SYNTHESIS OF 2-(4-ARYL-1*E*,3*E*-BUTADIENYL)BENZOXAZOLES BY THE HORNER-WADSWORTH-EMMONS REACTION

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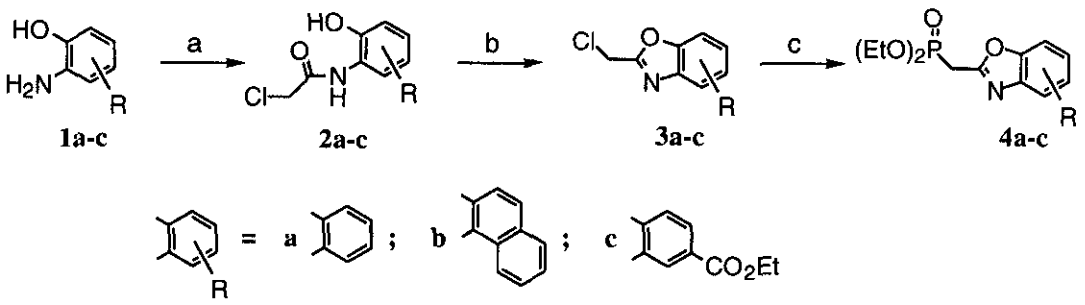
Abstract - 2-(4-Aryl-1*E*,3*E*-butadienyl)benzoxazole derivatives were synthesized by the Horner-Wadsworth-Emmons reaction of 2-phosphorylmethyl-benzoxazoles with cinnamaldehydes in fair to good yield.

In our antiasthmatic drug research project, we planned to synthesize a variety of 2-(4-aryl-1*E*,3*E*-dienyl)benzoxazole derivatives. There are many kinds of 2-substituted benzoxazoles in natural products,[1] synthetic drugs[2] and fluorescent whiteners.[3] However, 2-(4-aryl-1*E*,3*E*-dienyl) derivatives have not been reported.

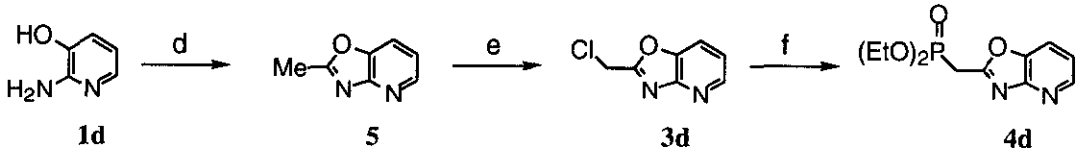
Recently, synthesis of 2-styrylbenzoxazole by means of the Horner-Wadsworth-Emmons (HWE) reaction of 2-phosphorylmethylbenzoxazole with benzaldehyde was reported.[4] We also investigated this type of reaction for the synthesis of a variety of 2-(4-aryl-1*E*,3*E*-dienyl)oxazoles using cinnamaldehyde derivatives with 2-phosphorylmethylbenzoxaloles and 2-phosphorylmethyloxazolopyridine.

2-Phosphorylmethylbenzoxaloles (**4a-c**) were prepared in three steps from *o*-aminophenols (**1a-c**) by i) *N*-chloroacetylation with chloroacetyl chloride in the presence of $NaHCO_3$; ii) oxazole formation by treatment with ethyl polyphosphate,[5] and iii) the Arbuzov reaction with triethyl phosphite. For the preparation of oxazolopyridylmethyl phosphonate (**4d**), the 2-chloromethyl precursor (**3d**)[6] was obtained by trichloroisocyanuric acid-mediated chlorination[7] of **5**, which was derived from **1d** by cyclization with triethyl orthoacetate.[8]

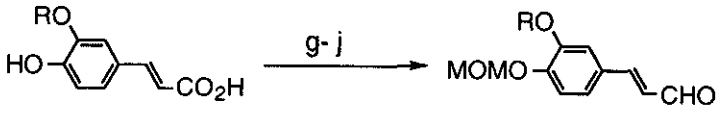
Aldehydes (**7a**)[9] and (**7b**) were prepared from ferulic acid (**6a**) and caffeic acid (**6b**) by esterification,



Reagents: (a) $ClCH_2COCl$, $NaHCO_3$, acetone, room temperature; (b) ethyl polyphosphate, $ClCH_2CH_2Cl$, reflux; (c) $(EtO)_3P$, 150 °C.



Reagents: (d) $MeC(OEt)_3$, 100 °C; (e) trichloroisocyanuric acid, CH_2Cl_2, 40°C; (f) $(EtO)_3P$, 150 °C.



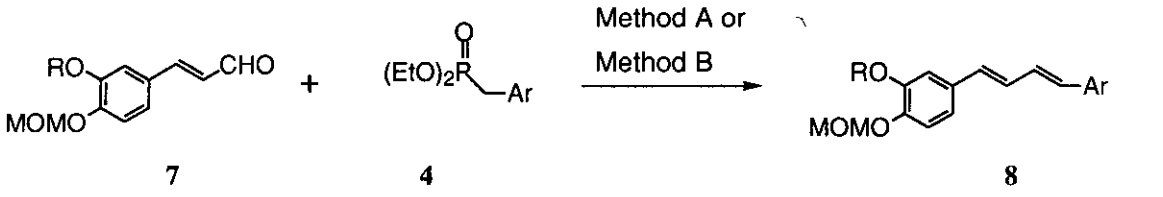
6a R=Me
6b R=H

7a R=Me
7b R=MOM

Reagents: (g) EtOH, H_2SO_4, reflux: (h) MOMCl, $^iPr_2NEt$, CH_2Cl_2, room temperature; (i) DIBAH, THF, -78 °C; (j) MnO_2, CH_2Cl_2, room temperature.

protection of the ring hydroxyl group as the MOM ether, DIBAH reduction to alcohol, and oxidation by MnO_2.

Our preliminal investigation of the HWE reaction was carried out with sodium hydride as a base. Typically, 2-phosphorylmethylbenzoxalole (**4a**)[4] was treated with sodium hydride (1.1 eq.) in tetrahydrofuran at -15 °C for 10 min under an argon atmosphere followed by the addition of aldehyde (**7a**) (1 eq.) and stirring at 0 °C for 2.5 h to give **8a** in 79% yield (Method A). Similarly, the phosphonates (**4b** and **4c**) afforded **8b**, **8c** and **8d** in good yields (Table). The geometry of the newly produced double bonds was assigned as *E* based on ^1H nmr spectra which exhibits a doublet of J = 15-16 Hz at *ca.* 6.6-6.8 ppm.



7 4 8

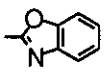
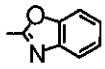
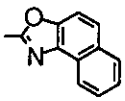
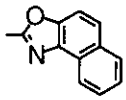
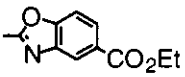
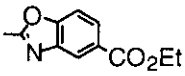
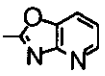
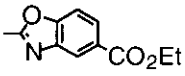
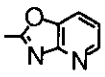
	R		Ar		R	Ar
7a	Me	**4a**		**8a**	Me	
7b	MOM	**4b**		**8b**	Me	
		4c		**8c**	Me	
		4d		**8d**	MOM	
				8e	Me	

Table. The Horner-Wadsworth-Emmons Reaction of 2-Phosphoryl-methylbenzoxazoles with Cinnamaldehydes

entry	Aldehyde	Phosphonate	Method	Product	Yield (%)
1	**7a**	**4a**	A	**8a**	79
2	**7a**	**4a**	B	**8a**	67
3	**7a**	**4b**	A	**8b**	69
4	**7a**	**4c**	A	**8c**	69
5	**7b**	**4c**	A	**8d**	59
6	**7a**	**4d**	A	**8e**	6
7	**7a**	**4d**	B	**8e**	47

On the other hand, the HWE reaction of oxazolopyridylmethyl phosphonate (**4d**) did not proceed smoothly resulting in only a 6% yield of **8e**, but a much higher yield was successfully obtained under phase transfer catalytic conditions.[10]

Thus, the reaction of **4d** and **7a** in the presence of tetrabutylammonium bromide (0.2 eq.), under 50% $NaOH/CH_2Cl_2$ system at room temperature for 1 h (Method B) afforded **8e** in 47% yield. This phase transfer procedure was also applied to **4a** to give **8a** in 67% yield.

The MOM group of aryldienyloxazoles (**8a-e**) were deprotected. The bioassay of the resulting phenolic compounds is undergoing investigation.

In conclusion, this work provides a general synthesis for a variety of 2-(4-arylbutadienyl)benzoxazoles and for 2-(4-arylbutadienyl)oxazolopyridines.

EXPERIMENTAL

All mps are uncorrected. The ^1H nmr spectra were determined on a Varian Gemini 200 spectrometer using tetramethylsilane as an internal standard. The ir spectra were recorded with a JASCO VALOR III Fourier transform spectrophotometer.

N-(2-Hydroxyphenyl)choloroacetoamide (2a).

To a stirred suspension of 2-aminophenol (**1a**) (2.05 g, 18.8 mmol) and $NaHCO_3$ (3.16 g, 37.6 mmol) in acetone (30 ml) under an argon atmosphere was added, dropwise, chloroacetyl chloride (1.57 ml, 19.7 mmol). The reaction mixture was stirred for 2 h at room temperature, then the precipitate was separated by suction and washed with acetone. The combined filtrate was concentrated under vacuum and the residue was recrystallized from ethyl acetate to give **2a** as colorless crystals (2.58 g, 74%), mp 139-140.5 °C; ir (KBr): 1656 cm^{-1}; ^1H nmr ($CDCl_3$) δ 4.27 (s, 2H), 6.85-7.10 (m, 2H), 7.10-7.35 (m, 2H), 7.85 (br s, 1H), 8.55 (br s, 1H). Anal. Calcd for $C_8H_8NO_2Cl$: C, 51.76; H, 4.34; N, 7.55. Found: C, 51.46; H, 4.29; N, 7.48.

N-(2-Hydroxy-1-naphthyl)chloroacetoamide (2b).

This product was prepared by a method similar to that of **2a**, from 1-amino-2-naphthol hydrochloride (**1b**) (85% purity, 2.51 g, 10.9 mmol) and was washed with acetone-Et_2O (1 : 10) to give **2b** as a red solid (2.21

g, 86%), which was used without further purification for the next step.

Ethyl 3-(*N*-Chloroacetyl)amino-4-hydroxybenzoate (2c).

This product was prepared by a method similar to that of **2a**, from ethyl 3-amino-4-hydroxybenzoate hydrochloride (**1c**) (6.35 g, 29.2 mmol) and was purified by recrystallization from acetone-hexane to afford **2c** as a gray powder (6.58 g, 87%). Recrystallization from MeOH gave colorless prisms, mp 178-179 °C; ir (KBr): 1702, 1665 cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.29 (t, J = 7 Hz, 3H), 4.26 (q, J = 7 Hz, 2H), 4.40 (s, 2H), 6.98 (d, J = 9 Hz, 1H), 7.64 (dd, J = 9 Hz, 2 Hz, 1H), 8.56 (d, J = 2 Hz, 1H), 9.57 (s, 1H), 10.97 (s, 1H). Anal. Calcd for $C_{11}H_{12}NO_4Cl$: C, 51.27; H, 4.69; N, 5.44. Found: C, 51.31; H, 4.62; N, 5.56.

2-Chloromethylbenzoxazole (3a).

To a solution of ethyl polyphosphate (10.0 g) in 1,2-dichloroethane (30 ml) under an argon atmosphere was added, portionwise, **2a** (2.50 g, 13.5 mmol) and the mixture was heated to reflux for 2 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (50 ml), washed with water, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2-hexane = 1 : 3) to afford **3a** as a colorless oil (1.47 g, 60%) (lit.,[11] oil).

2-Chloromethylnaphth[1,2-*d*]oxazole (3b).

This product was prepared by a method similar to that of **3a**, from **2b** (2.04 g, 8.66 mmol) and was purified by flash column chromatography on silica gel (CH_2Cl_2-hexane = 1 : 12) to afford **3b** as colorless crystals (1.01 g, 54%), mp 104-105.5 °C (from CH_2Cl_2-hexane); ^1H nmr ($CDCl_3$) δ 4.85 (s, 2H), 7.45-7.80 (m, 3H), 7.81 (d, J = 9 Hz, 1H), 7.95 (d, J = 8 Hz, 1H), 8.46 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{12}H_8NOCl$: C, 66.22; H, 3.70; N, 6.44. Found: C, 66.42; H, 3.65; N, 6.37.

Ethyl 2-Chloromethylbenzoxazole-5-carboxylate (3c).

This product was prepared by a method similar to that of **3a**, from **2c** (5.00 g, 19.4 mmol) and was purified by flash column chromatography on silica gel (CH_2Cl_2-hexane = 1 : 3) to afford **3c** as colorless crystals (3.59 g, 77%), mp 90-90.5 °C (from CH_2Cl_2-hexane); ir (KBr): 1713, 1623, 1577 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.43 (t, J = 7 Hz, 3H), 4.42 (q, J = 7 Hz, 2H), 4.78 (s, 2H), 7.60 (d, J = 9 Hz, 1H), 8.15 (dd, J = 9 Hz, 1.5 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H). Anal. Calcd for $C_{11}H_{10}NO_3Cl$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.23;

H, 4.15; N, 5.86.

2-(Diethoxyphosphorylmethyl)benzoxazole (4a).

A stirred mixture of **3a** (987 mg, 5.89 mmol) and triethyl phosphite (1.70 ml, 9.82 mmol) was heated at 150 °C for 3.5 h, and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2-ethyl acetate = 5 : 1) to give **4a** as a brown oil (1.55 g, 98%) (lit.,[4] oil).

2-(Diethoxyphosphorylmethyl)naphth[1,2-*d*]oxazole (4b).

This product was prepared by a method similar to that of **4a**, from **3b** (784 mg, 3.60 mmol) and was purified by flash column chromatography on silica gel (CH_2Cl_2-ethyl acetate = 15 : 1) to afford **4b** as a yellow oil (1.15 g, 100%); ir (neat): 1590 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.35 (t, J = 7 Hz, 6H), 3.68 (d, J = 22 Hz, 2H), 4.10-4.35 (m, 4H), 7.50-7.70 (m, 3H), 7.80 (d, J = 9 Hz, 1H), 7.97 (d, J = 8 Hz, 1H), 8.48 (d, J = 8 Hz, 1H).

Ethyl 2-(Diethoxyphosphorylmethyl)benzoxazole-5-carboxylate (4c).

This product was prepared by a method similar to that of **4a**, from **3c** (3.40 g, 14.2 mmol) and was purified by flash column chromatography on silica gel (CH_2Cl_2-ethyl acetate = 19 : 1) to afford **4c** as colorless crystals (4.41 g, 91%), mp 71-72 °C (from Et_2O-hexane); ir (KBr): 1700, 1623 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 6H), 1.42 (t, J = 7 Hz, 3H), 3.59 (d, J = 22 Hz, 2H), 4.18 (q, J = 7 Hz, 2H), 4.22 (q, J = 7 Hz, 2H), 4.41 (q, J = 7 Hz, 2H), 7.56 (d, J = 9 Hz, 1H), 8.10 (dd, J = 9 Hz, 1.5 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H). Anal. Calcd for $C_{15}H_{20}NO_6P$: C, 52.79; H, 5.91; N, 4.10. Found: C, 52.88; H, 5.85; N, 4.14.

2-Methyloxazolo[4,5-*b*]pyridine (5).

A stirred mixture of 2-amino-3-hydroxypyridine (**1d**) (4.03 g, 36.6 mmol) and triethyl orthoacetate (22.4 g, 138 mmol) under an argon atmosphere was heated at 100 °C for 7 h. Excess orthoacetate was removed under vacuum, and the residue was recrystallized from hexane to give **5** as slightly brown needles (4.20 g, 86%), mp 66-68 °C (lit.,[8b] mp 67-69 °C).

2-Chloromethyloxazolo[4,5-*b*]pyridine (3d).

A stirred mixture of **5** (2.27 g, 16.9 mmol) in 1,2-dichloroethane (100 ml) and trichloroisocyanuric acid (4.33 g, 18.0 mmol) was heated to reflux for 3 h. After cooling, the precipitate was separated by suction and

washed with CH_2Cl_2. The combined filtrate was concentrated under vacuum and the residue was purified by column chromatography on silica gel (CH_2Cl_2). The first fraction gave 2-trichloromethyloxazolo[4,5-*b*]pyridine as a brown solid (2.30 g, 58%), mp 100-103 °C (from CH_2Cl_2-hexane). The second fraction afforded 2-dichloromethyloxazolo[4,5-*b*]pyridine as a brown solid (320 mg, 9%), mp 63-65 °C (from CH_2Cl_2-hexane). The third fraction gave **3d** as a brown solid (760 mg, 27%), mp 113 °C (decomp., from CH_2Cl_2-hexane) (lit.,[6] mp 115-118 °C).

2-(Diethoxyphosphorylmethyl)oxazolo[4,5-*b*]pyridine (4d).

This product was prepared by a method similar to that of **4a**, from **3d** (520 mg, 3.10 mmol) and was purified by column chromatography on silica gel (CH_2Cl_2-acetone = 15 : 1) to afford **4d** as a brown oil (530 mg, 64%); ^{1}H nmr ($CDCl_3$) δ 1.36 (t, J = 7 Hz, 6H), 3.64 (d, J = 22 Hz, 2H), 4.10-4.35 (m, 4H), 7.32 (dd, J = 8 Hz, 5 Hz, 1H), 7.85 (dd, J = 8 Hz, 1.5 Hz, 1H), 8.58 (dd, J = 5 Hz, 1.5 Hz, 1H).

Method A. The HWE Reaction Under Homogeneous Conditions. 2-[(1*E*,3*E*)-4-(3-Methoxy-4-methoxymethoxyphenyl)-1,3-butadienyl]benzoxazole (8a).

To a stirred suspension of NaH (60% in oil, 34 mg, 0.858 mmol) in tetrahydrofuran (1 ml) under an argon atmosphere at -15 °C was added, dropwise, a solution of phosphonate (**4a**) (210 mg, 0.780 mmol) in tetrahydrofuran (1.5 ml). The mixture was stirred for 8 min, and then aldehyde (**7a**) was added in one portion. The mixture was allowed to warm to 0 °C and stirred for 2.5 h, then quenched by the slow and careful addition of EtOH (0.5 ml). The mixture was diluted with CH_2Cl_2, passed through a short column of silica gel (CH_2Cl_2-EtOH = 30 : 1 as an eluent) and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2) to give **8a** as a yellow solid (208 mg, 79 %), mp 123-125 °C (from CH_2Cl_2-MeOH); ir (KBr): 1630, 1585 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.53 (s, 3H), 3.95 (s, 3H), 5.26 (s, 2H), 6.60 (d, J = 16 Hz, 1H), 6.80-7.90 (m, 10H). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.26; H, 5.67; N, 4.14.

2-[(1*E*,3*E*)-4-(3-Methoxy-4-methoxymethoxyphenyl)-1,3-butadienyl]naphth[1,2-*d*]oxazole (8b).

Yield 69%. Yellow solid, mp 137.5-138 °C (from CH_2Cl_2-MeOH); ir (KBr): 3447, 1592 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.53 (s, 3H), 3.97 (s, 3H), 5.27 (s, 2H), 6.72 (d, J = 16 Hz, 1H), 6.85-7.20 (m, 5H), 7.50-7.70 (m, 4H), 7.79 (d, J = 9 Hz, 1H), 7.96 (d, J = 8 Hz, 1H), 8.51 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{24}H_{21}NO_4$: C,

74.40; H, 5.46; N, 3.62. Found: C, 74.52; H, 5.46; N, 3.64.

Ethyl 2-[(1*E*,3*E*)-4-(3-Methoxy-4-methoxymethoxyphenyl)-1,3-butadienyl]benzoxazole-5-carboxylate (8c).

Yield 69%. Yellow solid, mp 127-128 °C (from CH_2Cl_2-MeOH); ir (KBr): 1712, 1634, 1591 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.43 (t, J = 7 Hz, 3H), 3.53 (s, 3H), 3.95 (s, 3H), 4.41 (q, J = 7 Hz, 2H), 5.27 (s, 2H), 6.61 (d, J = 15 Hz, 1H), 6.80-7.00 (m, 2H), 7.03 (d, J = 9 Hz, 1H), 7.05 (s, 1H), 7.15 (d, J = 9 Hz, 1H), 7.53 (d, J = 9 Hz, 1H), 7.50-7.67 (m, 1H), 8.07 (d, J = 9 Hz, 1H), 8.37 (s, 1H). Anal. Calcd for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.39; H, 5.56; N, 3.41.

Ethyl 2-[(1*E*,3*E*)-4-[3,4-Bis(methoxymethoxy)phenyl]-1,3-butadienyl]benzoxazole-5-carboxylate (8d).

Yield 59%. Yellow solid, mp 135-136 °C (from CH_2Cl_2-MeOH); ir (KBr): 1720, 1630, 1592 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.42 (t, J = 7 Hz, 3H), 3.53 (s, 3H), 3.56 (s, 3H), 4.42 (q, J = 7 Hz, 2H), 5.27 (s, 2H), 5.29 (s, 2H), 6.60 (d, J = 16 Hz, 1H), 6.80-7.00 (m, 2H), 7.05-7.35 (m, 3H), 7.52 (d, J = 8.5 Hz, 1H), 7.50-7.67 (m, 1H), 8.07 (dd, J = 8.5 Hz, 1.5 Hz, 1H), 8.38 (d, J = 1.5 Hz, 1H). Anal. Calcd for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.18. Found: C, 65.40; H, 5.64; N, 3.20.

Method B. The HWE Reaction under Heterogeneous Conditions. 2-[(1*E*,3*E*)-4-(3-Methoxy-4-methoxymethoxyphenyl)-1,3-butadienyl]oxazolo[4,5-*b*]pyridine (8e).

To a vigorously stirred mixture of tetrabutylammonium bromide (16 mg, 0.050 mmol) in 50 % aqueous sodium hydroxide solution (0.3 ml) and CH_2Cl_2 (0.5 ml) was added, dropwise, a solution of **4d** (68 mg, 0.25 mmol) and **7a** (56 mg, 0.25 mmol) in CH_2Cl_2 (2 ml). After stirring at room temperature for 30 min, the organic layer was separated and washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (CH_2Cl_2-acetone = 20 : 1) to afford **8e** as a yellow solid (40 mg, 47 %), mp 118-119.5 °C (from CH_2Cl_2-Et_2O); ir (KBr): 1618, 1593 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.53 (s, 3H), 3.95 (s, 3H), 5.27 (s, 2H), 6.65 (d, J = 15.5 Hz, 1H), 6.90-7.30 (m, 6H), 7.62-7.80 (m, 1H), 7.77 (d, J = 8 Hz, 1 Hz, 1H), 8.53 (dd, J = 5 Hz, 1.5 Hz, 1H). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found: C, 67.30; H, 5.29; N, 8.21.

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