CHEMISTRY LETTERS, pp. 1755-1758, 1988.

Application of Host-Guest Complexation Method to Isolation of Natural Product

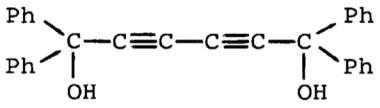
Mari SEGAWA, Koji MORI, and Fumio TODA*

Department of Industrial Chemistry, Faculty of Engineering,

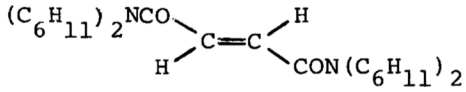
Ehime University, Matsuyama 790

Application of host-guest complexation method to isolation of caffeine, nicotine, and cholesterol from tea and tabaco leaves, and gallstone, respectively, has been reported. Separations of strychnine and brucine, and sparteine and brucine by the same method were also reported.

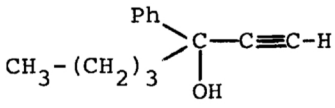
Development of new isolation method of compound in pure state is still an important subject in Chemistry. Especially, Natural Organic Chemists are searching good isolation method of labile natural product of low content. We report application of host-guest complexation method with simple host compounds to isolation of caffeine, nicotine, and cholesterol from tea and tabaco leaves, and gallstone, respectively. Separations of two alkaloids, strychnine and brucine, and sparteine and brucine by the same method were also reported.



1

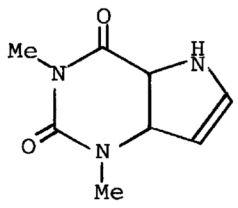


2

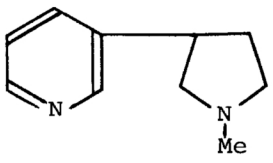


3

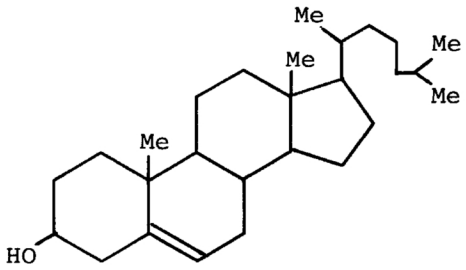
Caffeine was isolated from tea leaves by complexation with 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (1).[1] A mixture of green tea leaves (5 g) of the name of Uji tea and MeOH (40 ml) was heated under reflux for 8 h. Mixture was filtered and the MeOH solution was concentrated to 10 ml. To the MeOH solution, 1 (0.5 g) was dissolved by heating, and the solution was kept at room temperature for 5 h to give a 1:2 complex of 1 and caffeine (150 mg) as colorless crystals, mp 168-170 °C. Recrystallization of the complex from acetone gave a 1:2 complex[1,2] of 1 and



4



5



6

acetone as colorless crystals in almost quantitative yield. The acetone solution left after filtration of the complex was evaporated to give pure caffeine (4) (59 mg, corresponding to 81% of the caffeine contained in the Uji tea leaves treated). This method is much more simple in comparison to usual one. For example, Gattermann's extraction method of caffeine[3] consists of more than seven experimental procedures and takes a long time.

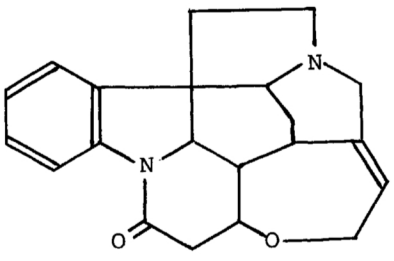
Nicotine was isolated from tabacco leaves by complexation with 1. A mixture of tabacco leaves (7 g) of Japanese cigarette of the name of Peace and 5% aqueous NaOH solution (210 ml) was stirred at room temperature for 15 min. The mixture was filtered, and the filtrate was extracted with ether (150 ml). The residue obtained by evaporation of ether and 1 (300 mg) was dissolved in MeOH (20 ml) and the solution was kept at room temperature for 5 h to give a 1:1 complex of 1 and nicotine (135 mg) as colorless crystals, mp 112-115 °C. When this complex was dissolved in acetone (15 ml), a 1:2 complex of 1 and acetone was formed. The acetone solution left after filtration of the complex was evaporated to give pure nicotine (5) (35 mg, corresponding to 86% of the nicotine contained in the tabacco leaves treated). Although the extraction method of 5 from tabacco leaves by picrate formation with picric acid is known, this can only be applied to the natural product of π-basic nature.[4] Contrarily, a wide variety of organic compounds forms complex with 1.[1,2]

Cholesterol was isolated from gallstone by complexation with N,N,N',N'-tetracyclohexylfumaramide (2).[5] Powdered gallstone (0.63 g) was treated with hot dioxane (3.5 ml) according to the reported procedure[6] to give crude cholesterol (0.4 g) as colorless crystals, mp 145-147 °C. When a solution of this crude cholesterol (0.4 g) and 2 (0.47 g) in acetone (5 ml) was kept at room temperature for 5 h, a 1:2 complex of 2 and cholesterol (0.34 g) was obtained as colorless crystals. Recrystallization of this complex from MeOH gave a 1:3 complex of 2 and MeOH as

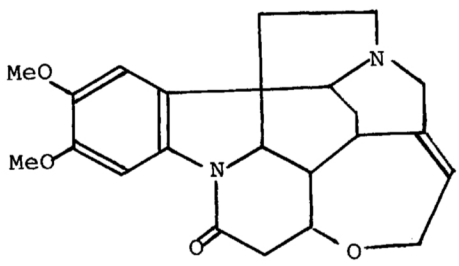
colorless crystals. Evaporation of the MeOH solution left after filtration of the complex gave pure cholesterol (6) (0.13 g), mp 149-150 °C. Purity of 6 obtained was determined to be higher than commercially available cholesterol of 99.4% purity by the reported coloring test with H_2SO_4-AcOH.[6] This purification method of crude cholesterol is very simple and effective in comparison to the reported one which consists of more than fifteen complicated procedures.[6]

Strychinine and brucine were separated from their mixture by complexation with 1. To a solution of strychinine (7) (1 g) and brucine (8) (1 g) in EtOH (35 ml), was dissolved 1 (1 g) by heating. The solution was kept at room temperature for 5 h to give a 1:2 complex of 1 and 7 (1.56 g, 96%) as colorless crystals, mp 152-154 °C. Recrystallization of the complex from acetone gave a 1:2 complex of 1 and acetone as colorless crystals. Evaporation of the acetone solution left after filtration of the acetone complex of 1 gave pure 7 (0.62 g, 62%) as colorless crystals, mp 285-290 °C. The EtOH solution left after filtration of a 1:2 complex of 1 and 7 was evaporated, and the residue was dissolved in acetone to give a 1:2 complex of 1 and acetone. The acetone solution left after filtration of the acetone complex was evaporated to give pure 8 (0.9 g, 90%) as colorless crystals, mp 178 °C.

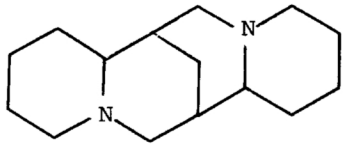
Separation of brucine and sparteine by complexation with 3-phenylhepta-1-yn-3-ol (3)[7] was carried out according to the following procedure. To a solution of 8 (1.25 g) and sparteine (9) (0.74 g) in acetone (10 ml) was dissolved 3 (0.6 g) by warming. The solution was kept at room temperature for 5 h to give a 1:1 complex of 3 and 8 (1.58 g, 85%) as colorless crystals, mp 135-138 °C. A solution of this complex (1.58 g) in benzene (30 ml) was treated with dil HCl. Basification of the HCl solution gave 8 (1.05 g, 84%) as colorless crystals, mp 178 °C. From the benzene solution, 3 (0.48 g, 80%) was recovered. Evaporation of the acetone solution left after filtration of a 1:1 complex of 8 and 3 gave pure 9 (0.7 g, 95%) as colorless oil.



7



8



9

Since host-guest complexation occurs under mild neutral conditions, the isolation of natural products by this method has many advantages, especially for labile compounds. Formation of crystalline host-guest complex from oily guest compound is also useful for an isolation of oily natural product of low content. Furthermore, since host-guest complexes described above are formed by relatively weak interactions of both the components such as hydrogen bond and van der Waals interaction, decomposition of the complex to the components can easily be done under mild conditions. This is also an advantage in isolation of labile natural products.

Sometimes, labile compounds are stabilized by forming a host-guest complex. This phenomenum is useful not only for isolation and storage but also for structural study of the labile compound in the state of complex.

References

1) F. Toda and K. Akagi, *Tetrahedron Lett.*, 1968, 3698.

2) F. Toda, *Top. Curr. Chem.*, 140, 43 (1987).

3) L. Gattermann, "Die Praxis des organischen Chemikers," fortgeführt von H. Wieland, Walter de Gruyter & Co., Berlin (1962), p. 354.

4) M. L. Swain, A. Eisner, C. F. Woodward, and B. A. Brice, *J. Am. Chem. Soc.*, 71, 1341 (1949).

5) F. Toda, Y. Tagami, and T. C. W. Mak, *Chem. Lett.*, 1986, 1909.

6) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Company, Boston (1957), p. 68.

7) F. Toda, K. Tanaka, H. Ueda, and T. Ōshima, *Israel J. Chem.*, 25, 338 (1985).

(Received July 6, 1988)