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Studies on Ketene and Its Derivatives. XLVIII.[1] Reaction of Diketene with Hydroxylamine

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The reaction of diketene with hydroxylamine was reinvestigated. Hydroxylamine, O-methylhydroxylamine and O-benzylhydroxylamine reacted with two equimolar amounts of diketene in the presence of triethylamine to give the corresponding 1-substituted 5-acetyl-6-hydroxy-4-methyl-2(1*H*)-pyridones; *i.e.*, 1-hydroxy (VI), 1-methoxy (XIII), and 1-benzyloxy (XVI) derivatives. Treatment of O-benzylhydroxylamine with an equimolar amount of diketene in the absence of triethylamine yielded O-benzylacetoacetohydroxamic acid (XVII) in good yield. Catalytic reduction of XVII with palladium charcoal afforded an oily substance (XVIII), which was treated with dry hydrogen chloride to give 3-hydroxy-5-methylisoxazole (XIX).

While the reaction of diketene with the carbonyl reagent is now well known, only a few literatures can be available concerning the reaction with hydroxylamine.[3-5] In 1950, Khromov[4] reported the reaction of hydroxylamine with diketene to give acetoacetic acid oxime, which, on allowing to stand for a long time, was transformed into 3-methyl-5(4*H*)-isoxazolone (I). Also, Fujimoto and Sakai[5] reported that diketene reacted with hydroxylamine and N-arylsulfonhydroxamic acid giving I and its N-arylsulfonyl derivative (III), the former of which was transited to 3,3′-dimethyl-5-hydroxy-4,5′-biisoxazole (II) by the treatment with triethylamine.

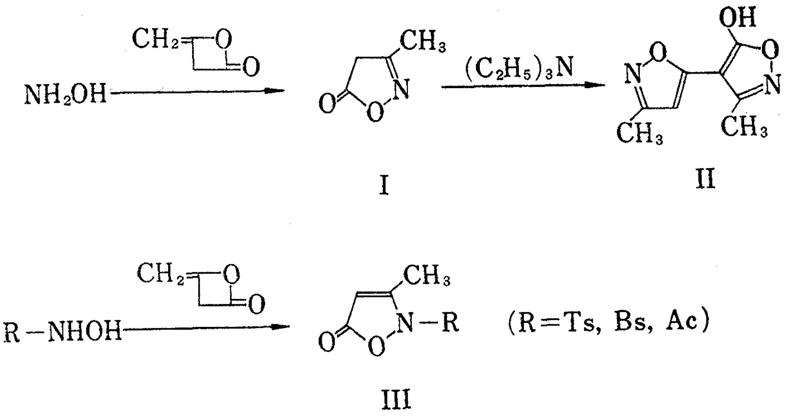

Chart 1

Usually, hydroxylamine reacts with the acylating agent such as acyl halide or acid anhydride yielding the N-acyl derivative. However, diketene reacts with the OH function of hydroxylamine resulting in the formation of the 5-isoxazolone derivative (I). During the course of the investigation of some potential uses of diketene, we reinvestigated this reaction in an effort to obtain the N-acetoacetylated product, and found some interesting results, which are reported in the present paper.

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[1] XLVII: T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.* (Tokyo), **21**, 142 (1972).

[2] Location: *Aobayama, Sendai, 980,* Japan.

[3] A. Gleason, USP 2,174,239 (1939).

[4] N. Khromov, *Zhur. Obshchei Khim.*, 20, 1858 (1950).

[5] M. Fujimoto and M. Sakai, *Chem. Pharm. Bull.* (Tokyo), **13**, 248 (1965).

When hydroxylamine hydrochloride reacted with an equivalent amount of diketene in the presence of triethylamine below 5° followed by treatment with benzene diazonium chloride prepared from aniline and nitrous acid, 3-methyl-4-phenylhydrazono-5(4*H*)-isoxazolone (IV) was obtained with the formation of 2-phenylhydrazonoacetoacetohydroxamic acid (V) as a by-product. IV was identical with an authentic sample prepared from benzene diazonium chloride and I. Though the yield was very poor, the formation of V suggested that diketene had reacted with the NH function of hydroxylamine.

When hydroxylamine hydrochloride was allowed to react with two equimolar amounts of diketene under the same condition as above, colorless needles of mp 180°, $C_8H_9O_4N$ (VI), were obtained with the formation of colorless needles of mp 118—120°, $C_7H_9O_2N$ (VII), as a by-product. VII was characterized as 4-isopropylidene-3-methyl-5(4*H*)-isoxazolone by the comparison with an authentic sample prepared from I and acetone.

Hydrolysis of VI with 10% hydrochloric acid afforded the deacetylated compound (VIII), which was reduced, on catalytic reduction with Raney nickel, to 6-hydroxy-4-methyl-2(1*H*)-pyridone (IX). Catalytic reduction of VI with Raney nickel gave compound XII, which was hydrolyzed to IX. When VI was heated with hydrochloric acid for a long time, the ring opened product, hydroxylamine and the mixture of *cis* and *trans* 3-methylglutaconic acid

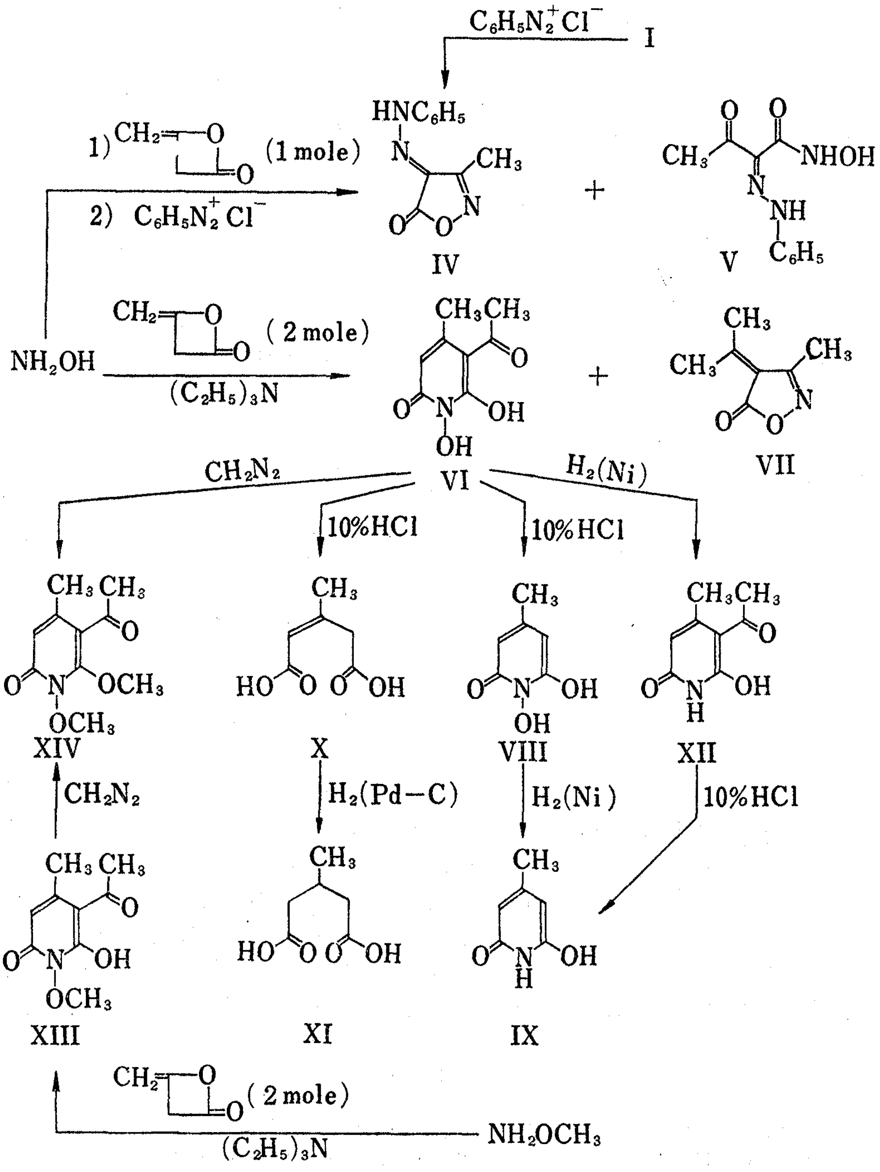

Chart 2

(X), were obtained. X was reduced readily to 3-methylglutaric acid (XI). Treatment of VI with diazomethane gave the O-methyl derivative (XIV). These reactions suggest that the structure of VI is uniquely 5-acetyl-1,6-dihydroxy-4-methyl-2(1*H*)-pyridone (VI). The infrared (IR) and nuclear magnetic resonance (NMR) spectra supported the structure of VI.

Similarly, O-methylhydroxylamine was allowed to react with diketene in the presence of triethylamine giving 5-acetyl-6-hydroxy-1-methoxy-4-methyl-2(1*H*)-pyridone (XIII). XIII was treated with diazomethane to yield the dimethoxy derivative (XIV).

O-Benzylhydroxylamine (XV) reacted with two equimolar amounts of diketene in the presence of triethylamine yielding 5-acetyl-1-benzyloxy-6-hydroxy-4-methyl-2(1*H*)-pyridone (XVI), which, on catalytic reduction with palladium charcoal, was reduced to VI.

When an equimolar amount of diketene was allowed to react with XV in the absence of triethylamine. O-Benzylacetoacetohydroxamic acid (XVII) was obtained in good yield. Catalytic reduction of XVII with Raney nickel afforded acetoacetamide and benzylalcohol, however, when palladium charcoal was used as a catalyst instead of Raney nickel, XVII was transformed to an oily substance (XVIII), which was dissolved in glacial acetic acid followed by treating with dry hydrogen chloride yielding 3-hydroxy-5-methylisoxazole (XIX).

Since there are quite few literatures dealing with the synthesis of 3-hydroxyisoxazole derivatives, this reaction to give XIX seems to be worthy of note.

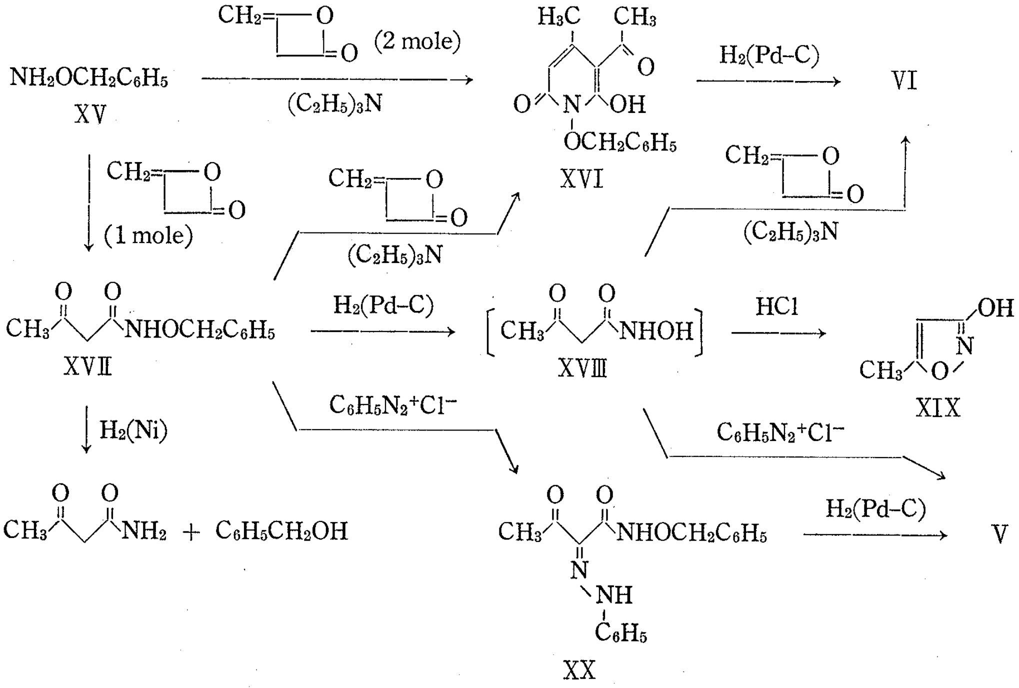

Chart 3

When an oily product (XVIII) was allowed to react with diketene in the presence of triethylamine, compound VI was obtained in 55% yield. Reaction of XVIII with benzene diazonium chloride afforded V, whose NMR and IR spectra were identical in every respect with those of a specimen obtained in the reaction of diketene with an equimolar amount of hydroxylamine in the presence of triethylamine followed by treating with benzene diazonium chloride described before (Chart 1). V was also obtained by the reaction of XVII with benzene diazonium chloride followed by catalytic reduction with palladium charcoal.

Experimental

Reaction of Hydroxylamine with Diketene——1) Diketene (1.7 g) was added dropwise to a solution of hydroxylamine hydrochloride (1.4 g) and triethylamine (4 g) in H_2O (8 ml) below 5°. After being neutralized with acetic acid, the reaction mixture was added to benzene diazonium chloride solution prepared from aniline (1.9 g), conc. HCl (5 ml), $NaNO_2$ (1.4 g), and H_2O (8 ml). The reaction mixture was neutralized with Na_2CO_3, stirred for 30 min, and crystals separated were collected by suction. After washing with ether, the crystalline residue was extracted with MeOH, and recrystallized from excess MeOH to yellow plates (IV), mp 183° (decomp.), whose IR spectrum was identical with that of an authentic sample prepared from I and benzene diazonium chloride. Yield, 1.9 g (47%). *Anal.* Calcd. for $C_{10}H_9O_2N_3$ (IV): C, 59.10; H, 4.46; N, 20.68. Found: C, 58.89; H, 4.55; N, 20.79. The MeOH fraction was evaporated to give a crystalline residue, which, after washing with a small amount of $CHCl_3$, was purified by recrystallization from MeOH to yellow needles (V), mp 174—176° (decomp.). *Anal.* Calcd. for $C_{10}H_{11}O_3N_3$ (V): C, 54.29; H, 5.01; N, 19.00. Found: C, 54.26; H, 5.18; N, 19.10. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3240, 1660. NMR (CF_3COOH, ppm): 3.04 (3H, singlet), 7.3—8.2 (7H, multiplet).

2) Diketene (33.6 g, 0.4 mole) was added dropwise to a solution of hydroxylamine hydrochloride (13.9 g, 0.2 mole) and triethylamine (40 g, 0.4 mole) with stirring over a period of 1 hr, during which time the temperature of the mixture was maintained below 5°. Stirring was continued for additional 1 hr at room temperature. The mixture was acidified with 10% HCl, and crystals separated were collected by suction, and dried. Recrystallization from EtOH gave 5-acetyl-1,6-dihydroxy-4-methyl-2(1*H*)-pyridone (VI) as cololess needles, mp 180° (decomp.). Yield, 9.5 g (26.0%). *Anal.* Calcd. for $C_8H_9O_4N$ (VI): C, 52.46; H, 4.95; N, 7.65. Found: C, 52.51; H, 4.89; N, 7.78. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3460, 2560, 1650, 1580, 1530. NMR (CF_3COOH, ppm): 2.60 (3H, singlet), 2.80 (3H, singlet), 6.27 (1H. singlet). The mother liquor was condensed to dryness, and the residue was extracted with ether. The ether soluble fraction was condensed to give 1.2 g of 4-isopropylidene-3-methyl-5(4*H*)-isoxazolone (VII) as colorless needles, mp 118—120°, undepressed on admixture with an authentic sample prepared from I and acetone. *Anal.* Calcd. for $C_7H_9O_2N$ (VII): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.56; H, 6.61; N, 10. 06.

Hydrolysis of VI with 10% HCl——1) A suspension of VI (1.8 g) in 10% HCl (20 ml) was heated at reflux for 1 hr. The mixture was evaporated under reduced pressure to dryness. The residue was washed with ether, and recrystallized from acetone to 1,6-dihydroxy-4-methyl-2(1*H*)-pyridone (VIII) as colorless leaves, mp 158—160°. Yield, 0.73 g (51.7%). *Anal.* Calcd. for $C_6H_7O_3N$ (VIII): C, 51.06; H, 5.00; N, 9.93. Found: C, 51.22; H, 5.10; N, 9.87. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3420, 2860, 1650, 1470. NMR (CF_3COOH, ppm): 2.15 ($^{1}/_{2}$H, singlet), 2.46 ($^{15}/_{6}$H, singlet), 3.77 ($^{1}/_{3}$H, singlet), 6.22 ($^{1}/_{6}$H, singlet), 6.60 ($^{5}/_{3}$H, singlet).

2) A suspension of VI (1.2 g) in 10% HCl (15 ml) was heated at reflux for 5 hr. The mixture was condensed *in vacuo* to dryness. The residue was extracted with ether, and dried over anhyd. Na_2SO_4 and evaporated to give a crystalline substance which was recrystallized from benzene to afford *cis*, *trans* 3-methylglutaconic acid (X) as colorless needles, mp 100—108°. Yield, 0.6 g (62.5%). *Anal.* Calcd. for $C_6H_8O_4$ (X): C, 50.00; H, 5.60. Found: C, 49.84; H, 5.76. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3020, 2680, 1705, 1650. NMR (CF_3COOH, ppm): 2.14 ($^{6}/_{5}$H, doublet, $J=2$ cps), 2.33 ($^{9}/_{5}$H, doublet, $J=2$ cps), 3.38 ($^{6}/_{5}$H, singlet), 3.84 ($^{4}/_{5}$H, singlet), 5.94 ($^{3}/_{5}$H, doublet, $J=2$ cps), 6.04 ($^{2}/_{5}$H, doublet, $J=2$ cps). The ether insoluble residue was recrystallized from EtOH to give hydroxylamine hydrochloride as colorless needles, mp 152—154°. Yield, 0.33 g (72.0%).

Catalytic Reduction of VIII——A mixture of VIII (0.2 g) and Raney Ni (0.1 g) in MeOH (10 ml) was shaken in H_2 until 36 ml of H_2 had been absorbed. Time required was 20 min. An equivalent amount of H_2 was 32.8 ml at 15°. The catalyst was removed by filtration, and the filtrate was condensed to give 0.13 g (72.2%) of colorless prisms (IX), mp 187—189° (decomp.), whose IR spectrum was identical with that of an authentic sample of 6-hydroxy-4-methyl-2(1*H*)-pyridone.[6]

Catalytic Reduction of XI——A mixture of XI (0.2 g) and 20% Pd-C (0.1 g) in MeOH (10 ml) was shaken in H_2, and 35 ml of H_2 was absorbed for 1 hr. An equivalent amount of H_2 was 33 ml at 17°. After removing catalyst by filtration, the filtrate was condensed to give crystalline residue. Recrystallization from benzene gave 0.15 g (71.3%) of colorless prisms (XI), mp 82—84°, undepressed on admixture with an authentic sample of 3-methylglutaric acid.[7]

Catalytic Reduction of VI——A suspension of VI (1.83 g) and Raney Ni (0.5 g) in MeOH (20 ml) was shaken in H_2 for 3 hr. H_2 of 240 ml (theoretical amount, 238 ml at 17°) was absorbed for 3 hr. The reaction mixture was extracted with hot MeOH, and the MeOH layer was evaporated to give a crystalline substance. After washing with ether, residue was recrystallized from MeOH to give 5-acetyl-6-hydroxy-4-methyl-2(1*H*)-pyridone (XII) as colorless needles, mp 230—232° (decomp.). Yield, 1.1 g (65.9%). *Anal.* Calcd. for $C_8H_9O_3N$ (XII): C, 57.48; H, 5.43; N, 8.38. Found: C, 57.57; H, 5.42; N, 8.38. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3080, 2940, 1655, 1590. NMR (CF_3COOH, ppm), 2.76 (3H, singlet), 2.84 (3H, singlet), 6.45 (1H, singlet).

Hydrolysis of XII with 10% HCl——A suspension of XII (0.3 g) in 10% HCl (10 ml) was heated under reflux for 1 hr. The mixture was evaporated under reduced pressure to dryness. The residue was neutralized with 10% Na_2CO_3, and crystals separated were collected by suction, dried, and recrystallized from MeOH to give IX. Yield, 0.15 g (62.5%).

5-Acetyl-6-hydroxy-1-methoxy-4-methyl-2(1*H*)-pyridone (XIII)——To a mixture of O-methylhydroxylamine hydrochloride[8] (4.2 g), anhyd. K_2CO_3 (6.9 g) and triethylamine (2 ml) in H_2O (15 ml) was added

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[6] H. Rogerson and J. F. Thorpe, *J. Chem. Soc.*, **1905**, 1689.

[7] R. E. Kent and S. M. McElvain, *Org. Syn.*, **23**, 60 (1943).

[8] W. Traube, H. Ohlendorf and H. Zander, *Ber.*, **53**, 1477 (1920).

diketene (8.4 g) dropwise with cooling. The mixture was allowed to stand overnight at room temperature, and acidified with 10% HCl. The crystals separated were collected by suction, purified by recrystallization from benzene to XIII as colorless prisms, mp 158—160°. Yield, 3 g (30.5%). *Anal.* Calcd. for $C_9H_{11}O_4N$ (XIII): C, 54.82; H, 5.62; N, 7.10. Found: C, 55.18; H, 5.42; N, 6.89. IR $\nu_{\mathrm{max}}^{\mathrm{CHCl_3}}$ cm^{-1}: 3000, 1680, 1595. NMR ($CDCl_3$, ppm): 2.39 (3H, singlet), 2.61 (3H, singlet), 4.01 (3H, singlet), 5.90 (1H, singlet), 18.01 (1H, singlet).

5-Acetyl-1,6-dimethoxy-4-methyl-2(1*H*)-pyridone (XIV)——1) To an excess of an ethereal solution of diazomethane was added VI (1.83 g) dropwise with cooling. After being allowed to stand overnight at room temperature, the mixture was evaporated to give a crystalline substance, which was washed with a small amount of ether, and purified by recrystallization from ether to colorless needles (XIV), mp 113—114°. Yield, 1.2 g (56.9%). *Anal.* Calcd. for $C_{10}H_{13}O_4N$ (XIV): C, 56.86; H, 6.20; N, 6.63. Found: C, 57.25; H, 6.32; N, 6.27. IR $\nu_{\mathrm{max}}^{\mathrm{KBr}}$ cm^{-1}: 1675, 1655, 1580. NMR ($CDCl_3$, ppm): 2.29 (3H, singlet), 2.55 (3H, singlet), 3.94 (3H, singlet), 3.96 (3H, singlet), 5.36 (1H, singlet).

2) As above, XIII (1.97 g) was treated with diazomethane in ether to give colorless needles (XIV). Yield, 1.5 g (76.1%).

5-Acetyl-1-benzyloxy-6-hydroxy-4-methyl-2(1*H*)-pyridone (XVI)——1) A solution of O-benzylhydroxylamine[9] (1.23 g), diketene (1.68 g) and a small amount of triethylamine in benzene (8 ml) was refluxed for 3 hr. The mixture was condensed to dryness, and the residue was washed with ether. Recrystallization from benzene gave XVI as colorless needles, mp 147—149°. Yield, 1.4 g (51.3%). *Anal.* Calcd. for $C_{15}H_{15}O_4N$ (XVI): C, 65.92; H, 5.53; N, 5.13. Found: C, 65.47; H, 5.63; N, 4.92. IR ${}_{\mathrm{max}}^{\mathrm{CHCl_3}}$ cm^{-1}: 3040, 1675, 1595. NMR ($CDCl_3$, ppm): 2.30 (3H, singlet), 2.52 (3H, singlet), 5.07 (2H, singlet), 5.80 (1H, singlet), 7.1—7.6 (5H, ring protons), 18.90 (1H, singlet).

2) A solution of XVII (0.42 g), diketene (0.26 g) and a small amount of triethylamine was refluxed for 2 hr. The reaction mixture was condensed *in vacuo* to give a residue, which was washed with ether. Recrystallization from benzene gave colorless needles (XVI). Yield, 0.38 g (69.6%).

Catalytic Reduction of XVI——A suspension of XVI (1.4 g) and 20% Pd-C (0.5 g) in MeoH (30 ml) was shaken in H_2. 135 ml of H_2 (theoretical amount, 121 ml at 21°) was absorbed for 10 min. The catalyst was removed off by filtration, and the filtrate was condensed to dryness. After washing with ether, the residue was purified by recrystallization from EtOH to give VI. Yield, 0.75 g (82.0%).

O-Benzylacetoacetohydroxamic Acid (XVII)——A solution of O-benzylhydroxylamine (2.46 g) and diketene (1.68 g) in benzene (20 ml) was refluxed for 1 hr. The reaction mixture was condensed *in vacuo* to give crystalline substanse, which was purified by recrystallization from ether to colorless needles (XVII), mp 77—79°. Yield, 3.0 g (72.5%). *Anal.* Calcd. for $C_{11}H_{13}O_3N$ (XVII): C, 63.75; H, 6.32; N, 6.76. Found: C, 63.37; H, 6.33; N, 6.84. IR $\nu_{\mathrm{max}}^{\mathrm{CHCl_3}}$ cm^{-1}: 3280, 1705, 1680. NMR ($CDCl_3$, ppm): 2.15 (3H, singlet), 3.28 (2H, singlet), 4.80 (2H, singlet), 7.26 (5H, ring protons), 9.45 (1H, broad).

Catalytic Reduction of XVII——1) A suspension of XVII (2.07 g) and 20% Pd-C (0.5 g) in MeOH (30 ml) was shaken in H_2 until 280 ml of H_2 (an equivalent amount, 243 ml at 23°) had been absorbed. The time required was 3 hr. The catalyst was removed off by filtration, and the filtrate was condensed *in vacuo* to give a colorless oily substance (XVIII). A solution of glacial acetic acid saturated with dry HCl was added to XVIII. After being allowed to stand for 16 hr at room temperature, the reaction mixture was condensed *in vacuo* to give a crystalline solid. Recrystallization from petroleum benzine (bp 60—65°) gave 3-hydroxy-5-methylisoxazole (XIX) as colorless needles, mp 84—85° (lit.[10] 84—85°). Yield, 0.7 g (70.7%). *Anal.* Calcd. for $C_4H_5O_2N$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.17; H, 5.21; N, 14.42.

To a mixture of XVIII (prepared from 2.07 g of XVII), H_2O (10 ml), and Et_3N (1 ml) was added diketene (1.68 g) with cooling. After allowing to stand for 1 hr at room temperature, the reaction mixture was acidified with 10% HCl, and crystals separated were collected by suction, and dried. Recrystallization from EtOH gave VI. Yield, 1.0 g (54.6%). XVIII prepared from 2.07 g of XVII as above was added to a solution of benzene diazonium chloride, which was prepared from aniline (0.9 g), conc. HCl (2 ml), H_2O (15 ml) and $NaNO_2$ (0.8 g). The reaction mixture was neutralized with CH_3COONa, and crystals separated were collected by suction, washed with H_2O, and dried. Purification by recrystallization from MeOH gave yellow needles (V). Yield, 0.27 g (23.5%).

2) A suspension of XVII (2.07 g) and Raney Ni (1 g) in MeOH (30 ml) was shaken in H_2 for 40 min. 280 ml of H_2 was absorbed (1 equivalent amount of H_2, 247 ml at 27°). Catalyst was removed off by filtration, and the filtrate was evaporated under the reduced pressure. The residue was purified by column chromatography on alumina using ether as an eluent. The ether eluted fraction was evaporated to give benzylalcohol (0.6 g) and acetoacetamide, whose IR spectrum was identical with that of an authentic sample.

O-Benzyl-2-phenylhydrazonoacetoacetohydroxamic Acid (XX)——To a solution of XVII (1 g) in EtOH (5 ml) was added a solution of benzene diazonium chloride prepared from aniline (0.5 g), conc. HCl (1 ml), H_2O (10 ml) and $NaNO_2$ (0.4 g). After stirring for 20 min, the reaction mixture was neutralized with CH_3-

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[9] R. Behrend and K. Leuchs, *Ann.*, **257**, 207 (1890).

[10] I. Iwai and N. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **14**, 1277 (1966).

COONa, and stirred for 1 hr at room temperature. Crystals separated were collected by suction, and dried. Recrystallization from benzene gave XX as yellow needles, mp 158—160°. Yield, 1.0 g (64.1%). *Anal.* Calcd. for $C_{17}H_{17}O_3N_3$ (XX): C, 65.58; H, 5.50; N, 13.50. Found: C, 65.58; H, 5.55; N, 13.17.

Catalytic Reduction of XX——A suspension of XX (0.31 g) and 20% Pd-C (0.2 g) in MeOH (15 ml) was shaken in H_2. 38 ml of H_2 was absorbed for 15 min (1 equivalent, 24 ml at 25°). The reaction mixture was extracted with hot MeOH. The MeOH fraction was evaporated, and the residue was washed with $CHCl_3$. Recrystallization from MeOH gave yellow needles (V). Yield, 0.1 g (45.2%).

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