increased temperature might have a positive effect on particle size reduction.

5) Solubilities at 20°, 30°, and 40° of the metharbital powder obtained by interaction with ammonia were greater than those of commercial metharbital powder and the lines drawn through the van't Hoff plots of these solubility data became almost parallel. These facts will suggest that the solubility increase is attributable to size reduction and ammonia adduct formation of metharbital is highly possible.

6) Heat of fusion for barbiturates recovered *via* ammonia adducts was found smaller than for commercial products.

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