350. Tatsuo Moroe, Terumi Matsushima, and Osamu Miyamoto :
 Synthesis of 3,4-Benzotropolone*.

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Among many tropoloid compounds, benzotropolone which possesses both tropoloid and benzenoid ring systems in its molecule, is an interesting one, in view of its biological and physiological properties as tropolone and colchicine. As somewhat large quantities of benzotropolone were needed in order to obtain benzotropolone derivatives which have biologically active groups, such as the amino, methoxyl, and acetyl amino, the authors tried to find a convenient method for its synthesis.

There are two processes^{1,2)} for the synthesis of this compound. Cook's process is a very convenient method but the yield of benzotropolone is unsatisfactory. The other process by Tarbell has some difficulties in preparing *o*-phthaldehyde.

The authors were able to obtain 3,4-benzotropolone and its new derivative, monobromobenzotropolone, in a good yield through improving the Cook's method by the following scheme. The present paper describes this synthesis.

The starting material, phenylvaleric acid, was prepared by the condensation of cinnamic aldehyde and malonic acid, followed by catalytic hydrogenation and decarboxylation.

Benzosuberone, a seven-membered cyclic ketone, was prepared in 67% yield through self cyclization of phenylvaleryl chloride, in the presence of aluminum chloride, in benzene as a solvent. This procedure involves an improvement of the method which was described by Kipping and Hunter³⁾ who obtained this compound in 27~50% yield by using carbon disulfide or petroleum ether as a solvent. Although Plattner⁴⁾ was later able to raise the yield of this compound (87% of theory) by using a high dilution method, it is inconvenient to apply such method which he used to a large scale. When carbon disulfide or petroleum ether was used as a solvent, the reaction product of phenylvaleryl chloride and aluminum chloride forms a precipitate, and therefore, the reaction proceeds in an undesirable direction. However, when benzene is used as a solvent, the reaction proceeds homogeneously because of the larger solubility of the addition compound of aluminum chloride and phenylvaleryl chloride in benzene.

Benzosuberone was oxidised to benzosuberandione with selenous oxide in methanolic

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1) J. W. Cook, A. R. Sommerville: *Nature*, **163**, 410 (1950).

2) D. S. Tarbell, G. P. Scott, A.D.Kemp: *J. Am. Chem. Soc.* **72**, 379 (1950).

3) Kipping, Hunter: *J. Chem. Soc.* **76**, 605.

4) Plattner: *Helv. Chim. Acta*, **27**, 804 (1944).

solution in a sufficient yield. Benzosuberandione was transformed into the bromide by treating with bromosuccinimide in benzene solution. On the distillation of the dione, including some selenium from selenous oxide, the dione was partially dehydrogenated to benzotropolone.

Dehydrogenation of the bromide through heating under reduced pressure gave about an equal amount of benzotropolone and bromobenzotropolone. The yield of the former was about 27% against the dione. As benzotropolone was more soluble in petroleum ether than the bromine derivative, the isolation of both tropolones was effected by utilizing the difference of their solubilities. Our experiments showed that the direct dehydrogenation of the dione through Pd-charcoal method gave a smaller amount of benzotropolone than the Cook's¹⁾.

It was also found that bromobenzotropolone was almost the only product and benzotropolone was not produced if benzosuberandione was treated with one mole of bromine in glacial acetic acid, at a room temperature. The yield of bromobenzotropolone was 40% against the dione, and it was assumed that its bromine atom was in the *o*-position to the carbonyl group⁵⁾.

3,4-Benzotropolone was obtained as pale yellow needles, m.p. 85~86°, gave brown red coloration with ferric chloride, and dissolved in concentrated hydrochloric acid to a bright solution. Monobromobenzotropolone came in light brown needles, m.p. 148~150°, and gave the same dark red coloration as bromotropolone.

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Experimental

Phenylvaleric Acid—109 g. of cinnamylidene-malonic acid (prepared from cinnamic aldehyde and malonic acid by Perkins method, m.p. 206~208°) was hydrogenated in alkaline solution with Pd-charcoal as a catalyst, under atmospheric pressure. The crude cinnamalmalonic acid was converted into phenylvaleric acid through heating at 180~200° under a slightly reduced pressure until carbon dioxide no longer generated. The resulting crude phenylvaleric acid was purified by distillation from which 85 g. of pure phenylvaleric acid, m.p. 56~57°, was obtained. Yield, 95%.

Benzosuberone—Phenylvaleryl chloride (prepared from 20 g. of phenylvaleric acid and 16 g. of thionyl chloride) was added to the mixture of 300 cc. of benzene and 6 g. of finely powdered aluminum chloride, under vigorous stirring at a room temperature. The stirring was continued for 4 hours, and the reaction mixture was decomposed with water under cooling. After removing aluminum chloride solution, 12 g. of benzosuberone was obtained from benzene solution of the neutral portion. It boiled at 130~135°/13 mm. and its semicarbazone melted at 202°. Yield, about 67%.

Benzosuberandione—A solution of 9 g. of selenium dioxide dissolved in 20 cc. of absolute methanol was added to the solution of 12 g. of benzosuberone in 80 cc. of methanol at 60~70° during one hour, and the reaction mixture was refluxed for 6 hours. After the solvent was distilled off, the residue was distilled in vacuo as rapidly as possible, and 8 g. of crude oily benzosuberandione, which boiled at 110~115°/10 mm., was obtained. The crude product was redistilled under reduced pressure and 6.5 g. of pure benzosuberandione, b.p.₁₀ 140~145°, was obtained. Yield, 66% (Crude dione, 81%).

One g. of unreacted benzosuberone was recovered and 0.5 g. of benzotropolone was obtained from the last distillation residue by sublimation.

Benzotropolone—A mixture of 14 g. of *N*-bromosuccinimide, 10 g. of benzosuberandione, and 100 cc. of dried benzene, was stirred for three hours at a room temperature with irradiation of sunlight. As the reaction proceeded, succinimide began to deposit. The precipitate was removed through filtration and the solvent was driven off. The residue was heated at 100° for three hours and extracted with 30 cc. of hot petroleum ether. The ether solution was allowed to vaporize, and 3.5 g. of crude benzotropolone was obtained. The crude product was purified through sublimation in vacuo and 2.7 g. of pure benzotropolone was obtained. It melted at 85~86°. Yield, about 27%.

On extraction with petroleum ether, the portion insoluble in petroleum ether was extracted with 20 cc. of ethanol. After removing ethanol, 2.8 g. of brown colored crystals remained which

5) Nozoe, et al.: Proc. Japan Acad. 27, 107 (1951).

gave dark red color reaction with ferric chloride. This product was recrystallized from aqueous ethanol to 2.3 g. of monobromobenzotropolone, brown needles, m.p. 149~150°. *Anal.* Calcd. for $C_{11}H_7O_2Br$: C, 52.50; H, 2.78. Found: C, 52.45; H, 3.14.

Bromination of benzosuberandione with bromine in glacial acetic acid—A mixture of 3 g. of benzosuberandione, 3 g. of bromine, and 30 cc. of glacial acetic acid was stood for 24 hours at 10~15°. A white precipitate deposited and this was recrystallized from aqueous ethanol (50%) to 1.6 g. of bromobenzotropolone, m.p. 148~150°. The mixed fusion with above monobenzotropolone showed no depression of the melting point.

Summary

In order to discover an advantageous method of preparing 3,4-benzotropolone, the Cook's synthetic procedure was reexamined. This compound was obtained in a good yield from cinnamic aldehyde, via phenylvaleric acid. At the same time, monobromobenzotropolone was obtained. (Received June 9, 1952)

351. Kenjiro Kimura*, Reinosuke Hara**, and Noboru Iijima***: Studies on the Metabolism of some Inorganic Elements in Secondary Hemorrhagic Shock. I. Critical Examination of the Analytical Method of Iron, Copper, Zinc, Cobalt, Nickel, Manganese, and Magnesium in Tissues.

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In the field of clinical medicine, systematic studies of the clinical state called "shock" have been one of the interesting subjects, both from the basic and the clinical points of view. Although various works have been made to find a clue to clarifying the state of shock, the metabolism of inorganic elements has received little attention to the present. Systematic studies on the mineral metabolism in secondary hemorrhagic shock are described in the present series of works.

The main part of these works lies in the metabolism of iron, as well as dealing with the effect of copper, zinc, cobalt, nickel, manganese, and magnesium, which may be closely related with the iron metabolism. The methods of analysis of these elements are examined in the present report, prior to the commencement of these studies. Owing to their minute content and the co-existence with large amounts of iron and phosphate, the precise determination of these elements in tissue is one of the most difficult problems. Also, attention must be called to the fact that, in microdetermination, the results obtained are partly effected by errors due to a delicate change in experimental conditions. The series of works need relative values in each case, and therefore, the reproducibility in analysis must be the main point of examinations.

Experimental

Preparation of samples.

Serum—After taking blood in a centrifuge tube, it is allowed to stand in an ice box overnight. Supernatant serum is taken with strict care so as to minimize hemolysis.

Organ—A small piece of each organ is surgically removed before, during, and after completion of each experiment. Excess blood is removed by washing in physiological saline solution, and

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