Synthesis of 2-Phenyltropone and its Bromo-derivatives from 2-Phenylsuberone[1]

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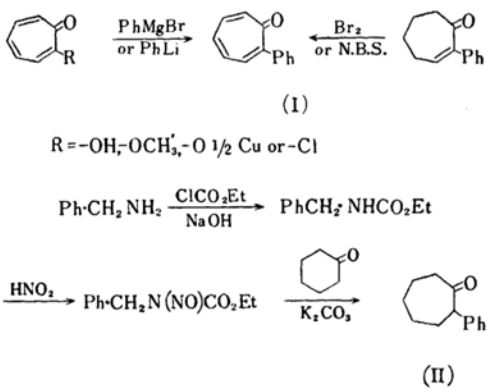
Nozoe, Mukai and their collaborators[2,3] have already reported that 2-phenyltropone (I) is obtained by the reaction of tropolone methyl ether and phenylmagnesium bromide in a good yield. Doering and others[4,5] have also obtained I by the treatment of tropolone and its derivatives with phenylmagnesium bromide or phenyllithium. On the other hand, it is well known that[6-9] various troponoid compounds are derived from cycloheptanons by their direct bromination-dehydrobromination. Nozoe and Ito[10,11] have obtained bromo-derivatives of I by the reaction of bromine and 2-phenylcyclohept-2-enone derived from cycloheptanone. Ginsburg and others[12] have also obtained I by the application of *N*-bromosuccinimide to 2-phenylcycloheptenone.

The present author has examined the reaction of 2-phenylsuberone (II) and bromine, and obtained I and its bromo-derivatives in a good yield. This paper describes these results.

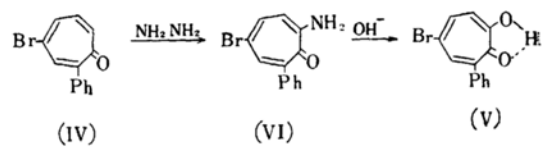
2-Phenylsuberone (II) was prepared by the treatment of cyclohexanone with phenyldiazomethane derived from benzylamine according to Gutsche's method[13].



Scheme 1

When three molar equivalents of bromine were added dropwise into a solution of II dissolved in glacial acetic acid, the reaction of bromine proceeded smoothly with the liberation of hydrogen bromide, and yellow needles (III), decomp. p. 185~187°C, were yielded. By the treatment with water, III was decomposed to give yellow needles (IV) m. p. 91~92°C. The yield of IV is about 30% calculated from II. From the mother liquor, a small amount of I was obtained.

Previously, Nozoe and others[10] confirmed the structure of 4-bromo-2-phenyltropone (IV) by deriving from it 5-bromo-3-phenyltropolone (V) through 7-amino-4-bromo-2-phenyltropone (VI). The present author has also obtained V from IV by the same treatment, and the melting point and the ultraviolet spectrum of IV (Fig. 1) are also identical with those of 4-bromo-2-phenyltropone[10]. It is obvious, therefore, that III is a hydrogen bromide adduct of 4-bromo-2-phenyltropone.



Scheme 2

In some cases, especially, when the reaction was carried out at a lower temperature, a small amount of colorless needles (VII), m. p. 155~156°C and colorless needles (VIII), m. p. 128~129°C were obtained besides IV and I. Though the details of the structure of VII and VIII are not clarified yet, each of them has been proved to be a dibromo-derivative of II from their analytical value.

When four molar equivalents of bromine

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2) T. Nozoe, T. Mukai and J. Minegishi, *Proc. Japan Acad.*, **27**, 419 (1951).

3) T. Nozoe, T. Mukai, J. Minegishi and T. Fujisawa, Science Repts., *Tohoku Univ.*, I, 388 (1953).

4) W. von E. Doering and C. H. Hyskey, *J. Am. Chem. Soc.*, **74**, 5688 (1952).

5) W. von E. Doering and J. R. Mayer, ibid., **75**, 2387 (1953).

6) H. J. Dauben and H. J. Ringold, ibid., 73, 876 (1951).

7) T. Nozoe, Y. Kitahara, T. Ando and S. Masamune, *Proc. Japan Acad.*, **27**. 415 (1951).

8) T. Nozoe, Y. Kitahara, T. Ando, S. Masamune and H. Abe, *Science Repts. Tohoku Univ.*, I, 36, 166 (1952).

9) P. L. Pauson, *Chem. Revs.*, 55, 9, (1955).

10) T. Nozoe, S. Ito and K. Sonobe, *Science Repts, Tohoku Univ.*, I, 38, 141 (1954).

11) T. Nozoe, S. Ito and K. Sonobe, *Proc. Japan Acad.*, **29**, 101 (1953).

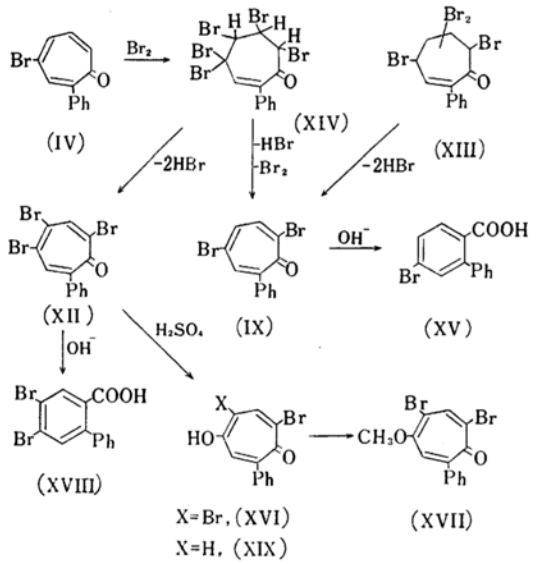
12) D. Elead and D. Ginsburg, *J. Chem. Soc.*, **1954**, 471.

13) D. Gutsche, "Organic Syntheses", 35, 91 (1955).

were applied to II, it was found that the yield of IV increased remarkablly to about 80%. In this case, moreover, yellow needles (IX), m. p. 117~118°C, and yellow acid crystals (X), decomp. p. ca 200°C, were obtained, though in a small amount.

The reaction of five molar equivalents of bromine and II was found to be somewhat complicated. In this case, prolonged heating and stirring were required to complete the reaction, and the yield of IX was increased to about 78%. From the neutral portion of the mother liquor, besides IX and IV, the following compounds were obtained: pale yellow plates (XI) m. p. 79~80°C pale yellow needles (XII) m. p. 112~113°C and colorless needles (XIII) m. p. 149~150°C. From the acidic portion, a fair amount of X was obtained.

Previously, Mukai[14] reported that a dibromo-derivative of I was obtained by the decomposition of 4, 4, 5, 6, 7-pentabromo-2-phenyl-2-cyclohepten-1-one (XIV) which was derived from IV, and that its structure was assumed to be 4, 7-dibromo-2-phenyltropone.



Scheme 3

The author also obtained IX by the bromination of IV as Mukai reported, and moreover found that, when IX was treated with dilute alkali, it easily rearranged itself to give 4-bromo-2-phenylbenzoic acid (XV)[15]. Therefore, IX seems to be 4, 7-dibromo-2-phenyltropone as Mukai assumed.

The crystal (XI) was proved to be identical with the authentic sample of 7-bromo-2-phenyltropone[12] by the mixed melting point.

The crystal (XII) was found to be a tribromo-derivative of I from its analytical value and U. V. spectrum, (Fig. 1) and it was also obtained from XIV by treating with pyridine. When XII was heated for a long period with 75% sulfuric acid, it gave 5, 7-dibromo-4-hydroxy-2-phenyltropone (XVI)[16], whose structure was confirmed by deriving from it 5, 7-dibromo-4-methoxy-2-phenyltropone (XVII)[16]. It was also found that, by heating with dilute alkali, XII was easily rearranged to give colorless needles of m. p. 180~181°C of 4, 5-dibromo-2-phenylbenzoic acid (XVIII). These facts, therefore, indicated that XII was 4, 5, 7-tribromo-2-phenyltropone.

The crystal (XIII) was a tetrabromo-derivative of 2-phenylsuberenone. When XIII was heated to effect dehydrobromination, it gave IX. It is, therefore, found that two of four bromine atoms of XIII, at least, are presented in the C-4 and C-7 position, and XIII is probably one of the intermediate products in the formation of IX from II.

Though the detailed studies on the acidic product (X) will be described in the near future, it will be noted here that X is a mixture of 7-bromo-4-hydroxy-2-phenyltropone-(XIX) and XVI, and that they are isolated from each other with difficulty.

Even when five molar equivalents of bromine were applied to II, the formation of X was very small, if the addition of bromine was carried out at 30~60°C and the duration of heating was shortened. In this case, the yield of IX was about 30% and that of XIII proved to be increased.

In order to prevent the formation of X completely, II was treated with five moles of bromine in a mixture of acetic acid and acetic anhydride but a considerable amount of X was still found in the acidic portion. In this case, IV was obtained mainly in about 30% yield but IX was in poor yield and, moreover, a trace of yellow needles (XX) m. p. 144~145°C was obtained. This compound XX was proved to be a monobromo-derivative of I from its analytical value and U. V. spectrum (Fig. 1) and gave by the further bromination a dibromo compound XXI as pale yellow needles m. p. 141~142°C.

As it is known that, on the bromination of tropone derivatives, the bromine atom enters at the carbon atoms adjacent to the carbonyl carbon (i. e., C-2 and C-7) preferentially[14,17], at least the one of bromine atoms of XXI was assumed to be in the C-7 position. It was proved, however, that XXI was identical

14) T. Mukai, *Science Repts. Tohoku Univ.*, I, **38**, 280 (1954).
15) I. M. Heilbron et al., *J. Chem. Soc.*, **1938**, 115.
16) T. Muroi, to be published.
17) T. Mukai, This Bulletin, **31**, 846 (1958).

with neither 3, 7-[18], 4, 7-, 5, 7-[14] and 6, 7-dibromo-derivative[14] of I. Therefore, the other bromine atom of XXI, i.e., that of XX is assumed not to be in the tropone nucleus but in the phenyl group.

In the above reactions, the yield of I was poor but, as it is known that IV is easily debrominated to give I, this reaction is considered to be a useful synthetic method for the preparation of I. As the mechanism of this reaction is not clarified yet this is considered to be an interesting question in future.

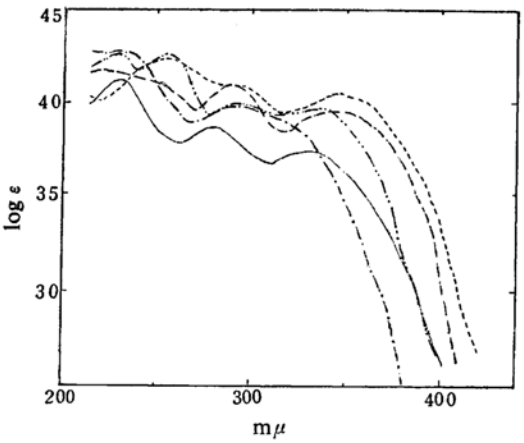


Fig. 1. U. V. Absorption spectra of IV, IX, XII, XX and XXI in methanol.
——— (IV) – – – (IX) ------ (XII)
–·–· (XX) –··–·· (XXI)

Experimental[19]

Action of Bromine on 2-Phenylsuberone (II).—II was prepared according to the description of "Organic Syntheses"[13], and the fraction of b. p. 110~111°C/0.3~0.4 mmHg; n_D^{27}: 1.5390, was used[20].

a) Application of 3 Molar Equivalents of Bromine.—i) To a solution of 4.7 g. of II in 7.5 cc. of acetic acid, a mixture of 12 g. of bromine and 2 cc. of acetic acid was added dropwise with stirring for a period of 1 hr. at 30~40°C. After the addition, the reaction mixture was heated on a water bath to about 80°C and kept at the same temperature for 30 min. and then yellow crystals were separated out. Additional heating and stirring were continued until there was no liberation of hydrogen bromide. After cooling, the crystals were collected by filtration and washed with a small amount of acetic acid and benzene, successively. Yellow crystals (III) decomp. p. 185~187°C, 3.7 g. were obtained. On standing overnight, the filtrate gave the second crop of III, 0.28 g. When III was treated with about 50 cc. of water, 2.3 g. of pale yellow crystals were obtained. Recrystallization from alcohol or methanol gave yellow needles (IV) m. p. 91~92°C.

Found: C, 60.06; H, 3.63. Calcd. for $C_{13}H_9OBr$: C, 59.74; H, 3.74%.

The mother liquor was evaporated under reduced pressure and the residue, treated with water, was extracted with chloroform. The extract was washed with 10% sodium carbonate solution. After the removal of the solvent, the residual oil, dissolved in a mixture of benzene and petroleum ether (1 : 1), was chromatographed through a silica-gel column. It was eluted successively with a mixture of benzene and petroleum ether, benzene, chloroform and alcohol. From the chloroform eluent, 0.2 g. of raw crystals of I was obtained but the other eluent gave no crystals.

Acidification of the sodium carbonate solution gave no crystalline products.

ii) As in the above case, 4.7 g. of II in 7.5 cc. of acetic acid was treated with 12 g. of bromine dissolved in 2 cc. of acetic acid. In this case, however, heating was stopped at ones when the separation of III occurred. After cooling, III was collected by filtration and treated with water to give 2.0 g. of IV. The filtrate, after standing for a few days, gave 0.22 g. of pale yellow crystals, m. p. 115~120°C. This was decomposed with water to give colorless crystals m. p. 175~180°C. Recrystallization from alcohol or benzene gave sparingly soluble colorless needles (VII) m. p. 155~156°C and comparatively soluble colorless needles (VIII) m. p. 128~129°C, respectively.

Found for VII: C, 45.41; H, 3.95. Calcd. for $C_{13}H_{14}OBr_2$: C, 45.12; H, 4.08%.

Found for VIII: C, 45.23; H, 3.97. Calcd. for $C_{13}H_{14}OBr_2$: C. 45.12; H, 4.08%.

After being treated as in i), the mother liquor gave 0.5 g. of I.

b) Application of 4 Molar Equivalents of Bromine.—To a solution of 4.7 g. of II in 7.5 cc. of acetic acid, 16 g. of bromine dissolved in 2.7 cc. of acetic acid was added dropwise during about 1.5 hr. at 30~60°C. In this case, when treated as in a), it gave three kinds of crystals from the neutral portion as follows: 5.2 g. of IV, 0.28 g. of IX and a small amount of I. Recrystallization of IX from alcohol gave yellow needles, m. p. 117~118°C.

Found: C, 45.68; 2.38. Calcd. for $C_{13}H_9OBr_2$: C, 45.93; H, 2.36%.

The acidic portion gave yellow crystals (X) decomp. p. 185~190°C, 0.02 g.

c) Application of 5 Molar Equivalents of Bromine.—i) To a solution of 4.7 g. of II in 7.5 cc. of acetic acid, 20 g. of bromine dissolved in 3.5 cc. of acetic acid was added dropwise over a period of 2.5 hr. at 30~65°C. After the addition, the mixture was heated on a water bath for 4 hr., until there was no liberation of hydrogen bromide. By chilling with ice no crystals were separated out, then the solvent was distilled off under reduced

18) T. Nozoe, T. Mukai and I. Murata, *Proc. Japan Acad.*, **28**, 142 (1952).

19) M. p. are uncorrected. The microanalyses and the measurement of U. V. spectra were carried out by Mrs. K. Kodaira of Tohoku University, to whom the author's deep gratitude is hereby expressed.

20) The fractional distillation of II was carried out at Kitahara's Laboratory in the Chemical Research Institute of Non-aqueous Solution, Tohoku University, using the Stedtmann type fractional column (40 plates). The author expresses hereby his deep gratitude to Professor Yoshio Kitahara for his kindness.

pressure. The residue, decomposed with water, was extracted with chloroform. After washing the extract with 10% sodium carbonate solution, the solvent was evaporated off. The residual oil (10 g.), digested with alcohol or ether, gave 0.9 g. of IX m. p. 113~115°C. After being treated as in a) i), the mother liquor was chromatographed through a silica-gel column. The benzene-petroleum ether eluent gave 1.0 g. of XIII, 0.8 g. of XII and 1.0 g. of IX, successively.

Recrystallization of XIII from alcohol gave colorless needles m. p. 149~150°C.

Found: C, 31.49; H, 2.13. Calcd. for $C_{13}H_{10}OBr_4$: C, 31.11; H, 2.00%.

Recrystallization of XII from alcohol gave pale yellow needles m. p. 113~114°C.

Found: C, 37.41; H, 1.19. Calcd. for $C_{13}H_7OBr_3$: C, 37.28; H, 1.99%.

The benzene eluent gave 0.6 g. of IX, 0.7 g. of IV and 0.1 g. of XI, successively. From the chloroform eluent, 0.1 g. of I was obtained, acompanied with a resinous substance. Alcohol eluent did not give any crystals.

In this case, the alkaline washing solution gave no crystals by acidification.

ii) To a solution of 4.7 g. of II in 7.5 cc. of acetic acid, 20 g. of bromine dissolved in 3.5 cc. of acetic acid was added. About 3/4 vols. of bromine solution was added at 40~75°C for a period of 1.5 hrs., then yellow crystals were separated out. These were dissolved again in a dark red solution when the rest of the bromine was added at 85°C. The mixture was further heated for 6 hr. until there was no liberation of hydrogen bromide. After cooling, the yellow crystals (a) thereby separated were collected by filtration. There were digested with benzene and an insoluble portion (b) was filtered off. The filtrate was shaken with 10% sodium carbonate solution and the aqueous layer was combined with (b). This alkaline solution, after being treated with active carbon, was acidified to give 0.27 g. of X, m. p. 200~205°C. The benzene layer, after removal of the solvent, left a crystalline residue which was recrystalized from alcohol or ether to give 4.5 g. of IX.

The mother liquor of (a), treated as in a, i), gave the following crystals: 1.0 g. of IX, 0.44 g. of X, 0.1 g. of XI, 0.2 g. of XII and 0.15 g. of XIII.

iii) To a solution of 4.7 g. of II in 7.5 cc. of acetic acid and 2.5 cc. of acetic anhydride, 20 g. of bromine dissolved in 3.5 cc. of acetic acid was added as in the above case. In this case, no crystals were separated during the reaction. On cooling, 5.3 g. of III was obtained and this was decomposed to 3.1 g. of IV. After being treated as in a, i), 0.2 g. of X was obtained from the 10% sodium carbonate soluble part of the mother liquor. The chromatographic separation of the neutral substance gave successively the following crystals: 0.35 g. of IX, 0.40 g. of IV, 0.15 g. of XX and 0.1 g. of I.

The recrystallization of XX from methanol gave yellow needless of m. p. 144~145°C.

Found: C, 60.29; H, 3.58. Calcd. for $C_{13}H_9OBr$: C, 59.79; H, 3.47%.

Action of Hydrazine on 4-Bromo-2-phenyltropone (IV). — A mixture of 0.2 g. of IV, 0.2 cc. of 80% hydrazine hydrate and 2 cc. of alcohol was refluxed on a water bath for 30 min., and the crystals that separated out were collected by filtration. Recrystallization from alcohol gave orange yellow needles of VI, m. p. 210°C.

A mixture of 0.08 g. of VI, 0.3 cc. of 6 N sodium hydroxide solution and 1.6 cc. of alcohol was refluxed for 3 hr. The alcohol was distilled off, the residue was acidified, and the precipitate thereby formed was recrystallized from methanol to give yellow needles of m. p. 135~136°C. This was found to be identical by mixed fusion with the authentic sample of 5-bromo-3-phenyltropolone (V)[10].

Bromination of 4-Bromo-2-phenyltropone (IV).— To a solution of 2.6 g. of IV in 40 cc. of acetic acid, 4.8 g. of bromine in 5 cc. of acetic acid was added and this mixture was allowed to stand over night. The crystals that separated out were collected and recrystallized from alcohol and benzene to give colorless prisms of XIV, m. p. 121~122°C (decomp.). Yield, 4.7 g.

Found: C, 27.26; H, 1.68. Calcd. for $C_{13}H_9OBr_5$: C, 26.89; H, 1.56%.

The filtrate was evaporated under reduced pressure and the residue, after being treated with water, was extracted with benzene. After removal of solvent, the extract left a crystalline residue which was recrystallized from alcohol to give yellow crystals of m. p. 110~113°C. This showed no depression of melting point on admixture with IX obtained in the above cases.

Decomposition of 4,4,5,6,7-Pentabromo-2-phenyl-2-cyclohepten-1-one (XIV). — i) By heating 0.15 g. of XIV in an oil bath at 120~130°C for 10 min., XIV melted with effervescence and underwent decomposition to an oil. After cooling, this was dissolved in benzene and washed with a diluted sodium hyposulfate solution. The benzene layer, after the removal of solvent, left a crystalline residue that was recrystallized from alcohol to give yellow crystals of m. p. 116~117°C, undepressed on admixture with IX. Yield, 0.05 g.

ii) A mixture of 0.58 g. of XIV, 0.6 cc. of pyridine and 0.3 g. of benzene was heated for 15 min. at 55~60°C. This was diluted with water and extracted with benzene. The extract after evaporation, left yellow crystals. Recrystallization from alcohol gave yellow needles of m. p. 112~113°C, undepressed on admixture with XII obtained above.

Action of Alkali on 4, 7-Dibromo-2-phenyltropone (IX).—A mixture of 0.06 g. of IX, 1.5 cc. of alcohol and 1 cc. of 2 N sodium hydroxide solution was refluxed on a water bath for 30 min. After the removal of solvent it was acidified and extracted with benzene. The benzene layer gave colorless crystals that were recrystallized from cyclohexane to give XV as colorless needles of m. p. 173~175°C.

Found: C, 56.75; H, 3.47. Calcd. for $C_{13}H_9OBr$: C, 56.34; H, 3.27%.

Action of Alkali on 4, 5, 7-Tribromo-2-phenyltropone (XII).—A mixture of 0.05 g. of XII, 0.7 cc. of alcohol and 0.5 cc. of 2 N sodium hydroxide was refluxed on a water bath for 15 min. This, treated as in the above case, gave colorless needles of XVIII, m. p. 180~181°C.

Found: C, 43.76; H, 2.15. Calcd. for $C_{13}H_8O_2Br_2$: C, 43.76; H, 2.26%.

Action of Sulfuric Acid on 4, 5, 7-Tribromo-2-phenyltropone(XII).—A solution of 0.25 g. of XII and 2.5 cc. of 75% sulfuric acid was heated for 10 hr. at 170~180°C. This was poured into about 20 cc. of ice water, and thereby precipitated crystals were collected. The crystals, after being dried, were washed with benzene and dissolved in 10% sodium carbonate solution. After being treated with active carbon, the solution was acidified and 0.1 g. of yellow crystals of d. p. ca 190°C were obtained. This was treated with a 2.8% diazomethane-ether solution and the thereby obtained oily product was dissolved in a mixture of benzene and petroleum ether. This was chromatographed on a silica-gel column and gave yellow crystals of m. p. 128~129°C. Recrystallization from methanol gave yellow needles of m. p. 131~132°C, which showed no depression with authentic sample of XVI.

Thermal Decomposition of 4, 7, *x*, *x*-Tetrabromo-2-phenylsuberenone(XIII). — By heating 0.12 g. of XIII on an oil bath for 20 min. at 150~160°C, it melted and underwent decomposition. The fused mass, dissolved in benzene, was washed sufficiently with water. The benzene solution was passed through a silica-gel column and yellow needles of m. p. 117~118°C were obtained. These showed no depression on admixture with IX obtained above.

Bromination of *x*-Bromo-2-phenyltropone(XX). —To a solution of 0.06 g. of XX in 1 cc. of acetic acid, 0.06 g. of bromine was added and the whole was heated on a water bath for 30 min. Then this was diluted with water and extracted with chloroform. After the removal of solvent, this gave colorless crystals of m. p. 135~140°C, which were recrystallized from benzene or alcohol to give pale yellow needles, m. p. 141~142°C.

Found: C, 45.94; H, 2.36. Calcd. for $C_{13}H_9OBr_2$: C, 45.93; H, 2.36%.

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