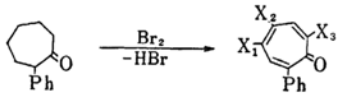
The Acid Product Obtained in the Synthesis of 2-Phenyltropone Derivatives from 2-Phenylsuberone[1]

By Tadashi MUROI*

(Received February 20, 1960)

Previously Nozoe, Kitahara and others[2] reported that in the direct bromination-dehydrobromonation of suberone, a considerable amount of an acid product was sometimes obtained besides the 2, 4, 7-tribromotropone, and thereafter confirmed the structure of this acid product to be 2, 4, 7-tribromo-5-hydroxytropone[3].

The present author also reported[4] previously that by the application of 4~5 molar equivalents of bromine on 2-phenylsuberone (I), 4-bromo-and 4, 7-dibromo-2-phenyltropone (II and III) were obtained in a good yield and that these products were occasionally accompanied by a considerable amount of an acid substance (A), assumed to be a mixture of bromo-derivatives of 4-hydroxy-2-phenyltropone (IV). This paper describes the details of A and the four methyl ethers derived from A.



(I) (II): X_1=Br, X_2=X_3=H
(III): X_1=X_3=Br, X_2=H
(IV): X_1=OH, X_2=X_3=H

Scheme I

The yield of A was found to increase remarkably, when somewhat impure I, or a solvent containing a trace of water was used, i. e. when fairly prolonged heating had to be applied in order to complete the reaction. Compound A separated as yellow needles or pale yellow scales of decomp. point ca. 200°C, and was sparingly soluble in chloroform, alcohol and acetic acid, and insoluble in benzene, ether and water. It gave no coloration with ferric chloride characteristic of tropolone or enol. It gave, however, a sparingly soluble yellow sodium salt when treated with sodium hydroxide or sodium carbonate solution. When treated with diazomethane, A afforded four kinds of methyl ethers; pale yellow needles (V), m. p. 173~174°C, yellow needles (VI), m. p. 131~132°C, yellow prisms (VII), m. p. 74~75°C, and pale yellow plates (VIII), m. p. 112~113°C. Their formation ratio was not constant but, in general, V and VI were always obtained in a better yield than VII or VIII and some times the yield of VII and VIII was so small that they can not be isolated.

Both V and VII had the molecular formula of $C_{14}H_{11}O_2Br$ and were obtained chiefly from the sparingly soluble portion of A in alcohol. On the other hand VI and VIII analyzed for $C_{14}H_{10}O_2Br_2$ and were obtained from the comparatively soluble portion of A.

Previously, Kitahara and others reported[5] that 2, 4, 7-tribromo-5-hydroxytropone (IXa) gave two kinds of methyl ethers and predicted from this fact that IXa existed as an equilibrium mixture of IXa and its tautomeric isomer, i. e. 2, 4, 6-tribromo-5-hydroxytropone (IXb).

(IXa) (IXb)

Scheme II

Acid hydrolysis of V gave yellow needles (X), $C_{13}H_9O_2Br$ m. p. ca. 210°C (decomp.), treatment of which with diazomethane afforded V and VII, with the former predominating. This fact indicates that X exists in a tautomeric mixture (Xa and Xb) and that V and VII are the respective methyl ethers of Xa and Xb.

When refluxed with sodium methoxide in absolute methanol, VII underwent aromatization, and the successive hydrolysis of its product yield pale yellow crystals (XI), m. p. 98~103°C. When treated with concentrated sulfuric acid, XI was converted to give yellow scales (XII), m. p. 93~94°C, which was proved to be 3-methoxyfluorenone[6] by mixed fusion with the authentic sample. It is, therefore, clear

* Present address, Hitachi Research Laboratory of Hitachi Ltd., Sukegawa-machi, Hitachi.

1) Presented at the 11th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 3, 1958.

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

3) T. Nozoe, Y. Kitahara and H. Abe, *Proc. Japan Acad.*, **29**, 347 (1953).

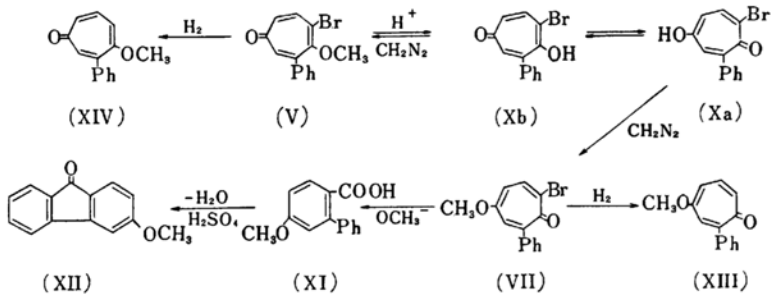
4) T. Muroi, This Bulletin, **33**, 1166 (1960).

5) Y. Kitahara, J. Shin and T. Toda, Presented at the Local Meeting of Tohoku District of the Chemical Society of Japan, Yamagata, Oct. 6, 1955.

6) F. Ullmann and H. Bleier, *Ber.*, **35**, 4272 (1902).

that XI is 4-methoxy-2-phenyl-benzoic acid and VII is 7-bromo-4-methoxy-2-phenyltropone, and X is a tautomeric mixture of 7-bromo-4-hydroxy-2-phenyltropone (Xa) and 5-bromo-4-hydroxy-3-phenyltropone (Xb).

Catalytic debromination of VII and V in the presence of palladium-carbon gave 4-methoxy-2-phenyltropone (XIII), m. p. 93~94°C, and 4-methoxy-3-phenyltropone (XIV), m. p. 75~76°C, respectively.



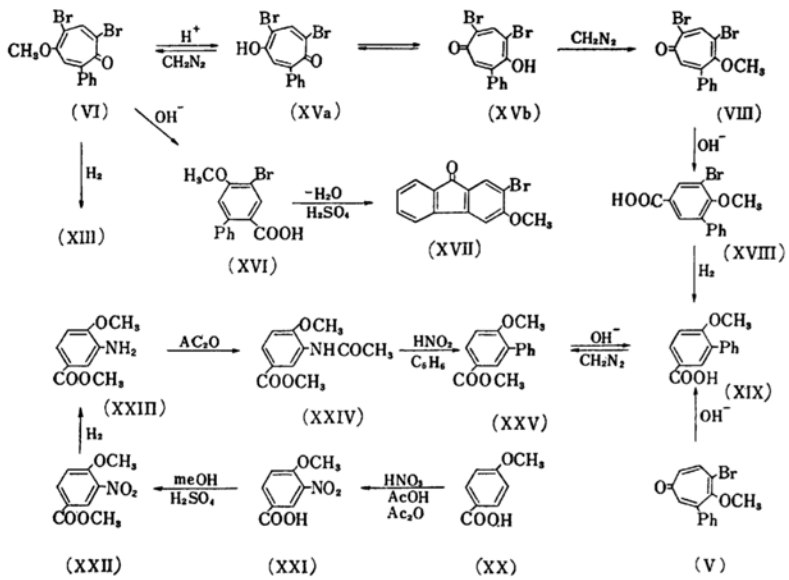
Scheme III

Acid hydrolysis of VI afforded pale yellow needles (XV), $C_{13}H_8O_2Br_2$ m. p. ca. 200°C (decomp.) which when treated with diazomethane, gave a mixture of VIII and VI. Catalytic debromination of VI gave XIII in a good yield. These facts indicate that XV also exists in a equilibrium mixture of two tautomeric forms (XVa and XVb) as in the case of IX and X, and moreover, that VI and VIII are respective methyl ethers of XVa and XVb.

When heated with alkali in alcohol, VI easily underwent aromatization to give colorless needles (XVI) m. p. 168~169°C, accompanied by a small amount of XV. When treated with concentrated sulfuric acid, XVI afforded yellow scales (XVII) m. p. 235~237°C, which was assumed to be monobromo-derivatives of XII. It follows therefore that one of the bromine atoms of VI occupies its C-7 position.

It was also found that VIII underwent aromatization very easily with alkali to give colorless needles (XVIII), m. p. 187~188°C, in a good yield. Catalytic debromination of XVIII gave colorless needles (XIX), m. p. 208~210°C. The structure of XIX is proved to be 4-methoxy-3-phenylbenzoic acid by the synthetic method shown in scheme IV.

These facts indicate, that VI and VIII are 5, 7-dibromo-4-methoxy-2-phenyltropone and 5, 7-dibromo-4-methoxy-3-phenyltropone, respectively, and XV is 5, 7-dibromo-4-hydroxy-2-phenyltropone as shown in the Scheme IV.



Scheme IV

From the fact mentioned above, the acid substance(A) is clarified to be a mixture of 7-bromo- and 5,7-dibromo-4-hydroxy-2-phenyltropone (Xa and XVa) and their respective tautomeric isomers. As the reaction of bromine on I is fairly complicated as reported previously[4], the mechanism of the formation of A can not be discussed at this stage. It is, however, assumed that A is derived through II or III by their hydroxylation or successive bromination during the reaction.

When treated with alkali, V was easily converted to give XIX in a good yield with the elimination of bromine at the C-5 position. Similar reaction was reported previously[7] by the present author, and this reaction is considered to be very interesting from the viewpoint that, in the rearrangement reaction of troponoid compound, the elimination of the substituents other than in C-2 (i. e. C-7) position has not been observed so far[8].

The synthesis and some reactions of IV and its bromoderivatives will be reported in the next paper.

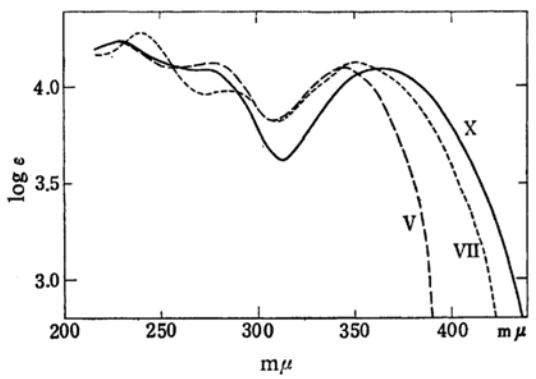


Fig. 1. Ultraviolet absorption spectra of V, VII and X in methanol.

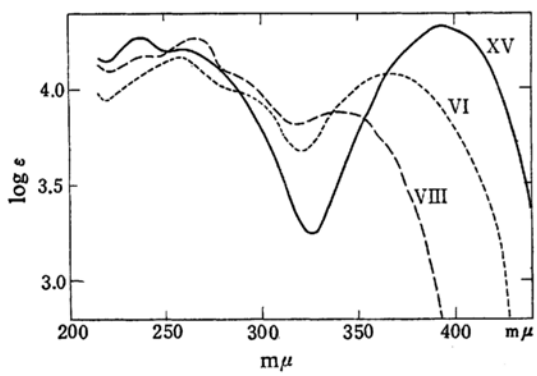


Fig. 2. Ultraviolet spectra of VI, VIII and XV in methanol.

7) T. Muroi, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 303 (1959).

Experimentals[9]

Formation of Acid Substance (A) from 2-Phenylsuberone(I).—i) To a mixture of 4.7 g. of I, (b. p. 110~111°C/0.3~0.4 mmHg, n_D^{25}: 1.5390) 7.5 cc. of acetic acid and 1 cc. of water, a solution of 20 g. of bromine dissolved in 3.5 cc. of acetic acid was added dropwise over a period of 2 hr. at 50~80°C. The whole was heated on a water bath for about 3 hr. until there were no liberations of hydrogen bromide, cooled, and diluted with about 200 cc. of methanol, and yellow crystals (a) thereby separated were collected by filtration. Yield, ca. 4.3 g., m. p. 110~130°C. Crystalline residue, obtained after the evaporation of the solvent under reduced pressure, was digested with water and chloroform to give 0.25 g. of yellow crystals (b), m. p. 200°C (decomp.). The chloroform solution was shaken with 10% sodium carbonate solution and the aqueous layer was acidified with hydrochloric acid to give pale yellow crystals (c), m. p. 195°C (decomp.). Yield, 0.25 g.

The crystals (a) were digested with benzene and the insoluble portion (d), m. p. 195°C (decomp.) was collected by filtration. Yield, 0.85 g. The crystals (b), (c), and (d) were combined and dissolved in sodium carbonate solution. After treated with active carbon, the solution was acidified again and an acid product (A) was obtained as pale yellow crystals, m. p. 195~200°C (decomp.). Yield, 1.3 g.

The benzene soluble parts of (a) gave 2.8 g. of III. Similarly, chromatographic separation of the chloroform solution (aforementioned)[4] through a silica-gel column gave small amounts of III, II and 7-bromo-2-phenyltropone.

ii) To a solution of 4.7 g. of impure I (b. p. 140~149°C/2~3 mmHg, n_D^{20}: 1.5339) dissolved in 7.5 cc. of acetic acid, a solution of 16 g. of bromine in 3 cc. of acetic acid was added dropwise at 50~80°C. The whole was heated on a water bath for about 20 hr. till the liberation of hydrogen bromide was ceased. The solvent was evaporated under reduced pressure and the residue was washed with chloroform and water by which 1.8 g. of yellow crystals (a), m. p. 150~180°C (decomp.) were obtained. After the treatment of the chloroform solution with 10% sodium carbonate solution as in the above case, 0.2 g. of pale yellow crystals (b), m. p. ca. 175°C (decomp.) were obtained. The combined crystals (a) and (b) were repeatedly recrystallized from ethanol. Yellow needles (A_1) m. p. 207~210°C (decomp.) and pale yellow scales (A_2) m. p. 195~198°C (decomp.) were obtained from the sparingly soluble portion and comparatively easily soluble portion in alcohol, respectively.

Further recrystallization did not give pure substances and the analytical values of A_1 and A_2 were as below:

8) a) S. Seto, *Sci. Repts. Tohoku Univ., Ser.* I., **37**, 377 (1953). b) Y. Kitahara, ibid., **38**, 280 (1954). b) T. Mukai, ibid., **39**, 250 (1956). d) P. L. Pauson, *Chem. Revs*, **55**, 9 (1955).

9) Melting points are uncorrected. The micro analyses and the measurement of U. V. spectra were carried out by Mrs. K. Kodaira of Tohoku University, to whom deep gratitude is hereby expressed.

A_1: Found: C, 51.08; H, 2.88. Calcd. for $C_{13}H_9O_2Br$: C, 56.35; H, 3.27%.

A_2: Found: C, 44.11; H, 2.33. Calcd. for $C_{13}H_8O_2Br_2$: C, 45.15; H, 2.33%.

The neutral portion, when treated as in i), gave a small amount of the bromo derivatives of 2-phenyltropone whose structures were confirmed by mixed fusion with their authentic samples, respectively.

Methylation of A.—i) To a suspension of 1.15 g. of A, m. p. 185~190°C (decomp.) in 10 cc. of ether, ethereal diazomethane was added and the whole was kept standing overnight in a refrigerator. The crystals, m. p. 110~115°C, thereby separated, were collected by filtration and recrystallized from benzene or methanol to give 0.5 g. of VI as yellow needles m. p. 131~132°C.

Found: C, 46.00; H, 2.84. Calcd. for $C_{14}H_{10}O_2Br_2$: C, 45.44; H, 2.74%.

The filtrate was evaporated and the residue, dissolved in a mixture of benzene and petroleum ether, was chromatographed through a silica-gel column. This was eluted successively with benzene-petroleum ether mixture, benzene, and chloroform to give 0.15 g. of VI and 0.05 g. of V.

ii) A mixture of 0.7 g. of A_1 and 5 cc. of ether was treated with diazomethane as in i). The raw crystals thereby obtained were recrystallized from benzene or methanol to give 0.2 g. of V, as pale yellow needles, m. p. 173~174°C.

Found: C, 58.53; H, 4.14. Calcd. for $C_{14}H_{11}O_2Br$: C, 58.09; H, 3.81%.

The mother liquor, chromatographed as above, gave 0.1 g. of VI, 0.05 g. of V and a trace of VII as in their respective raw crystals.

iii) A mixture of 0.7 g. of A_2 and 5 cc. of ether was treated with diazomethane as above, and 0.3 g. of VI was separated. The chromathographic separation of the mother liquor through a silica-gel column gave 0.03 g. of VII, 0.05. of VI and 0.03 g. of V.

Acid Hydrolysis of 5-Bromo-4-methoxy-3-phenyltropone (V).—To a solution of 0.2 g. of V dissolved in 0.6 cc. of concentrated sulfuric acid, 6 cc. of water was added and the mixture was refluxed for 2 hr. After cooling, additional 10 cc. of water was added and the yellow crystals that separated were collected by filtration and washed with hot benzene. Yield 0.23 g. Recrystallization from ethanol gave X as yellow needles, m. p. 210~212°C (decomp.).

Found: C, 56.30; H, 3.40. Calcd. for $C_{13}H_9O_2Br$: C, 56.35; H, 3.27%.

From benzene solution 0.05 g. of V was recovered.

Acid Hydrolysis of 5, 7-Dibromo-4-methoxy-2-phenyltropone (VI).—A mixture of 0.37 g. of VI, 2 cc. of concentrated sulfuric acid and 4 cc. of water was refluxed for 30 min. After cooling the whole, the separated crystals were collected by filtration and washed with benzene. Yield 0.32 g. Recrystallization from ethanol gave XV as yellow scales, m. p. 195~198°C. (decomp.).

Found: C, 45.63; H, 2.46. Calcd. for $C_{13}H_8O_2Br_2$: C, 45.15; H, 2.33%.

Methylation of 7-Bromo-4-hydroxy-2-phenyltropone (X). — Treatment of X (0.3 g.) with diazomethane in ether followed by the removal of the solvent gave crystalline residue. Recrystallization from benzene gave 0.16 g. of raw crystals of V, m. p. 160~165°C. The mother liquor, after the removal of the solvent, was dissolved in a mixture of benzene and petroleum ether and chromatographed through a silica-gel column. About 0.07 g. of yellow crystals of VII, m. p. 62~65°C and a small amount of V were obtained. Recrystallization of VII from cyclohexane or dilute methanol gave yellow needles, m. p. 73~74°C.

VII: Found: C, 58.09; H, 3.60. Calcd. for $C_{14}H_{11}O_2Br$: C, 58.09; H, 3.81%.

Methylation of 5,7-Dibromo-4-hydroxy-2-phenyltropone (XV).—In the usual manner, 0.3 g. of XV was treated with diazomethane in ether. The crystals that separated were recrystallized from benzene or methanol to give 0.18 g. of VI as yellow needles, m. p. 129~130°C and 0.02 g. of VIII as pale yellow plates, m. p. 112~113°C.

VIII: Found: C, 45.51; H, 2.68. Calcd. for $C_{14}H_{10}O_2Br_2$: C, 45.44; H, 2.72%.

Chromatographic separation of the mother liquor through a silica-gel column gave additional 0.03 g. of VIII and a trace of VI.

Reaction of 7-Bromo-4-methoxy-2-phenyltropone (VII) and Sodium Methoxide.—To a solution of 0.04 g. of metallic sodium in 4 cc. of absolute methanol, 0.2 g. of VII was added and the solution was refluxed over a period of 20 hr. on an oil bath. After removal of the solvent, 5 cc. of water was added, and the solution was refluxed for an additional period of 3 hr. The solution was shaken with chloroform to remove the neutral portions and the water layer was acidified with dilute sulfuric acid. The acidic product that separated was extracted with chloroform. After removal of the solvent, the crystalline residue was recrystallized from cyclohexane to give 0.03 g. of XI as yellow crystals, m. p. 95~100°C. This was dissolved in 0.5 cc. of concentrated sulfuric acid and heated on a water bath for several min. After cooling, the solution was diluted with water and extracted with benzene. The benzene extract, after being washed with dilute sodium hydroxide solution, was evaporated and the residue was recrystallized from cyclohexane to give yellow needles, m. p. 95~97°C. This was proved to be identical by mixed fusion with the authentic sample of 3-methoxyfluorenone (XI).

Reaction of 5, 7-Dibromo-4-methoxy-2-phenyltropone (VI) and Alkali.—A mixture of 0.12 g. of VI, 3 cc. of ethanol and 1 cc. of 2 N sodium hydroxide was refluxed for 30 min. After removal of ethanol, the residue was acidified and extracted with benzene. Benzene extract gave 0.06 g. of pale yellow crystals which were digested, with a small amount of yellowish brown crystals, m. p. 185~193°C (decomp.). This was proved to be XV from its analytical value.

Found: C, 43.88; H, 2.20. Calcd. for $C_{13}H_8O_2Br_2$; C, 45.15; H, 2.33%.

The benzene solution was passed through a short silica-gel column to give 0.03 g. of raw crystals of m. p. 140~155°C. Recrystallization from dilute methanol gave XVI as colorless needles, m. p. 168~169°C.

Found: C, 54.51; H, 3.46. Calcd. for $C_{14}H_{11}O_3Br$: C, 54.75; H, 3.61%.

When XVI was heated with concentrated sulfuric

acid on a water bath for several minutes and then diluted with water, there were obtained yellow crystals of m. p. 235~237°C.

Found: C, 57.52; H, 3.04. Calcd. for $C_{14}H_9O_2Br$; C, 58.16; H, 3.14%.

Reaction of 5, 7-Dibromo-4-methoxy-3-phenyltropone (VIII) and Alkali.—A mixture of 0.06 g. of VIII, 3 cc. of methanol and 10 cc. of 2 N sodium hydroxide was refluxed on a water bath for 30 min. After treated as in the case of VII, 0.05 g. of raw crystals of m. p. 175~180°C were obtained. Recrystallization from methanol gave XVIII as colorless needles of m. p. 187~188°C.

Found: C, 55.28; H, 3.60. Calcd. for $C_{14}H_{11}O_3Br$: C, 54.75; H, 3.61%.

Debromination of 0.03 g. of XVIII dissolved in 3 cc. of methanol, in the presence of palladium carbon catalyst and sodium acetate, gave 0.02 g. of colorless crystals m. p. 190~200°C. This was recrystallized from methanol to give colorless needles of m. p. 210~211°C, which was proved to be identical with the authentic sample of XIX obtained from V.

Reaction of 5-Bromo-4-methoxy-3-phenyltropone (V) and Alkali.—A mixture of 0.14 g. of V, 2.5 cc. of ethanol and 0.8 cc. of 2 N sodium hydroxide was refluxed for 30 min. After treated as in the above cases, 0.12 g. of pale yellow acidic crystals were obtained. This was digested with hot benzene to give a minute amount of yellow crystals of m. p. 205~208°C (decomp.). Which was proved to be identical with X from its analytical value and ultraviolet spectrum.

Found: C, 56.28; H, 3.34. Calcd. for $C_{13}H_9O_2Br$: C, 56.35; 3.27%.

From the benzene solution, colorless needles of m. p. 207~209°C were obtained. This was proved to be identical with the sample of XIX obtained from 4-methoxybenzoic acid (XX).

Found: C, 73.97; H, 5.04. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30%.

Reduction of 7-Bromo-4-methoxy-2-phenyltropone (VII).—Catalytic reduction of 0.11 g. of VII dissolved in 3 cc. of ethanol, in the presence of 0.02 g. of sodium acetate and 0.02 g. of palladium carbon, resulted in absorption of hydrogen at room temperature. After removal of the catalyst by filtration, the filtrate was diluted with water and extracted with benzene. This extract, evaporated under reduced pressure, gave crystalline residue which was recrystallized from cyclohexane to give XIII as pale yellow needles m. p. 91~92°C.

Found: C, 79.63; H, 5.80. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70%.

Reduction of 5, 7-Dibromo-4-methoxy-2-phenyltropone (VI).—Catalytic reduction of 0.1 g. of VI, as in the case of VII, gave 0.02 g. of XIII.

Reduction of 5-Bromo-4-methoxy-3-phenyltropone (V).—Catalytic reduction of 0.1 g. of V dissolved in 40 cc. of ethanol, in the presence of 0.1 g. of palladium carbon and 0.1 g. of sodium acetate, resulted in absorption of hydrogen at room temperature. After removal of the catalyst and the solvent, the residue was diluted with water and extracted with benzene. This solution, passed through a silica-gel column, gave raw crystals of m. p. 70~74°C. Recrystallization from cyclohexane gave XIV, as pale yellow prisms, m. p. 75~76°C.

Found: C, 78.31; H, 5.81. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70%.

Synthesis of 4-Methoxy-3-phenylbenzoic Acid (XIX).—4-Methoxy-3-nitrobenzoic acid (XXI)[10], m. p. 191~192°C, was obtained by the nitration of 4-methoxybenzoic acid (XX) in a mixture of acetic acid and acetic anhydride with concentrated nitric acid.

The methylation of XXI with methanol and concentrated sulfuric acid gave methyl-4-methoxy-3-nitrobenzoate (XXII)[11] m. p. 110~111°C in a good yield. Catalytic reduction of XXII in ethyl acetate in the presence of Raney nickel catalyst (W-5), gave methyl-3-amino-4-methoxy benzoate (XXIII)[12], m. p. 83~85°C.

A solution of 0.7 g. of acetic anhydride and 3 cc. of acetic acid was heated for 30 min. To the cold reaction mixture, nitrous fume generated by the action of concentrated nitric acid to solid sodium nitrate, was passed in for a period of 1 hr. at about 5°C. When diluted with water, the reaction mixture separated a yellow oily product, which was extracted with benzene. After washed with water and dried over anhydrous sodium sulfate, the benzene solution was poured on a mixture of 0.7 g. of anhydrous sodium carbonate and 0.7 g. of anhydrous sodium sulfate. The whole was stirred for a period of 5 hr. and then kept to stand for 2 days. After removal of solid materials, the filtrate was evaporated to give 0.6 g. of an oily product. This was distilled under reduced pressure and about 0.2 g. of yellow crystalline oil was obtained. Recrystallization from ether and methanol gave methyl 4-methoxy-3-phenylbenzoate (XXV) as colorless prisms, m. p. 88~89°C. Hydrolysis of XXV gave XIX as colorless needles of m. p. 115~117°C which was proved to be identical by mixed fusion with the sample obtained from V or VII. Methylation of 0.04 g. of XIX with diazomethane gave about 0.03 g. of XXV.

The author takes this opportunity to express his sincere gratitude to Professor Tetsuo Nozoe of Tohoku University for his guidance and encouragement throughout the course of this work, to Professor Shuichi Seto, Professor Yoshio Kitahara of Tohoku University and to Assistant Professor Katsuo Kikuchi of Yamagata University for their very helpful and kind discussions.

Department of Chemistry
Faculty of Liberal Arts and Science
Yamagata University
Koshirakawa-machi, Yamagata

10) *Beilsteins Handbuch. Org. Chem.*, **10**, 181.
11) ibid., **10**, 182.
12) ibid., **14**, 594.