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Studies on 3-Substituted 1,2-Benzisoxazole Derivatives. II.[1] The Catalytic Reductions of 1,2-Benzisoxazole-3-acetamide Oxime and Related Compounds[2]

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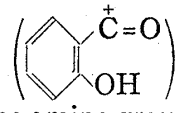
The hydrogenation of 1,2-benzisoxazole-3-acetamide oxime (**1**) proceeded as follows. At first **1** absorbed one molar hydrogen to give 2-hydroxybenzimidoylacetamide oxime (**2**) and then **2** was cyclized to 3-amino-5-(2-hydroxyphenyl)isoxazole (**4**) which absorbed one more molar hydrogen to give 2-hydroxybenzoylacetamidine (**3**).

The alkaline treatment of 2-hydroxybenzoylacetonitrile (**11**), which was obtained from 1,2-benzisoxazole-3-acetnitrile (**9**) by the catalytic reduction and successive hydrolysis, gave 2-coumarinimine (**12**). The acidic treatment of 2-hydroxybenzimidoylacetamide (**13**), which was the product of the catalytic reduction of 1,2-benzisoxazole-3-acetamide (**8**), afforded 4-aminocoumarin (**15**), an isomer of **12**.

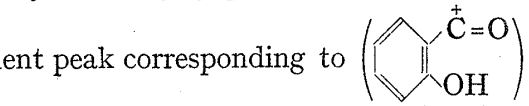
In the course of the studies on 3-substituted 1,2-benzisoxazole derivatives, we found that 1,2-benzisoxazole-3-acetamide oxime (**1**)[1] showed a strong antireserpinic activity in animals.[4] In this paper, the catalytic reduction of **1** and related compounds were described. Some reactions of products of these reductions were also described.

Casini, *et al.*[5] reported that N–O bond of benzisoxazole ring was cleaved when ethyl 1,2-benzisoxazole-3-acetate was reduced in the presence of palladium-carbon (Pd–C) catalyst.

The reduction of **1** was carried out at room temperature in the presence of 5% Pd–C and hydrogen at atomospheric pressure. The reaction was stopped when one molar equivalent of hydrogen was absorbed. The mass spectrum of the main product (**2**), which was analysed to $C_9H_{11}O_2N_3$, revealed the molecular ion (M^+) peak at *m/e* 193. When heated in ethanol or H_2O, **2** gave **3**, which was analyzed to $C_9H_8O_2N_2$. The mass spectrum of **3** revealed the M^+ peak at *m/e* 176 and a fragment peak corresponding to  at *m/e* 121. The infrared (IR) spectrum of **3** contained absorption bands due to the amino group at 3450 and 3330 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum of **3** revealed signals at δ 5.55 ppm (2H, singlet, NH_2), 10.33 ppm (1H, singlet, OH) and 6.40 ppm (1H, singlet, 4-H). From these data the structure of **3** was determined to be 3-amino-5-(2-hydroxyphenyl)isoxazole. Therefore the structure of **2** was determined as 2-hydroxybenzimidoylacetamide oxime.

When the reduction was carried out till no more hydrogen was absorbed, **1** absorbed two molar equivalent of hydrogen and gave **4** whose structure was determined from the results of elemental analysis and mass spectrum measurement. The reduction of **2** in ethanol also afforded **4**. Since **4** was obtained from **3** by the catalytic reduction, the hydrogenation of **1** proceeded as follows: at first **1** absorbed one mole of hydrogen and gave **2**, in which N–O band of isoxazole ring was cleaved as reported by Casini, *et al.*[5] and then **2** was cyclized to **3** which absorbed one more mole of hydrogen to give **4**.

1) Part I: H. Uno, M. Kurokawa, K. Natsuka, Y. Yamato (the late), and H. Nishimura, *Chem. Pharm. Bull.* (Tokyo), **24**, 632 (1976).
2) A part of this work was presented at the 95th Annual Meeting of the Pharmaceutical Association of Japan, Nishinomiya, April, 1975.
3) Location: *33–94, Enokicho, Suita, Osaka.*
4) M. Shimizu, K. Yoshida, T. Karasawa, M. Masuda, M. Oka, T. Ito, C. Kamei, M. Hori, and K. Furukawa, *Experientia*, **30**, 405 (1974).
5) G. Casini, F. Gualtieri, and M.L. Stein, *J. Heterocyclic Chem.*, **6**, 279 (1969).

The reaction of **3** and hydroxylamine gave **5**. When heated in ethanol, **5** was easily cyclized to give **6**, which was analyzed to $C_9H_8O_2N_2$. The mass spectrum of **6** revealed the M^+ peak at *m/e* 176 but no fragment peak corresponding to  at *m/e* 121. The NMR spectrum of **6** revealed signals at δ 6.83 ppm (2H, singlet, NH_2), 9.76 ppm (1H, singlet, OH) and 5.57 ppm (1H, singlet, 4-H). From these data, the structure of **6** was determined to be 5-amino-3-(2-hydroxyphenyl)isoxazole, an isomer of **3**.

When treated with dilute hydrochloric acid (HCl), **6** gave 4-hydroxycoumarin (**7**) and with aqueous sodium bicarbonate, **6** gave 1,2-benzisoxazole-3-acetamide (**8**).[5]

1, 2 - Benzisoxazole - 3 - acetonitrile (**9**),[1] the starting material for the preparation of **1**, was reduced in the presence of Pd–C and gave **10**, which was easily hydrolysed with HCl and gave **11**. The reaction of **11** and hydroxylamine afforded **6** and **12**. Compound **12** had the same experimental formula as **11**, $C_9H_7O_2N$. The IR spectrum of **12** showed no absorption band due to the cyano group but absorption bands due to the imino and hydroxyl group at 3300 and 3100 cm^{-1}. The NMR spectrum revealed signals at δ 7.55 ppm (2H, singlet, NH_2), and 5.27 ppm (1H, singlet, vinyl proton). From these data the structure of **12** was determined to be 4-hydroxy-2-coumarinimine. By the treatment with triethylamine, **11** gave **12** quantitatively. The hydrolysis of **12** with diluted HCl gave **7** and this result supported the proposed structure of **12**.

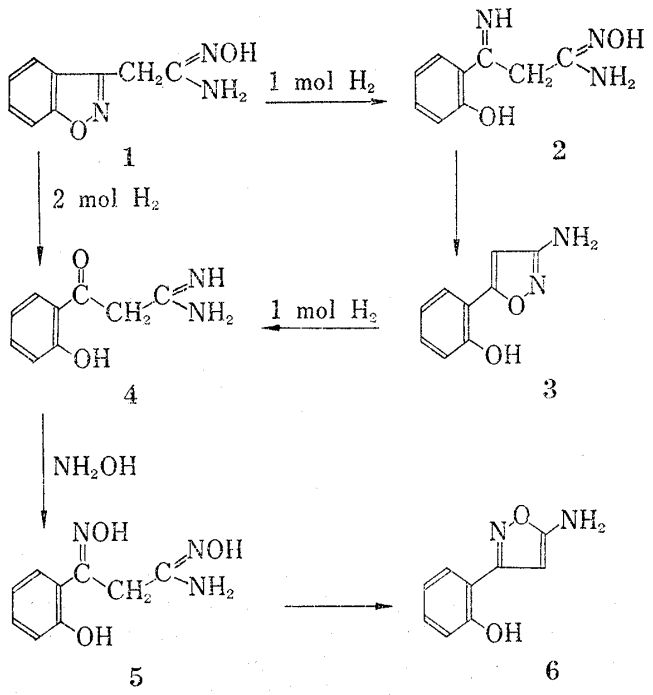


Chart 1

The catalytic reduction of **6** in the presence of Pd–C, gave **13**, which was also obtained by the reduction of **8**.[5] By the treatment with diluted HCl, **13** afforded **7**, **14** and **15**. The elemental analysis and mass spectrum measurement showed that **15** has the same experimental formula as that of **12**. The IR spectrum of **15** showed absorption bands due to the amino group at 3380 and 3200 cm^{-1}, and the carbonyl group at 1640—1600 cm^{-1}. The NMR spectrum revealed signals at δ 7.40 ppm (2H, singlet, NH_2) and 5.30 ppm (1H, singlet, vinyl proton). From these data, the structure of **15** was determined to be 4-aminocoumarin.

In 1962, Zagorevskii, *et al.*[6] reported that 4-aminocoumarin was obtained by the reaction of 4-chlorocoumarin and ammonia. They revised the structure of their compound obtained to be coumarylamide in the successive paper.[7] Therefore the present work was the first synthesis of 4-aminocoumarin.

Experimental[8]

2-Hydroxybenzenimidoylacetamide Oxime (**2**)——To 50 ml of EtOH were added **1**[1] (1.9 g) and 5% Pd-C (1 g). The mixture was submitted to the catalytic reduction at room temperature in the presence of hydrogen

6) V.A. Zagorevskii and N.V. Dudykina, *Zh. Obsch. Khim.*, **32**, 2384 (1962).
7) V.A. Zagorevskii, V.L. Savelev, and N.V. Dudykina, *Zh. Org. Khim.*, **4**, 2041 (1968).
8) All melting points are uncorrected. NMR spectra were taken with Varian A-60 spectrometer using TMS as an internal standard, and mass spectra with a Hitachi RMU-6L mass spectrometer.

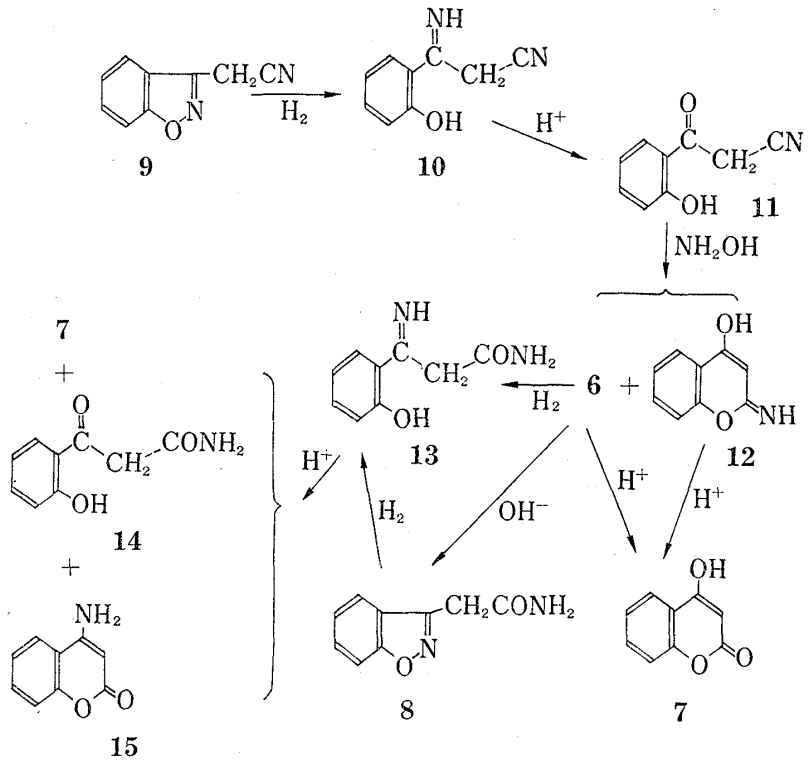
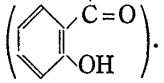
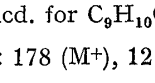


Chart 2

of atomospheric pressure.[9] The reaction was stopped when 320 ml of hydrogen was absorbed. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The resulting crystals were collected, dried and recrystallized from EtOH and acetone to give 1.1 g of **2**, mp 155—158°. *Anal.* Calcd. for $C_9H_{11}O_2N_3$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.23; H, 5.88; N, 21.21. Mass Spectrum *m/e*: 193 (M^+), 176, 161, 121, 120.

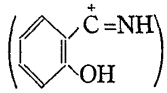
3-Amino-5-(2-hydroxyphenyl)isoxazole (3)——The solution of **2** (0.3 g) in 10 ml of EtOH was refluxed for 1 hr. The solvent was removed *in vacuo* and the residue was crystallized from EtOH and H_2O to give 0.25 g of **3**, mp 176—178°. *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.35; H, 4.57; N, 15.90. Found: C, 61.24; H, 4.71; N, 15.69. NMR (DMSO-d_6) δ: 5.55 (2H, singlet, NH_2), 10.33 (1H, singlet, OH), 6.40 (1H, singlet, 4-H).

Mass Spectrum *m/e*: 176 (M^+), 121  .

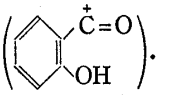
2-Hydroxybenzoylacetamidine (4)——To 150 ml of EtOH was added **1** (9.6 g) and 5% Pd-C (5 g). The mixture was submitted to the catalytic reduction. After 2.3 liter of hydrogen was absorbed, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was recrystallized from ether to give 6.0 g of **4**, mp 174—177°. *Anal.* Calcd. for $C_9H_{10}O_2N_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.49; H, 5.78; N, 15.49. Mass Spectrum *m/e*: 178 (M^+), 121  .

Oxime of 2-Hydroxybenzoylacetamidine (5)——To the ethanolic solution of NH_2OH (NH_2OH HCl 1.95 g, Na 0.6 g and EtOH 20 ml) was dissolved **3** (1.0 g) and the solution was allowed to stand at room temperature for 10 days. The solvent was removed *in vacuo*. The residue was dissolved in AcOEt and insoluble material was filtered off. The filtrate was concentrated and the resulting crystals were recrystallized from AcOEt to give 0.5 g of **5**, mp 122—130°. *Anal.* Calcd. for $C_9H_{11}O_3N_3$: C, 51.66; H, 5.30; N, 20.08. Found: C, 51.52; H, 5.33; N, 20.27.

5-Amino-3-(2-hydroxyphenyl)isoxazole (6)——The solution of **3** (1.5 g) in 60 ml of EtOH was refluxed for 3 hr. The solvent was removed *in vacuo* and the residue was recrystallized from $CHCl_3$ to give 1.5 g of **6**, mp 93—95°. *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.91. Found: C, 61.65; H, 4.56; N, 15.91.

2-Hydroxybenzimidoylacetonitrile (10)——To the solution of **9**[1] (5 g) in 100 ml of EtOH was added 5% Pd-C (2.0 g). The mixture was submitted to the catalytic reduction. After the catalyst was filtered off, the solvent was removed *in vacuo*. The residue was washed with *n*-hexane and dried to give 4.6 g of **10**. Mass Spectrum *m/e*: 160 (M^+), 120  . IR ν_{max}^{KBr} cm^{-1}: 3350, 3100—2600 (NH and OH), 2140 (CN).

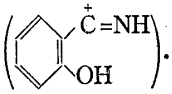
9) All catalytic reductions were carried out under this condition unless otherwise mentioned.

2-Hydroxybenzoylacetonitrile (11)——To 70 ml of 5% HCl was added **10** (4.6 g) under stirring. The mixture was stirred for 30 min. The resulting crystals were extracted with benzene. The benzene extract was washed with H_2O and dried over Na_2SO_4. The solvent was removed and the residue was crystallized from benzene to give 2.0 g of **11**, mp 106—109°. *Anal.* Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.90; H, 4.27; N, 8.62. NMR (DMSO-d_6) δ: 4.63 (2H, singlet, -CO-C$\underline{H_2}$CN), 11.10 (1H, singlet, OH). Mass Spectrum *m/e*: 161 (M^+), 121  .

Reaction of 11 with NH_2OH——To the ethanolic solution of NH_2OH (NH_2OH HCl 2.6 g, Na 0.7 g and EtOH 50 ml) was added **11** (1.0 g). The mixture was heated at 80° for 3 hr. The solvent was removed *in vacuo* and the residue was washed with H_2O, dried and then added to 50 ml of $CHCl_3$. The insoluble material was collected and recrystallized from EtOH to give 0.2 g of **12**, mp 285—292° (decomp.). *Anal.* Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.16; H, 4.15; N, 8.86.

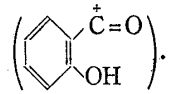
The $CHCl_3$ solution was evaporated to dryness and the oily residue was chromatographed on silicagel column. The $CHCl_3$ eluate was concentrated and the residue was crystallized from $CHCl_3$ to give 0.15 g of **6**, mp 93—95°.

4-Hydroxy-2-coumarinimine (12)——To 6 ml of Et_3N was added **6** (0.5 g) and the mixture was heated at 60° for 2 hr. The resulting crystals were collected, washed with benzene and dried to give 0.44 g of **12**, mp 285—292° (decomp.).

2-Hydroxybenzimidoylacetamide (13)——a) From **7**: To the solution of **7** (0.1 g) in 10 ml of EtOH was added 5% Pd-C (0.1 g). The mixture was submitted to the catalytic reduction till no more hydrogen was absorbed. The catalyst was filtered off and the filtrate was concentrated *in vacuo*, and 0.11 g of **13** was obtained as an oily residue. Mass Spectrum *m/e*: 178 (M^+), 120  . IR ν_{max}^{liq} cm^{-1}: 3500—3100 (OH and NH_2).

b) From **8**: To 100 ml of EtOH were added **8** (4.0 g) and 5% Pd-C (3.0 g). The mixture was submitted to the catalytic reduction. After the catalyst was removed, the filtrate was concentrated and 4 g of **13** was obtained.

Hydrolysis of 13——To the solution of **13** (2.7 g) in 100 ml of AcOEt was added 50 ml of 5% HCl. The mixture was shaken till the yellow color of the solution disappeared. Then the organic layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was washed with AcOEt and crude **15**, which was slightly soluble in AcOEt, was obtained. The recrystallization from EtOH gave 0.15 g of pure **15**, mp 241—243°. *Anal.* Calcd. for $C_9H_7O_2N$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.40; H, 4.65; N, 8.41.

The AcOEt washings was evaporated and the residue was crystallized from small amount of AcOEt to give 0.15 g of **14**, mp 135—138°. *Anal.* Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.70; H, 4.73; N, 7.89. Mass Spectrum *m/e*: 179 (M^+), 121  . IR ν_{max}^{KBr} 3450—3300 (NH_2), 3200 (OH), 1635 (CO).

The aqueous layer was allowed to stand in a refrigerator overnight. The resulting precipitate was collected, washed with H_2O and dried to give 1.5 g of **7**.

4-Aminocoumarin (15)——To 30 ml of 5% HCl was added **13** (1.5 g) and the mixture was allowed to stand at room temperature for 3 hr. The resulting precipitate was collected and recrystallized from EtOH to give 500 mg of **15**, mp 241—243°.

Acknowledgement The authors are grateful to Dr. H. Takamatsu, the Director of these laboratories, Drs H. Kaneko and S. Minami for their encouragement throughout the course of this work. Thanks are also due to the staffs of analytical section of these laboratories for their spectral measurement and elemental analyses.