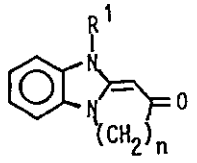
SYNTHESIS AND APPLICATION OF IMIDAZOLE DERIVATIVES. SYNTHESIS OF PYRIDO[1,2-a]BENZIMIDAZOLONE DERIVATIVES[1]

Shunsaku Ohta, Teruyuki Yuasa, Yoshihiro Narita,* Ikuo Kawasaki, Eiji Minamii, and Masayuki Yamashita

Kyoto Pharmaceutical University, Misasagi-Nakauchicho 5, Yamashina-ku, Kyoto 607, Japan

Abstract ----- Pyrido[1,2-a]benzimidazole derivatives (12a and 19a) were synthesized in moderate yields via an intramolecular aldol-condensation of 2-acetyl-1-formylmethylbenzimidazole (11) and an intramolecular acylation of the acylimidzolide (18) prepared from 2-ethoxycarbonylmethyl-1-(2-carboxyethyl)-benzimidazole (17), respectively.

From the interests in the synthetic chemistry and the biological activity,[2] we have investigated the synthesis of fused hetero-tricyclic benzimidazoles such as azepino-, *pyrido-, and pyrrolo*[1,2-a]benzimidazole derivatives (1a, 1b and 1c, respectively).[3,4]

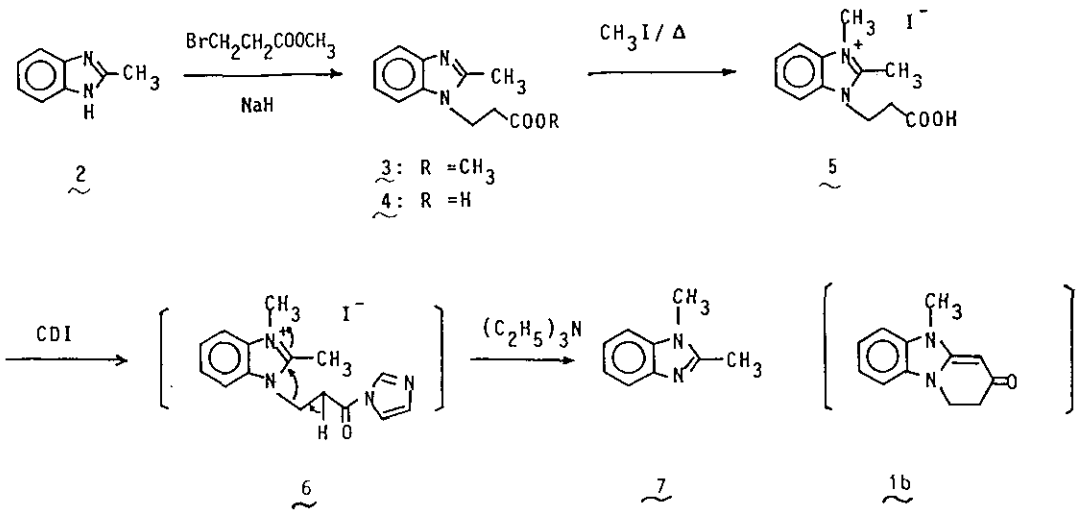


1a : n = 3
1b : n = 2
1c : n = 1
(R^1=CH_3 or $CH_2C_6H_5$)

Scheme 1

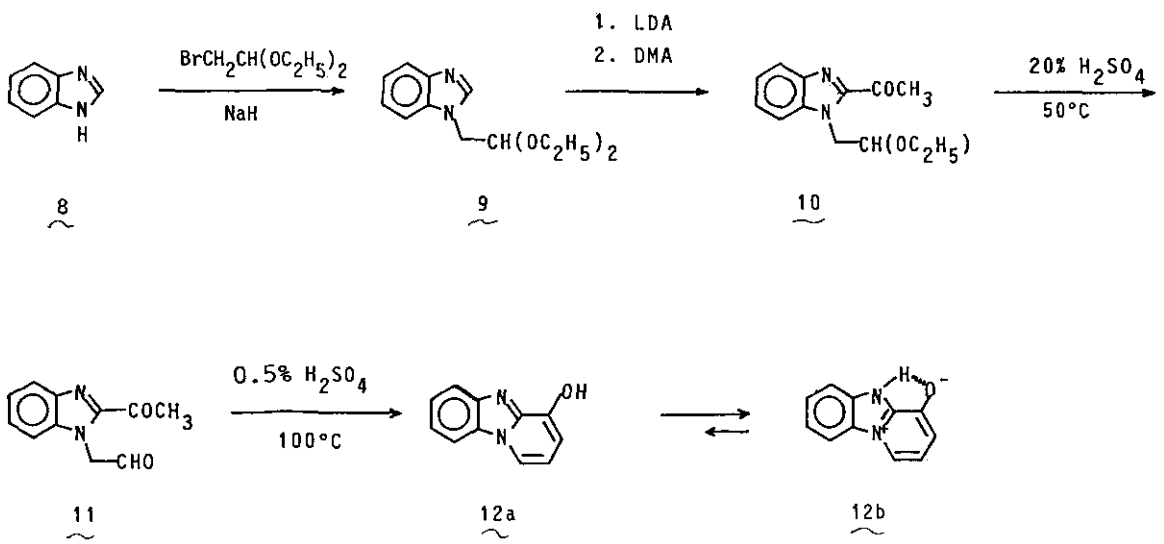
We would like to report here two methods for the synthesis of the pyrido[1,2-a]benzimidazole derivatives (1b).

Previously, 1a was synthesized via an intramolecular acylation of 1-[3-(1-imidazolyl)carbonyl]propyl-2,3-dimethylbenzimidazolium iodide.[3] We used a similar synthetic sequence for preparation of 1b as used for 1a. Thus 2-methylbenzimidazole (2) was alkylated in quantitative yield with methyl 3-bromopropionate, and the resulting ester (3) was hydrolyzed with sodium hydroxide to give the acid (4) in 91.7 % yield. Treatment of 4 with methyl iodide afforded the crystalline imidazolium salt (5) in 90.5 % yield. The salt (5) was treated with N,N'-carbonyldiimidazole (CDI) in the presence of triethylamine, however, only 1,2-dimethylbenzimidazole (7) was obtained in 82.0 % yield via a retro-Michael reaction of the corresponding benzimidazolium salt (6).



Scheme 2

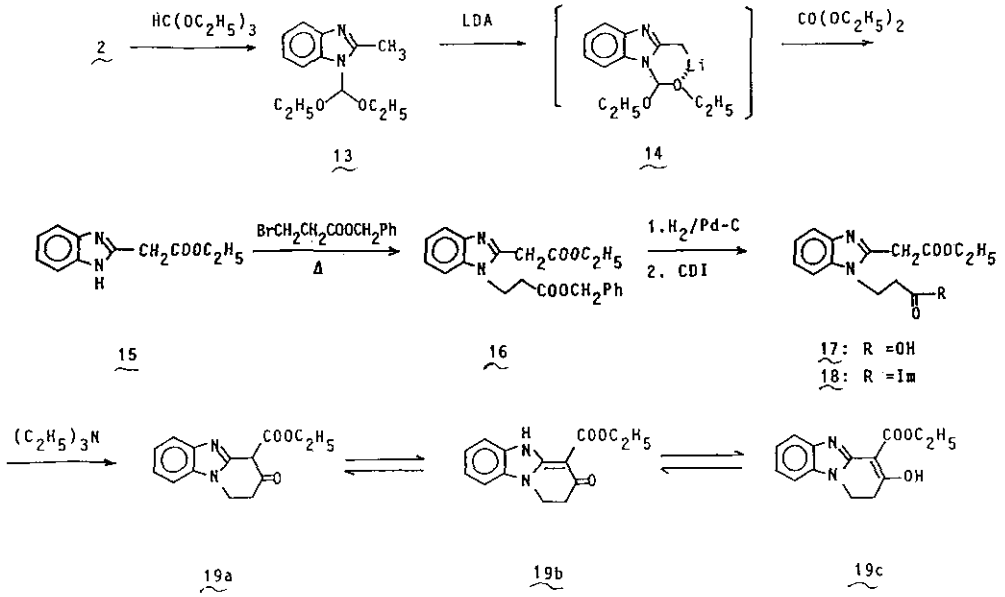
In order to avoid the retro-Michael reaction, we designed an alternative route as illustrated in Scheme 3. Thus benzimidazole (8) was alkylated with bromoacetal to give 9 in 90.2 %, and the 2-position of 9 was acetylated with dimethylacetamide (DMA) to give 10 in 95.3 % yield.[5] Hydrolysis of the acetal group was very slow in 10% hydrochloric acid and was performed by treatment with 20 % sulfuric acid at 50 ℃ for 8 - 10 h, affording the aldehyde (11) in 96.4 %. Treatment of 11 with 0.5% sulfuric acid at 100 ℃ gave 4-hydroxypyrido[1,2-a]benzimidazole (12a) in 88.0 % yield.



Scheme 3

The structure of 12a was supported by spectral (ir: ν_{OH} at 2930 cm^{-1}; ms m/z: M^+ = 184; ^{1}H-nmr: signals of only aromatic protons) and analytical data. The compound (12a) is presumed to present in the structure of 12b rather than 12a because the former is stabilized by aromatization into the pyridinium ring system.

Next, we examined preparation of 1-(2-carboxyethyl)-2-ethoxycarbonylmethylbenzimidazole (17). Ooi reported extensive enolization of the 2-acylmethyl moiety of 1-alkyl-2-benzoylmethylbenzimidazole.[7] Reactivity of the methylene group at 2-position of 17 is so increased by the adjacent ethoxycarbonyl group and the imidazole ring that intramolecular acylation via the corresponding imidazolylcarbonyl derivative (18) would produce the desired compound (19). Thus, the 1-position of 2-methylbenzimidazole (2) was protected with diethoxymethyl group, and the product (13), without purification, was



Scheme 4

treated with diethyl carbonate in the presence of lithium diisopropylamide (LDA) to give the 2-ethoxycarbonylmethylbenzimidazole (15)[9] in 63.4 % yield from 2. A solution of the ester (15) and benzyl 3-bromopropionate in benzene was heated at 90 ℃, and then the product (16) was hydrogenated to the acid (17) in the presence of 5 % Pd-charcoal. The resulting crude acid (17) was treated with CDI and triethylamine to give the desired pyridobenzimidzole (19) in 43.0 % overall yield from 15. The intermediates (16 and 17) were relatively unstable on storage, so they were used in the next reactions within several hours without purification. The pyridobenzimidazole (19), which presumed to be almost exist in an enol form (19c) in solution, gave a positive ferric (III) chloride test.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were taken with a Shimadzu IR-410

spectrophotometer. ^{1}H-Nmr were obtained at 80 MHz on a Varian CFT-20 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-nmr signal patterns are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Uv spectra were obtained on a Shimadzu UV-200S spectrophotometer. Low-resolution ms (lrms) and high-resolution ms (hrms) were obtained on a Hitachi M-80 spectrometer. All solvents were removed under reduced pressure in the usual work-up procedure. Unless othewise stated, anhydrous sodium sulfate was used as a drying agent. A Kugel-Rohr apparatus was used for vacuum distillations of oily crude products. Silica gel (Merck Art. 7734) was used in column chromatography.

1-(2-Methoxycarbonylethyl)-2-methylbenzimidazole (3) ----- A mixture of methyl 3-bromopropionate (18.40 g, 110 mmol) and 2 (13.20 g, 100 mmol) was added at room temperature to a suspension of NaH (97 %; 2.72 g, 110 mmol) in THF (100 ml), and the mixture was stirred overnight at room temperature. Water (50 ml) and $AcOC_2H_5$ (100 ml × 2) were added, and the separated organic phase was evaporated after drying to give an oily residue. The oil was purified by distillation in vacuo, bp 155 - 157 ℃ (3 mmHg). Yield, 21.75 g (quantitative). Ir ($CHCl_3$): 1740 cm^{-1} (C=O). ^{1}H-Nmr($CDCl_3$): δ 2.63 (3H, s, =CC$\underline{H}_3$), 2.81 (2H, t, $\underline{J}$ = 7 Hz, C$\underline{H}_2$CO), 3.66 (3H, s, -OC$\underline{H}_3$), 4.42 (2H, t, $\underline{J}$ = 7 Hz, NC$\underline{H}_2$), 7.62 - 7.74 (1H, m, Ar-H). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.76; H, 6.61; N, 12.52.

1-(2-Carboxyethyl)-2-methylbenzimidazole (4) ----- A mixture of 3 (21.00 g, 96.3 mmol), 4N NaOH (30 ml, 120 mmol) and methanol (100 ml) was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was neutralized with 2N HCl (60 ml, 120 mmol). After removal of the water, the solid residue was recrystallized from CH_3OH to give colorless prisms, mp 173 - 174 ℃. Yield, 18.00 g (91.7 %). Ir (KBr): 1710 cm^{-1} (C=O). ^{1}H-Nmr (DMSO-$\underline{d}_6$): δ 2.55 (3H, s, =CC$\underline{H}_3$), 2.74 (2H, t, $\underline{J}$ = 7 Hz, C$\underline{H}_2$CO), 4.39 (2H, t, $\underline{J}$ = 7Hz, NC$\underline{H}_2$), 7.08 - 7.20 (2H, m, Ar-H), 7.45 - 7.57

(2H, m, Ar-H). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; 13.72. Found: C, 64.41; H, 6.15; N, 13.56.

1-(2-Carboxyethyl)-2,3-dimethylbenzimidazolium Iodide (5) ----- A mixture of 4 (1.80 g, 8.8 mmol) and CH_3I (3.0 ml, 44 mmol) in t-C_4H_9OH (100 ml) was stirred at 80 ℃ for 2 h. Precipitated crystals were collected by suction and recrystallized from CH_3OH - $AcOC_2H_5$ to give 5 as colorless needles, mp 213 - 215 ℃ (decomp.). Yield, 2.76 g (90.5 %). Ir (KBr): 1730 cm^{-1} (C=O). ^{1}H-Nmr (DMSO-d_6): δ 2.88 (2H, t, J = 7 Hz, CH_2CO), 2.92 (3H, s, C-CH_3), 3.99 (3H, s, NCH_3), 4.68 (2H, t, J = 7 Hz, NCH_2), 7.57 - 7.74 (2H, m, Ar-H), 7.94 - 8.11 (2H, m, Ar-H). Anal. Calcd for $C_{12}H_{15}N_2O_2I$: C, 41.64; H, 4.37; N, 8.09. Found: C, 41.61; H, 4.63; N, 8.11.

Reaction of 5 with CDI ----- To a solution of 5 (692 mg, 2 mmol) in DMF (4 ml) CDI (340 mg, 2.1 mmol) was added, and the mixture was stirred at room temperature for 0.5 h. Triethylamine (0.35 ml, 2.5 mmol) was added and the mixture was stirred at room temperature for 5 h. Water (5 ml) and $AcOC_2H_5$ (25 ml) were added to the reaction mixture. The organic phase was washed with water (5 ml) and dried. Evaporation of the solution gave a residue, which was recrystallized from $AcOC_2H_5$ to give 1,2-dimethylbenzimidzole (7) as colorless needles, mp 111 - 112 (lit.,[8] mp 112). Yield, 240 mg (82.0 %). Structure of the product was confirmed by comparisons of its ^{1}H-nmr and mp with those of an authentic sample, prepared by N-methylation of 2-methylbenzimidazole (2) in a usual manner. ^{1}H-Nmr ($CDCl_3$): δ 2.56 (3H, s, CCH_3), 3.66 (3H, s, NCH_3), 7.13 - 7.33 (3H, m, Ar-H), 7.59 - 7.74 (1H, m, Ar-H).

1-(2,2-Diethoxyethyl)benzimidazole (9) ----- Benzimidazole (5.90 g, 50 mmol) and bromoacetaldehyde diethyl acetal (7.90 ml, 52.5 mmol) were added at 0 ℃ to a suspension of NaH (97 %; 1.32 g, 55 mmol) in DMF (50 ml). After being stirred overnight at room temperature, water (100 ml) and $AcOC_2H_5$ (200 ml) were added, and the organic phase was washed with water (50 ml × 2) and dried. Evaporation of the solvent gave an oily residue, which was subjected to column chromatography (solvent: $CHCl_3/CH_3OH$, 20:1). Vacuum distillation of the oil obtained from the main fraction gave 9 as a pale yellow oil, bp

190 - 193 ℃ (3 mmHg). Yield, 10.55 g (90.2 %). Ir ($CHCl_3$): 1060 cm^{-1} (C-O-C). ^{1}H-Nmr ($CDCl_3$): δ 1.00 - 1.37 (6H, m, CH_3 × 2), 3.13 - 4.03 (4H, m, $-OCH_2$), 4.26 (2H, d, J = 8 Hz, NCH_2), 4.71 (1H, t, J = 8Hz, $-CH(OC_2H_5)_2$), 7.06 - 8.07 (5H, m, Ar-H). Uv (C_2H_5OH) λmax nm (log ε): 208 (4.42). Hrms m/z: Calcd for $C_{13}H_{18}N_2O_2$ = 243.1362. Found = 234.1364 (M^+).

2-Acetyl-1-(2,2-diethoxyethyl)benzimidazole (10) ----- An LDA solution (prepared in a usual manner; 24 mmol) was added at -78 ℃ under an N_2 atmosphere to a solution of 9 (4.68 g, 20 mmol) in THF (20 ml), and the mixture was stirred at the same temperature for 0.5 h. N,N-Dimethylacetamide (DMA; 2.05 ml, 22 mmol) was added to the solution and the mixture was stirred at room temperature overnight. Water (20 ml) and $AcOC_2H_5$ (50 ml) were added to the reaction mixture and the aqueous phase was extracted with $AcOC_2H_5$ (25 ml × 2). The combined organic phase was dried and evaporated to give an oily residue, which was subjected to column chromatography ($(C_2H_5)_2O/C_6H_{14}$, 1:1). The oily product from the main fraction was distilled in vacuo to give 10 as an oil, bp 170 - 174 ℃ (3 mmHg). Yield, 5.26 g (95.3 %). Ir ($CHCl_3$): 1690 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$): δ 1.07 (6H, m, CH_3 × 2), 2.83 (3H, s, $COCH_3$), 3.10 - 4.03 (4H, m, OCH_2 × 2), 4.53 - 4.77 (4H, m, Ar-H). Hrms m/z Calcd for $C_{15}H_{20}N_2O_3$ = 276.1471. Found = 276.1422 (M^+).

2-Acetyl-1-formylmethylbenzimidazole (11) ----- A mixture of 10 (1.38 g, 5 mmol), THF (5 ml) and 20 % H_2SO_4 was stirred at 50 ℃ for 8 - 10 h. The pH of the reaction mixture was adjusted to 8 - 9 by addition of water (5 ml) and powdered K_2CO_3. The product was extracted with $AcOC_2H_5$ (20 ml × 3) and the extract was dried and evaporated to give a viscous residue, which was recrystallized from C_6H_6 to give 11 as colorless prisms, mp 118 - 119 ℃. Yield, 974 mg (96.4 %). Ir ($CHCl_3$): 1692, 1745 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$): δ 2.87 (3H, s, $COCH_3$), 5.38 (2H, s, NCH_2), 7.13 - 8.07 (4H, m, Ar-H), 9.70 (1H, s, -CH=O). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.19; H, 4.94; N, 13.86.

4-Hydroxypyrido[1,2-a]benzimidazole (12) ----- A solution of 11 (606 mg, 3 mmol) in 0.5 % H_2SO_4 (60 ml) was stirred at 100 ℃ for 6 h, then pH of the mixture was adjusted to 7 by addition of saturated $NaHCO_3$. The product was extracted with $AcOC_2H_5$ (50 ml ×2), and the

extract was dried and evaporated to give a crystalline residue, which was recrystallized from C_6H_6 to give slightly green prisms, mp 240 - 246 ℃ (decomp.). Yield, 484 mg (88.0 %). Ir (KBr): 2930 cm^{-1} (OH). ^{1}H-Nmr (DMSO-d_6): δ 6.76 - 6.96 (2H, m, -CH=CH- and OH), 7.05 - 7.72 (4H, m, Ar-H), 8.20 - 8.31 (1H, m, -N=CH-), 8.52 - 8.62 (1H, m, -C(OH)=CH-). Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.89; H, 4.21; N, 15.12. LRMS m/z: 184 (M^+).

Ethyl 2-Benzimidazolylacetate (15) ----- A solution of 2 (6.60 g, 50 mmol) in ethyl orthoformate (66 ml, 397 mmol) was heated at 130 ℃ under an N_2 atmosphere. During the heating, the C_2H_5OH produced was azeotropically removed by occasional addition of 10 ml of dry C_6H_6 as co-solvent to the reaction mixture. Excess of ethyl orthoformate was removed by evaporation and the oily residue was dissolved in dry THF (50 ml). An LDA (55 mmol) solution (prepared in a usual manner) was added to the THF solution at -78 ℃ under an N_2 atmosphere, and the mixtue was stirred for 0.5 h at the same temperature. Ethyl carbonate (6.1 ml, 50 mmol) was added to the mixture, and the resulting solution was stirred at -78 ℃ for 2 h then at room temperature for 1 h. Water (20 ml) and $AcOC_2H_5$ (100 ml) were added and the organic layer was dried and evaporated to give a crystalline residue, which was subjected to chromatography (solvent: $AcOC_2H_5$/hexane, 5:1). The residue was recrystallized from $AcOC_2H_5$ to give pale yellow needles, mp 130 - 132 ℃ (lit. mp 128.5 - 129.5 ℃). Yield, 6.47 g (63.4 %). Ir ($CHCl_3$): 3450 (NH), 1730 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$): δ 1.27 (3H, t, J = 7 Hz, CH_2CH_3), 3.95 - 4.35 (4H, m, CH_2CO and OCH_2CH_3), 7.00 - 8.95 (5H, m, Ar-H and NH). Lrms m/z: 204 (M^+).

Ethyl 1,2,3,4-Tetrahydro-3-oxopyrido[1,2-a]benzimidazole-4-carboxylate (19) ----- A solution of 15 (2.75 g, 13.5 mmol), benzyl 3-bromopropionate (3.65 g, 15 mmol) in dry C_6H_6 (5 ml) was stirred at 90 ℃ for 8 h, and the solvent was removed to give an oily residue. A solution of the residue in CH_3OH (27 ml) was hydrogenated for 2 h in the presence of 5 % Pd-C (4.40 g). Evaporation of the mixture after removal of the catalyst by filtration gave 17 as pale yellow crystals, yield 1.38 g. To a solution of the acid (17) in DMF (10 ml) CDI (1.14 g, 7 mmol) was added under a N_2 atmosphere, and the mixture was stirred for 1 h at room temperature. Triethylamine (15 ml) was added to the solution and

the mixture was stirred for 2 h. The resulting mixture was concentrated to dryness to give a solid, which was subjected to chromatography (solvent: $CHCl_3/CH_3OH$, 5:1). The crystals obtained from the main fraction were recrystallized from CH_3OH - $(C_2H_5)_2O$ to give 19 as slightly brown crystals, mp 210 - 213.5 ℃. Yield 1.49 g (43.0 % from 15). Ir ($CHCl_3$): 1630, 1740 cm^{-1} (C=O). ^1H-Nmr ($CDCl_3$): δ 1.40 (3H, t, J = 7 Hz, OCH_2CH_3), 2.84 (2H, t, J = 7 Hz, CH_2CH_2CO), 4.02 - 4.49 (4H, m, NCH_2 and OCH_2CH_3), 7.27 (4H, br-s, Ar-H), 11.44 - 11.61 (1H, br, $COCHCOOC_2H_5$). Lrms m/z: 258 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_3$ 1/8 H_2O: C, 64.54; H, 5.51; N, 10.75. Found: C, 64.51; H, 5.45; N, 10.77.

REFERENCES AND NOTES

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