Some Unexpected Reactions in the Synthesis of 1-Phenyl-2-aminopropane-1, 3-diol Starting from Phenyl β-Chlorovinyl Ketone*

By Haruhisa SHIRAHAMA and Takeshi MATSUMOTO

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In a previous paper[1] the synthesis of 1-phenyl-2-aminopropane-1, 3-diol (VI) from phenyl β-chlorovinyl ketone (I) was described. The reactions to be recorded below were examined in an attempt to find other routes to prepare VI from I. However, in each process, unexpected results were obtained. These new findings obtained in the course of this work will be reported here.

Route. 1.—The synthetic process described in the preceding paper involved two hydrogenation steps starting from α-oximino-β, β-dimethoxypropiophenone (V), derived from I. It was felt that the replacement of V by α-oximino-β, β-dibenzyloxypropiophenone (IV) might directly give the diol VI by a single hydrogenation through the hydrogenolysis of the benzyl group. Although the synthesis along this line was not successful, as will be described below, some interesting information about the reactivity of β, β-dibenzyloxypropiophenone (II) was obtained. Some chemical properties of II will therefore be reported on here.

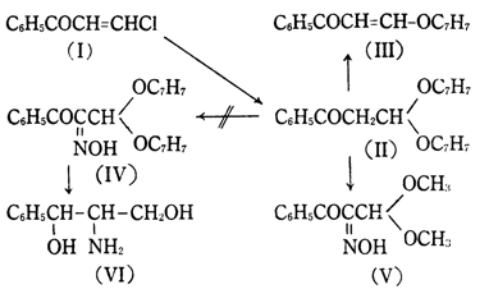

Fig. 1

The acetal (II) was prepared from I following the method for the preparation of VII.[1] A benzyl alcoholic solution of sodium benzyloxide was used as the alkaline reagent. Since the solution was very viscous and since a 5% solution gradually solidified at room temperature, a specially-designed separatory funnel was needed to add it portion by portion to the reaction vessel. The reaction proceeded as in the case of dimethyl acetal.[1] The product II looses benzyl alcohol upon prolonged heating and gives phenyl β-benzyloxyvinyl ketone (III). The elimination of alcohol from the β-keto acetal by heat was also observed in the case of the dimethyl acetal (VII). The oximation of II in methanol following Claisen's method[2] unexpectedly yielded V instead of IV. A possible explanation for the exchange of the alkoxy group of II may be that described in Fig. 2. In fact, V could be derived from II, III, VII and VII′ by the same treatment.

In order to prepare IV, therefore, it was anticipated that the oximation of II in benzyl

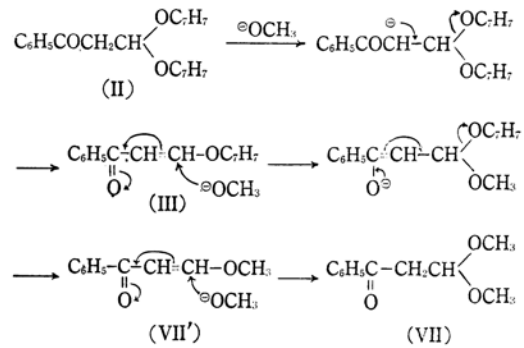

Fig. 2

* The Synthesis of 1-Phenylpropane Derivatives. V. Part IV: Ref. 1.

1) H. Shirahama and T. Matsumoto, This Bulletin, 38, 1289 (1965).

2) C. Claisen and O. Mannasse, *Ber.*, 20, 2194 (1887).

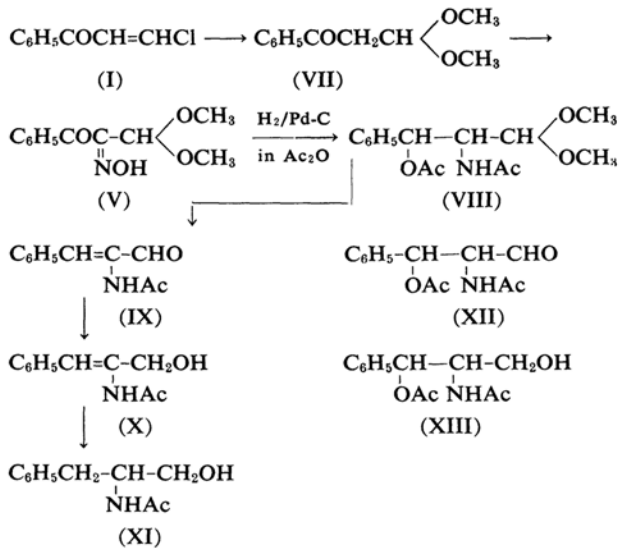

Fig. 3

alcohol would give favorable results. However, the reaction did not proceed in benzyl alcohol, and the original material was recovered after a few days treatment.[3] The inertness of II in a benzyl alcoholic solution may be due to the steric hindrance exerted by the benzyloxy group and/or to the polarity of the solvent.

Route 2.—The experiments outlined in Fig. 3 were originally attempted in order to convert VII to α-acetamido-β-acetoxyhydrocinnamaldehyed (XII), a possible intermediate for the synthesis of 1-phenyl-2-aminopropane-1, 3-diol. However, the hydrolysis of the α-acetamido-β-acetoxyhydrocinnamaldehyde dimethyl acetal under a variety of conditions was found to yield the α, β-unsaturated aldehyde (IX) invariably. Although the attempt along the original lines was thus unsuccessful, *N*-acetyl phenylalaninol was obtained for the first time in the crystalline state through the aldehyde (IX).

The hydrogenation of V with palladium charcoal in a mixture of acetic acid and acetic anhydride afforded a mixture of *threo* and *erythro* α-acetamido-β-acetoxyhydrocinnamaldehyde dimethyl acetals (VIII) in a ratio of 1 to 1. Although the separation of these isomers by recrystallization was difficult, it was achieved by forming large crystals and collecting the crystals of each component by hand. According to infrared studies of chloramphenicol and allied compounds by Suzuki and Shindo,[4] *threo O, N*-diacyl 1-phenyl-2-aminopropane-1-ol in its crystalline state invariably exhibits the amide I band at a higher wave number and the amide II band at a lower wave number than does the *erythro* isomer, and a strong absorption band always appears in the 950—1000 cm^{-1} region in the *threo* series and in the 900—950 cm^{-1} region in the *erythro* series. Of the two diacetyl compounds VIII, one absorbs at 1640, 1570 and 940 cm^{-1} and the other, at 1650, 1555 and 995 cm^{-1}. These results indicate that the former, which is in the form of needles and which melts at 132—133°C, belongs to the *erythro* series and that the latter, which is cubic and which melts at 137—138°C, belongs to the *threo* series. A solution of either *threo* or *erythro* VIII in acetic acid diluted with a small amount of water was boiled for a short time in order to hydrolyze the acetal group. The products (m. p. 125—126°C) reduced Fehling's solution, and the analytical data as well as its infrared spectrum suggested that the product was α-acetamidocinnamaldehyde (IX). The reduction of IX with sodium borohydride afforded the known[5] α-acetamidocinnamyl alcohol (X). The hydrogenation of X yielded crystalline *N*-acetylphenylalaninol (XI) (m. p. 90—95°C), which was hitherto known[6] only in the form of an oil.

The action of aqueous calcium chloride upon the acetal (VIII) was next examined for the purpose of preparing α-acetamido-β-acetoxyhydrocinnamaldehyde (XII). This treatment,

3) During the oximation reaction, the presence of oximino ketone was determined by means of ferrous sulfate.[1]

4) M. Suzuki and H. Shindo, *J. Pharm. Soc. Japan*, **76**, 927 (1956). An explanation of their results will be given in this paper.

5) T. A. Girard and R. J. Moshy, *J. Org. Chem.*, **23**, 1942 (1958).

6) L. Berlinguet, *Can. J. Chem.*, **32**, 1931 (1954).

however, also resulted in the formation of IX, with a loss of acetic acid. The treatment of finely-powdered VIII with dilute sulfuric acid at room temperature gave a small amount of IX, most of the starting material also being recovered.

Route 3.—The experiments were initially started in order to prepare 1-phenyl-2-phthalimidopropane-1, 3-diol from the same starting material (Fig. 4). However, the treatment of α-bromo-β, β-dimethoxypropiophenone (XIV), derived from I, with potassium phthalimide unexpectedly yielded the phenyl α-methoxy-β-phthalimidovinyl ketone (XVI) rather than the desired α-phthalimido-β, β-dimethoxypropiophenone (XVII). Moreover, the methoxyl group of XVI located at the α position to the carbonyl group was readily hydrogenolysed to afford 1-phenyl-3-phthalimidopropane-1-ol (XXX).

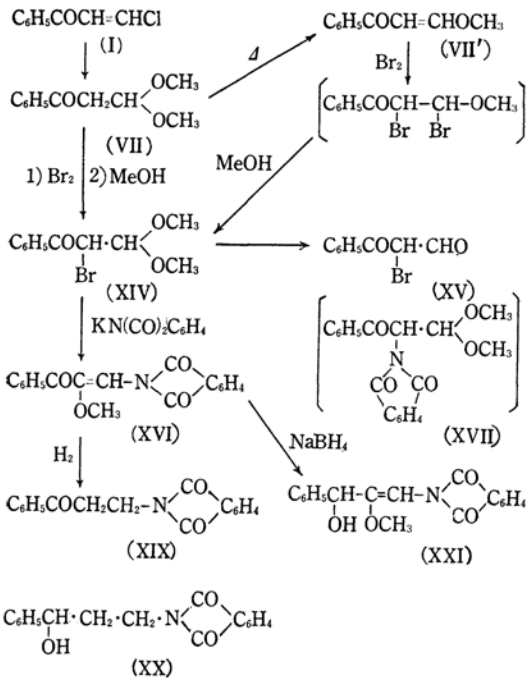

Fig. 4

The bromination of β, β-dimethoxypropiophenone[1] with bromine in carbon tetrachloride was attempted at first to prepare the bromo compound XIV. However, the reaction was accompanied by the hydrolysis of the acetal group by the hydrogen bromide generated during the reaction and yielded benzoyl-α-bromoacetaldehyde (XV). The product was identified by comparing it with an authentic sample prepared by a known method.[7] The desired bromoacetal was obtained by first adding bromine to the phenyl β-methoxyvinyl ketone (VII) formed from VII upon distillation at 20 mmHg in a carbon tetrachloride solution and subsequently treating the product with methanol. The bromoacetal was also obtained by treating VII in the same manner.

The reaction of the bromoacetal XIV and potassium phthalimide was carried out first in dimethylformamide.[8] However, only an intractable tar was obtained even though the reaction conditions were carefully controlled. When methanol was employed as the solvent, a crystalline product (m. p. 81.5—82.5°C λ_{max} 298 mμ (ε 22600), ν_{max} 1730, 1645, 1600 and 1585 cm^{-1}) was produced. The analytical and spectral data of the product first suggested that it was phenyl α-phthalimido-β-methoxyvinyl ketone (XVIII). The attempt to obtain the corresponding aldehyde by the hydrolysis of the vinyl ether group[9] was not successful, and the product (m. p. 82.5°C) was shown to be stable against cold aqueous sodium hydroxide and hydrochloric acid.

The hydrogenation of the product (m. p. 82.5°C) eventually revealed that the compound was not an α-, but a β-phthalimide derivative. Namely, by hydrogenation over platinum oxide in acetic acid, the compound yielded β-phthalimido propiophenone (XIX) (m. p. 128—129°C) and 1-phenyl-3-phthalimidopropane-1-ol (XXV) (m. p. 76.5—78°C), both of which are known in the literature.[10,11] Therefore, the compound with a m. p. of 82.5°C must be either the

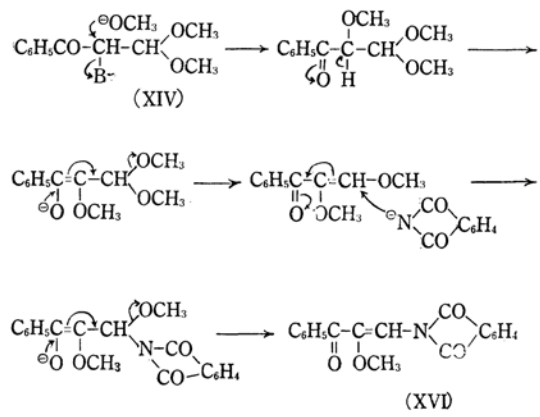

Fig. 5

7) M. S. Matta, R. Kaushal and S. S. Deshapande, *J. Indian Chem. Soc.*, **23**, 454 (1946).

8) J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).

9) It is known that, in alkaline conditions, β-methoxyvinyl ketone undergoes readily hydrolysis to give β-ketoaldehyde, which then further decomposes into methyl ketone.[1]

10) R. E. Davis and G. Powell, *J. Am. Chem. Soc.*, **67**, 1466 (1945).

11) R. E. Lutz, J. W. Wilson, A. J. Deinet, G. H. Harnest, H. A. Martin and J. A. Freek, *J. Org. Chem.*, **12**, 103 (1947).

phenyl α-methoxy-β-phthalimidovinyl ketone or the phenyl β-methoxy-β-phthalimidovinyl ketone. For the purpose of differentiating between these two alternatives, the compound was reduced by sodium borohydride to an unsaturated alcohol. The NMR spectrum of the product exhibited, in addition to aromatic proton signals, four singlets at τ 6.5 (CH_3O-), 5.7 (-$\underset{|}{C}$H-OH), 4.3 (OH) and 3.26 (-$\underset{|}{C}$=CH-). These results clearly indicate that the alcohol produced is phenyl α-methoxy-β-phthalimidovinyl carbinol (XXI) and that hence, the ketone is the α-methoxy-β-phthalimidovinyl ketone (XVI). The formation of XVI may be explained as follows (Fig. 5).

Experimental

β, β-Dibenzyloxypropiophenone (II).—Into a mixture of 10 g. of the phenyl chlorovinyl ketone (I) and 10 g. of benzyl alcohol, a solution of 1.4 g. of sodium in 23 g. of benzyl alcohol was gradually added and stirred. During the reaction period, the vessel was kept in an ice-salt bath and the temperature was adjusted so as not to rise over −5°C. Since the solution of sodium benzylate solidified at lower temperatures, the addition was carried out by the use of a specially-designed separatory funnel. After being set aside overnight, the reaction mixture was poured into ice water and extracted with ether. The extract was then dried and distilled. β, β-Dibenzyloxypropiophenone (II) was distilled out at 186°C (1.5 mmHg) as a sticky yellow oil; yield 5 g. (24%).

Found: C, 79.89; H, 6.19. Calcd. for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40%.

Phenyl β-Benzyloxyvinyl Ketone (III).—On the slow redistillation of the benzyl acetal (II), an appreciable amount of benzyl alcohol ran out first, and phenyl β-benzyloxyvinyl ketone distilled out as a deep yellow oil (b. p. 185°C (2 mmHg) ν_{max} 1655, 1600, 1585, 1570, 1491, 1185 and 1170 cm^{-1}). The vinyl ketone readily decolorized the permanganate solution, was unstable, and was used without purification for the oximation. The treatment of this ketone with alkyl nitrite and sodium methoxide in methanol, as described in the next section, yielded α-oximino-β, β-dimethoxypropiophenone.

The Oximation of II.—a) To a solution of 0.2 g. of sodium in 5 ml. of methanol, 1.2 ml. of isoamyl nitrite and 2 g. of β, β-dibenzyloxypropiophenone (II) were gradually added under cooling in an ice bath. After it had then been set aside for 2 or 3 days in a cool place, the reaction mixture was poured into ice water and washed three times with ether in order to remove the isoamyl alcohol and the unchanged ketone. The product was then taken up in ether after the addition of excessive ammonium chloride. The removal of the ether left white crystals (m. p. 83—85°C) which showed no depression on admixture with authentic α-oximino-β, β-dimethoxypropiophenone. The identity was confirmed by a comparison of the infrared spectra.

b) The same procedure was used as in a) except that 5 ml. of benzyl alcohol was used instead of 5 ml. of methanol. Even after 3 days the reaction mixture gave only a faint coloration in the ferrous complex test. After it had been set aside for 4 days, the reaction mixture was treated with ice water and ether. The working up of the ether extract afforded original β, β-dibenzyloxypropiophenone.

α - Acetamido - β - acetoxyhydrocinnamaldehyde Dimethyl Acetal (VIII).—A solution of 500 mg. of α-oximino-β, β-dimethoxypropiophenone (V) in a mixture of 10 ml. of acetic acid and 10 ml. of acetic anhydride was hydrogenated in the presence of 150 mg. of 10% palladium-on-charcoal[12] for 3 hr. The absorption ceased when 3.5 equivalents of hydrogen were taken up. The catalyst was then filtered off, and the solution was allowed to stand overnight with four drops of pyridine. After the removal of the solvent, the crystalline residue was recrystallized from ethyl acetate to afford colorless crystals of α-acetamido-β-acetoxyhydrocinnamaldehyde dimethyl acetal (m. p. 135—137°C).

Found: C, 60.77; H, 7.50; N, 4.75. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74%.

A sample of the acetal was recrystallized slowly to afford a mixture of two kinds of large crystals. Both the crystals, which were obtained in almost the same amounts, were separated by a pincette and recrystallized respectively to yield white needles, VIIIa (m. p. 132—132.5°C) and cubic crystals, VIIIb.

VIIIa: ν_{max}^{Nujol} 3300 (-NH-); 1735 (OAc); 1640, 1570 (-NHAc); 1120, 1090, 1060 (acetal); 940 cm^{-1}.

Found: C, 61.05; H, 7.24. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17%.

VIIIb: ν_{max}^{Nujol} 3350 (-NH-); 1730 (-OAc); 1650, 1555 (-NHAc); 1180, 1100, 1065 (acetal); 995 cm^{-1}.

Found: C, 60.96; H, 7.16. Calcd. for $C_{15}H_{21}NO_5$ C, 61.00; H, 7.17%.

The Hydrolysis of α-Acetamido-β-acetoxyhydrocinnamaldehyde Dimethyl Acetal (VIII).—*a) The Production of α-Acetamidocinnamaldehyde.* 1) To a solution of 100 mg. of the acetal (VIIIa or VIIIb) in 1 ml. of acetic acid, a few drops of water were added, and then the solution was boiled for a short time, until a light brown coloration was obtained. The removal of the solvent and recrystallization of the residue from ethyl acetate or benzene yielded white needles (m. p. 125—126°C); it reduced the Fehling solution and the Nessler reagent.

Found: C, 69.25; H, 5.93; N, 7.03. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40%.

2) To a 10% aqueous solution of calcium chloride the acetal (VIII) was added; the solution was then refluxed for 3 hr. and extracted with ethyl acetate. After drying, the removal of the solvent left crystalline aldehyde (IX).

b) An Attempt to Obtain α-Acetamido-β-acetoxyhydrocinnamaldehyde (XII).—A sample of 20 mg. of the crystalline acetal (VIII) was well ground into fine powder and dissolved in 4 ml. of 1 N sulfuric acid. After an hour, the solution was extracted with ethyl acetate. The working-up of a extract yielded the original acetate (VIII) and a small amount of the cinnamaldehyde (IX).

12) R. Mozingo, "Organic Syntheses," Vol. 26, 77 (1948).

α-Acetamidocinnamyl Alcohol. (X).—A solution of a sample (about 20 mg.) of α-acetamidocinnamaldehyde in ethanol was allowed to stand overnight with an excess of sodium borohydride. After the removal of the solvent, the residue was dissolved in dilute alkali and extracted with benzene. The evaporation of the benzene left a crystalline cake which was then recrystallized from benzene to yield the cinnamyl alcohol (X) quantitatively (m. p. 101—103°C). The melting point corresponded to that which appeared in the literature.[5]

***N*-Acetyl Phenylalaninol** (XI).—A solution of a sample (20 mg.) of cinnamyl alcohol (X) in ethanol was hydrogenated in the presence of 10% palladium charcoal. One mole of hydrogen was readily absorbed, and fine crystals (m. p. 90—95°C) were obtained. Though repeated recrystallizations from ethyl acetate - benzene had no effect in narrowing the melting point range, the analysis of the crystals gave good values for *N*-acetyl phenylalaninol.

Found: C, 68.39; H, 7.70. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82%.

The Bromination of β, β-Dimethoxypropiophenone (VII).—a) To a solution of the ketone VII in twice the volume of carbon tetrachloride, an equivalent amount of bromine was added slowly. The resulting mixture was distilled under reduced pressure to give a yellow oil (b. p. 110°C (10^{-2} mmHg)), which soon crystallized. Recrystallization from benzene gave a pure sample (m. p. 110—111°C) which shows no depression on admixture with authentic benzoylbromoacetaldehyde.

b) To a solution of the ketone VII in twice the volume of carbon tetrachloride, an equivalent mole of bromine was added drop by drop. The resulting mixture was diluted with an equal volume of methanol and allowed to stand overnight. The solution was then concentrated to a quarter and extracted with petroleum benzine, and the extract was dried and distilled to remove the volatile solvent. The residue, crude α-bromo β, β-dimethoxypropiophenone (XIV), exhibited in the infrared spectrum bands at 2800 (OCH_3), 1690, 1600 (COPh); 1115, 1160 (acetal) cm^{-1}. Although the compound was unstable and was not purified, it afforded benzoylbromoacetaldehyde in a very good yield upon hydrolysis and was pure enough for use in the next reaction. Yield, 70%.

Phenyl β-Methoxyvinyl Ketone (VII').—A sample of VII was distilled at reduced pressure with a small amount of potassium bisulfate. The β-methoxyvinyl ketone (VII') distilled off with methanol at 140°C. The distillate was redistilled, and the fraction boiling at 135°C (5—6 mmHg) was collected; ν_{max} 1660, 1600, 1590, 1578, 1200 cm^{-1}; yield 20%. Although it was difficult to remove completely the unchanged acetal VII (ν_{max} 2800, 1675, 1590, 1580, 1115, 1075, 1050 cm^{-1}), the distillate was pure enough for the next reaction. Treatment with semicarbazide yielded benzoylacetaldehyde monosemicarbazone.

Found: C, 58.39; H, 5.17; N, 20.40. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.50; H, 5.37; N, 20.50%.

The Bromination of the Phenyl β-Methoxyvinyl Ketone (VII').—In the same way as has been described in the bromination of VII—b), this yielded α-bromo-β, β-dimethoxypropiophenone.

Phenyl α-Methoxy-β-phthalimidovinyl Ketone (XVI).—The bromoacetal XVI (35.5 g.) and potassium phthalimide (23.9 g.) were added to methanol (40 g.), and the whole was refluxed for 6 hr. After the solvent had been removed, the residue was extracted with benzene. The extract was washed with 1 N sodium hydroxide and then with water, and dried over sodium sulfate. The evaporation of the benzene left a crystalline cake which was recrystallized from ethanol. The purified product, which melted at 81.5—82.5°C, weighed 14.6 g. and exhibited an ultraviolet absorption maximum at 298 mμ (ε 22600) in an ethanol solution and infrared bands at 1730, 1645, 1600 and 1585 cm^{-1}.

Found: C, 70.16; H, 4.07; N, 4.58. Calcd. for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56%.

The Hydrogenation of the Phenyl α-Methoxy-β-phthalimidovinyl Ketone (XVI).—A sample of XVI was dissolved in acetic acid and hydrogenated in the presence of platinum oxide. After the absorption of hydrogen had ceased, the catalyst and the solvent were removed. The residue, a colorless paste, was chromatographed to afford two kinds of crystals. They were recrystallized separately from a mixed solvent of benzene-petroleum. The one melting at 128—129°C was β-phthalimidopropiophenone.[11]

Found: C, 72.97; H, 4.71; N, 5.31. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11: H, 4.69; N, 5.02.

The other product melted at 76.5—78°C and was phenyl β-phthalimidoethyl carbinol (XX').

Found: C, 72.59; H, 5.32; N, 4.77. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98%.

The Reduction of the Phenyl α-Methoxy-β-phthalimidovinyl Ketone (XVI) with Sodium Borohydride.—A sample of XVI was treated with sodium borohydride in dioxane. After it had been set aside overnight, the reaction mixture was worked up in the usual way. The product was obtained as a colorless paste which was difficult to crystallize. The NMR spectrum of the product was measured at 56.4 Mc. in carbon tetrachloride. Four singlets at τ 6.5 (CH_3O-), 5.7 (C<u>H</u>-OH), 4.3 (OH), 3.26 (>C=C<u>H</u>), and an aromatic multiplet signal were observed. When the ethereal solution of the pasty alcohol was oxidized[13] with chromic acid and a few drops of sulfuric acid, the original ketone XVI was obtained.

Department of Chemistry
Faculty of Science
Hokkaido University
Sapporo

13) H. C. Brown and C. P. Gary, *J. Am. Chem. Soc.*, **83**, 2952 (1961).