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Studies on 3-Substituted 1,2-Benzisoxazole Derivatives. III.[1]
Mannich Reaction of 1,2-Benzisoxazol-3-acetic Acid

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Mannich reaction of 1,2-benzisoxazol-3-acetic acid (1) with excess of amine and formalin afforded 3-(1-aminomethyl)vinyl-1,2-benzisoxazole (2). The mechanism of the reaction was discussed.

Keywords——1,2-benzisoxazol-3-acetic acid; Mannich reaction; active methylene; 3-(1-aminomethyl)vinyl-1,2-benzisoxazole; mechanism

Yakhontov, *et al.*[3] have reported that Mannich reaction of malonic acid with piperazine and formalin afforded 1,4-bis(2-carboxy-2-propen-1-yl)piperazine. In the previous paper,[4] we have suggested that the α-methylene group of 1,2-benzisoxazol-3-acetic acid (**1**) is unusually activated to an electrophile. The α-methylene group of **1** seemed to have a similar structural feature to the methylene group of malonic acid. Therefore, it was expected that Mannich reaction of **1** might afford 3-(1-aminomethyl)vinyl-1,2-benzisoxazole derivatives (**2**).

In acetic acid, **1** was treated with excess of dimethylamine and formalin (each 5 equivalent moles) at 60° for 3 hours. The basic product was separated and converted to its hydrochloride (**2a**). Compound **2a**, mp 182—184°, was analyzed to $C_{12}H_{14}N_2O \cdot HCl$ and revealed the M^+ peak at *m/e* 202 in its mass spectrum. The nuclear magnetic resonance spectrum of **2a** in dimethylsulfoxide-d_6 revealed signals of six protons of two methyl groups at δ 2.85 ppm as singlet and two protons of *exo*-methylene group at δ 6.59 and 6.72 ppm. The infrared spectrum of **2a** did not show any absorption band due to a carboxyl group. From these data the structure of **2a** was determined to be expected 3-(1-dimethylaminomethyl)vinyl-1,2-benzisoxazole (**2a**).

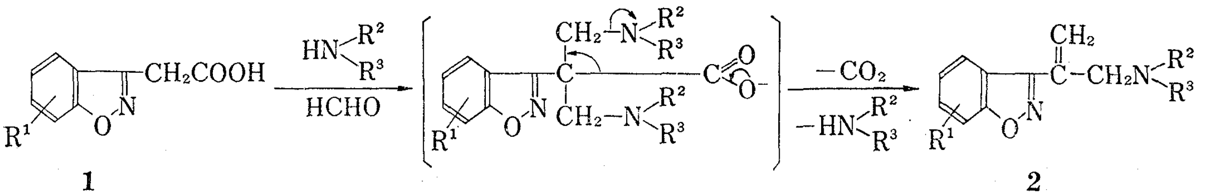

Chart 1

Mannich reaction of **1** with several primary and secondary amines afforded same type of products. Results of these reactions were summarized in Table.

Mannich reaction of 3-methyl-1,2-benzisoxazole (**3**) and methyl 1,2-benzisoxazol-3-acetate (**4**) were also investigated. By the reaction of **3** with excess of dimethylamine and formalin in acetic acid at 100° for 10 hours, only the starting material (**3**) was recovered. Compound **4** afforded an unknown neutral substance and small amount of **2a** by the reaction with excess

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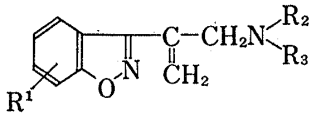
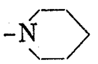
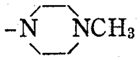
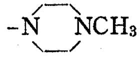
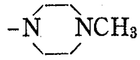
[1] Part II: H. Uno, M. Kurokawa, and H. Nishimura, *Chem. Pharm. Bull.* (Tokyo), **24**, 644 (1976).
[2] Location: *33–94, Enokicho, Suita, Osaka.*
[3] L.N. Yakhontov, L.B. Mrachkovskaya, A.I. Ermakov, K.F. Turchin, and T.F. Vlasova, *Zh. Org. Khim.*, **10**, 868 (1974).
[4] H. Uno, M. Kurokawa, K. Natsuka, Y. Yamato (the late), and H. Nishimura, *Chem. Pharm. Bull.* (Tokyo), **24**, 632 (1976).

of dimethylamine and formalin at 70° for 4 hours. Compound **4** may be hydrolyzed during the reaction to **1**, which may be converted to **2a** by Mannich reaction.

The mechanism of the reaction might be as shown in chart. At first, two aminomethyl groups substitute the methylene group and then one of amino groups leaves with decarboxylation, to form the *exo*-methylene group. In this reaction the carboxyl group seemed to play an important role.

Table I.



Compound No.	R^1	$N<^{R^2}_{R^3}$	mp (°C) (Solvent)	Yield (%)	Formula	Analysis (%) Calcd. (Found)				
						C	H	N	Cl	F
2a	H	$-N(CH_3)_2$	182—184 (EtOH)	53	$C_{12}H_{14}N_2O \cdot HCl$	60.37 (60.36)	6.33 (6.49)	11.74 (11.80)	14.85 (15.02)	
2b	H		193—196 (EtOH)	74	$C_{15}H_{18}N_2O \cdot HCl$	64.62 (64.56)	6.87 (6.78)	10.05 (9.86)	12.72 (12.84)	
2c	H		190—200 (MeOH)	41	$C_{14}H_{17}H_3O \cdot 2HCl$ $1/2\ H_2O$	51.69 (51.87)	6.19 (6.29)	12.92 (12.72)	21.80 (21.90)	
2d	H		190—200 (EtOH)	30	$C_{15}H_{19}N_3O \cdot 2HCl$ $4H_2O$	44.77 (45.02)	7.26 (6.69)	10.44 (10.47)	17.62 (17.83)	
2e	H	$-N<^{CH_3}_{CH_2CH_2OH}$	129—132 (EtOH)	58	$C_{13}H_{16}N_2O \cdot$ $3/2\ (COOH)_2$	52.45 (52.53)	4.95 (5.06)	7.65 (7.50)		
2f	H	$-NHCH_3$	220—223 (EtOH)	30	$C_{11}H_{12}N_2O \cdot HCl$	58.80 (58.67)	5.83 (6.02)	12.47 (12.50)	15.78 (15.89)	
2g	H		188—190 (EtOH)	30	$C_{14}H_{16}N_2O_2 \cdot HCl$	59.89 (59.35)	6.10 (5.86)	9.98 (9.81)	12.63 (12.90)	
2h	5-F		205—210 (MeOH)	40	$C_{14}H_{16}FN_3O \cdot 2HCl$ H_2O	47.76 (47.77)	5.72 (5.75)	11.93 (11.85)	20.13 (20.12)	5.39 (5.10)
2i	5-Cl		185—195 (MeOH)	45	$C_{15}H_{18}ClN_3O \cdot 2HCl$ $1/2H_2O$	48.20 (48.04)	5.66 (5.83)	11.24 (10.69)	28.46 (27.63)	
2j	6-F		175—180 (EtOH)	20	$C_{15}H_{18}FN_3O \cdot 2HCl$ $2H_2O$	46.88 (46.90)	6.30 (6.50)	10.94 (10.74)	18.45 (18.39)	4.94 (4.99)

Experimental[5]

Mannich Reaction of 1,2-Benzisoxazol-3-acetic Acid (1)——To a solution of appropriate amine (0.2 mol) and formalin (40%, 0.2 mol) in AcOH (35 ml) was added **1** (0.04 mol). The mixture was stirred at 60° for 3 hr. After cooled, the mixture was made alkaline with conc. NaOH and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The residual oil was converted to hydrochloride or oxalate and recrystallized from MeOH or EtOH. Melting points, yields and analytical data were summarized in Table.

Mannich Reaction of Methyl 1,2-Benzisoxazol-3-acetate (4)——To a solution of dimethylamine (40% aq. sol, 8.9 g) and formalin (40% aq. sol, 5.9 g) in AcOH (13 g) was added **4** (3.0 g). The mixture was stirred at 70° for 4 hr. The crystal deposited with cooling was collected, washed with H_2O and recrystallized from benzene to give 0.8 g of unknown substance, mp 143—145°. *Anal.* Calcd. for $(C_{11}H_9NO_3)_n$: C, 65.02; H, 4.46; N, 6.90. Found: C, 65.06; H, 4.61; N, 6.75. IR ν_{max}^{KBr} cm^{-1}: 1740, 1685, 1590.

The filtrate and aqueous washings were combined, made alkaline with conc. NaOH and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried over Na_2SO_4 and evaporated. As the residue, 0.5 g (16%) of the free base of **2a** was obtained.

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5) 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-6 mass spectrometer.