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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 Compounds²⁾

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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-hydroxybenzoylacetamidine (**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 antiserpentic 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 atmospheric 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 $\left(\text{C}_6\text{H}_4\text{C}(\text{OH})=\text{O}^+ \right)$ 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 bond 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 $\left(\text{C}_6\text{H}_4\text{C}(\text{OH})=\text{O}\right)^+$ 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**.

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.

Experimental⁸⁾

2-Hydroxybenzenimidoylacetonitrile 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

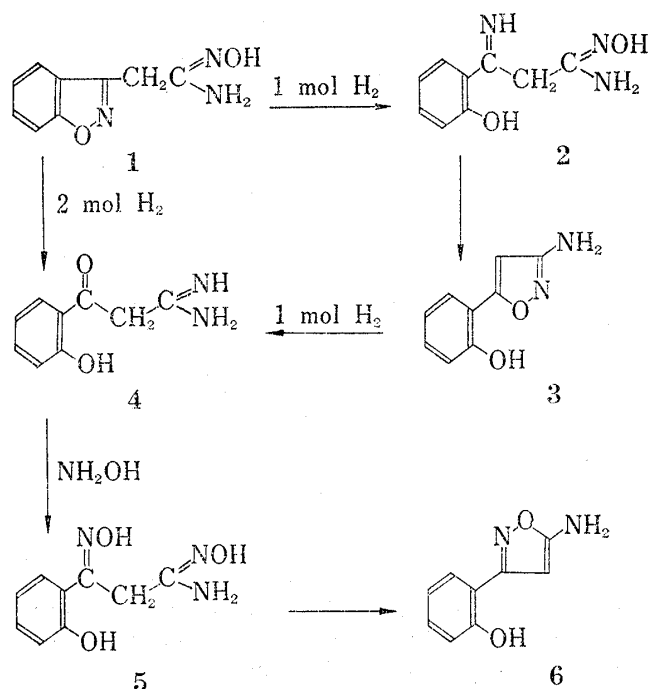


Chart 1

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.

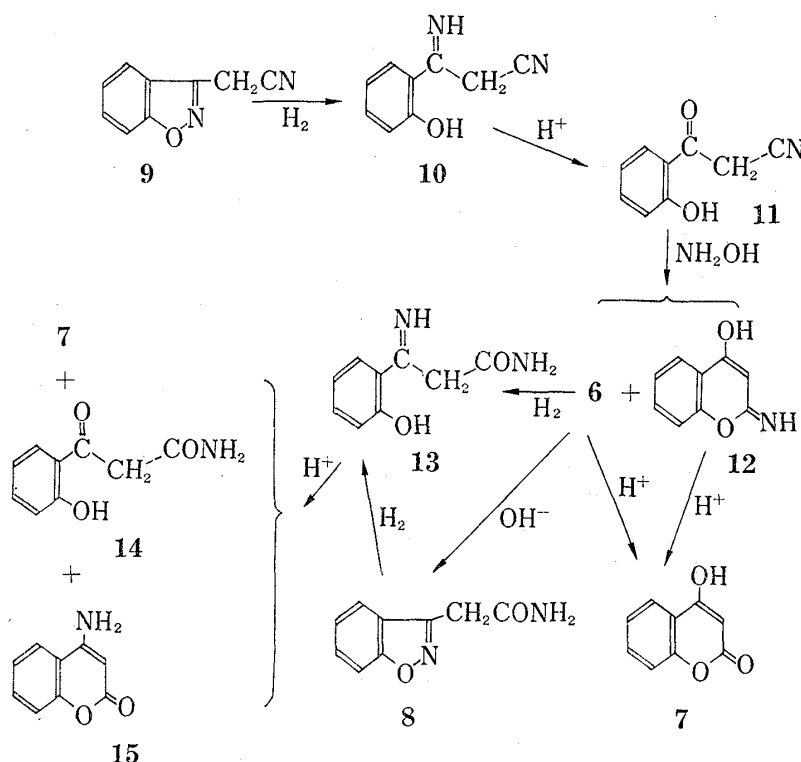


Chart 2

of atmospheric 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 ($\text{C}_6\text{H}_4\text{OH}-\text{C}^+=\text{O}$).

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 ($M^+-CH_2C(=NH)NH_2$).

Oxime of 2-Hydroxybenzoylacetamidine (5)—To the ethanolic solution of NH_2OH ($NH_2OH \cdot HCl$ 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.

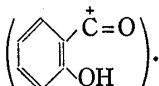
5-Amino-3-(2-hydroxyphenyl)isoxazole (6)—The solution of 3 (1.5 g) in 60 ml of EtOH was refluxed for 3 hr. The solvent was removed *in vacuo* and the residue was recrystallized from $CHCl_3$ to give 1.5 g of 6, mp 93—95°. *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.91. Found: C, 61.65;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

2-Hydroxybenzimidoylacetamidine (10)—To the solution of 9¹⁾ (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 ($\text{C}_6\text{H}_4\text{OH}-\text{C}^+=\text{NH}$). 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 H₂O and dried over Na₂SO₄. The solvent was removed and the residue was crystallized from benzene to give 2.0 g of 11, mp 106–109°. *Anal.* Calcd. for C₉H₇O₂N: 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-CH₂CN), 11.10 (1H, singlet, OH).

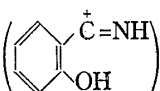
Mass Spectrum *m/e*: 161 (M⁺), 121 .

Reaction of 11 with NH₂OH—To the ethanolic solution of NH₂OH (NH₂OH 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 H₂O, dried and then added to 50 ml of CHCl₃. The insoluble material was collected and recrystallized from EtOH to give 0.2 g of 12, mp 285–292° (decomp.). *Anal.* Calcd. for C₉H₇O₂N: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.16; H, 4.15; N, 8.86.

The CHCl₃ solution was evaporated to dryness and the oily residue was chromatographed on silicagel column. The CHCl₃ eluate was concentrated and the residue was crystallized from CHCl₃ to give 0.15 g of 6, mp 93–95°.

4-Hydroxy-2-coumarinimine (12)—To 6 ml of Et₃N 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.).

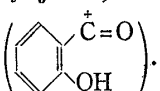
2-Hydroxybenzimidoylacetamide (13)—a) From 7: To the solution of 7 (0.1 g) in 10 ml of EtOH was added 5% Pd-C (0.1 g). The mixture was submitted to the catalytic reduction till no more hydrogen was absorbed. The catalyst was filtered off and the filtrate was concentrated *in vacuo*, and 0.11 g of 13 was ob-

tained as an oily residue. Mass Spectrum *m/e*: 178 (M⁺), 120 . IR $\nu_{\text{max}}^{\text{liq}}$ cm⁻¹: 3500–3100 (OH and NH₂).

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 H₂O, dried over Na₂SO₄ 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 C₉H₇O₂N: 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 C₉H₉O₃N: 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 $\nu_{\text{max}}^{\text{KBr}}$ 3450–3300 (NH₂), 3200 (OH), 1635 (CO).

The aqueous layer was allowed to stand in a refrigerator overnight. The resulting precipitate was collected, washed with H₂O 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°.

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