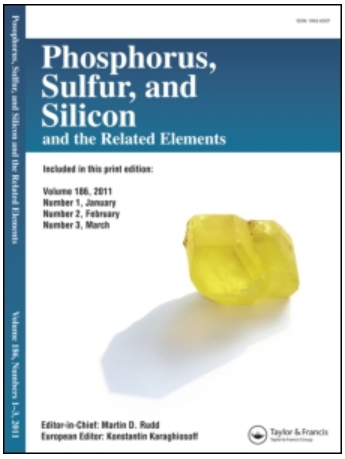

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SYNTHESIS OF O,O-DIPHENYL [SUBSTITUTED (2-SELENOMORPHOLIN-4-YL-ACETYL AMINO)] ALKYL PHOSPHONATES

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SYNTHESIS OF O,O-DIPHENYL [SUBSTITUTED (2-SELENOMORPHOLIN-4-YL-ACETYL AMINO)] ALKYL PHOSPHONATES

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A series of O,O-diphenyl [substituted (2-selenomorpholin-4-yl-acetyl amino)] alkyl phosphonates were synthesized by the reactions of selenomorpholine with O,O-diphenyl 2-chloro- acetylamino alkyl phosphonates. The structures of all new compounds have been confirmed by ^{1}H *NMR,* ^{31}P *NMR, IR spectroscopy, Mass spectroscopy and elemental analyses.*

Keywords: Glutathione peroxidase; phosphorylation; selenium; selenomorpholine

Since selenium was found to be an active center of glutathione peroxidase (GSH-Px), which can catalyze and decompose liquid hydroperoxide or hydrogen peroxide, the bioactivity of selenium has developed rapidly.[1–2] Selenoorganic compound Ebselen (2-phenyl-1,2-benzisoselenazolone) was found the function against biological damage caused in vivo by reactive hydroperoxides.[3–7] This increased a striking interest in developing new selenoorganic compound for therapy. They have been potentially used in a variety of fields varying from medicinal to agriculture application.[8–11] Recently, the antibiotic activity and plant systemic activity of selenomorpholine derivatives were studied.[12–14] In our previous articles, a number of amino acid ester derivatives of benzisoselenazolone were synthesized, and these compounds exhibited excellent pharmacological effect.[15–16] 2-Amino alkylphosphonats show varied biological activity, such as antibacterial, antitumor, herbicidal activity, and inhibitory to enzymes,[17–20] however, no attempt has been made to synthesize 2-amino alkyl phosphonates containing

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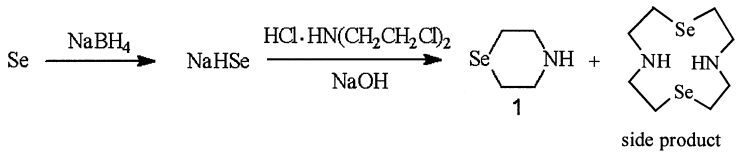


SCHEME 1

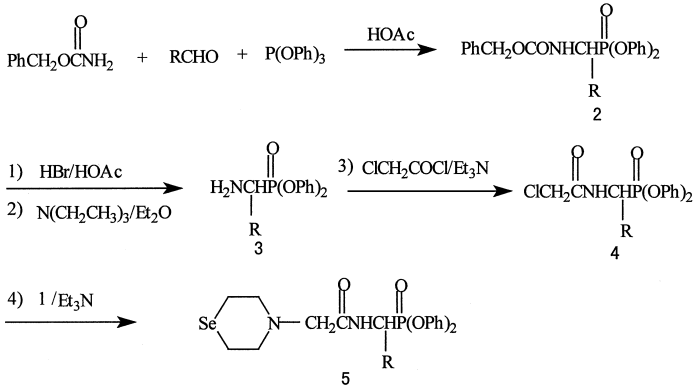
selenomorpholine. In the course of our studies on the application of selenomorpholinyl phosphonates, we found the compounds showed distinctly antifungal activity.[21]

RESULTS AND DISCUSSION

Synthesis of Synthesis of O,O-Diphenyl [substituted (2-selenomorpholin-4-yl-acetyl Amino)] Alkyl Phosphonates

There are several reports on the synthesis of substituted selenomorpholine.[22] However, there are few reports on the selenomorpholine. Herein we report the reaction of selenium power, sodium borohydride and nitrogen mustard hydrochloride to synthesize selenomorpholine under mild conditions in 56% yield as shown in Scheme 1. The low yield is partly because reaction of sodium selenhydrate with nitrogen mustard hydrochloride to produce a hetero-crown ether through 2 + 2 reaction.

The title compounds **5** were synthesized by a multistep route outlined in Scheme 2. Preparation of O, O-diphenyl 2-aminoalkyl phosphonates



R = Ph,2-ClPh, 3-ClPh, 4-ClPh, 3,4-Cl_2Ph, 4-CH_3OPh, 3,4-OCH_2OPh, 2,4-Cl_2Ph, 3-BrPh, 2-Furyl, Me, Et

SCHEME 2

3 were readily accomplished in a three-step sequence (51–76% overall yield) starting from benzyl carbamate, aldehyde and triphenyl phosphite. First, condensation of benzyl carbamate, aldehydes and triphenyl phosphite form O, O-diphenyl 1-benzyloxycarbonylamino 2-substituted alkyl phosphonates 2. Then, deproection with saturated hydrogen bromide acetic acid solution produces the hydrobromide salt of 3. Using ammonia or triethylamine as base in ether, the salt could be converted to 2-amino alkyl phosphonate 3 in high yield. The reaction of 3 with chloroacetic chloride was carried out in chloroform with an organic base as an acid acceptor in 40°C. After cooling to room temperature, the mixture was washed with water, and extracted with chloroform, the combined organic fractions were dried and solvent was removed under reduced pressure. The products 4 are a light yellowish syrup; TLC found the compounds to have high purity. The reaction of 4 with selenomorpholine was carried out in acetone in the presence of triethylamine under reflux to give the title compounds (yield 43–72%).

The Structures of the Products

^{1}H NMR, ^{31}P NMR, IR, MS spectroscopy, and elemental analysis confirmed the structures of the title compounds prepared. The ^{1}H NMR spectrum of all these compounds displayed a sharp multiplet at δ about 2.65 ppm and 2.75 ppm, respectively, which is characteristic for $SeCH_2$ and NCH_2 of the selenomorpholine moiety. There is a doublet at δ about 5.8 ppm, which corresponds to PCH_2. The IR spectra showed peaks at about 1680 cm^{-1} (C=O) and about 1260 cm^{-1} (P=O). The EI-MS spectra showed the existence of weak molecular ion peak. The fragment ion peaks were consistent with their structures; e.g., compound **5** show the existence of weak molecular ion peak. The major MS peaks, particularly m/z 164, 150, 136 are common to all compounds. Other peaks were consistent with their structures and can be clearly assigned, because there are two major isotopes of selenium (approximately 2:1).

EXPERIMENTAL

The melting points were determined on a hot stage apparatus and uncorrected, ^{1}H and ^{31}PNMR spectra were taken with tetramethylsilane as internal standard and 85% phosphoric acid as external standard, respectively, on Varian XL-200 spectrometer. Mass spectra were registered on Finngam Trace MS instrument. IR spectra were recorded on Nicolet Avatar 360. The elemental analyses were performed on a Perkin Elmer 2400CHN element analyzer. Unless other noted, all solvents

were dried over Na_2SO_4 or $MgSO_4$, and the solvent was removed in a rotary evaporator under reduce pressure, chromatography was performed on silica gel.

Selenomorpholine 1

Sodium borohydride (4.3 g, 0.11 mmol) was added to the mixture of power selenium (7.9 g, 0.10 mmol) and absolute ethanol (100 mL) as $-5^{\circ}C$ under argon with stirring until a colorless solution was formed, then sodium hydride (4.4 g, 0.11 mmol) was added and stirred vigorously for 20 min. The ethanol solution of nitrogen mustard hydrochloride (17.8 g, 0.10 mmol) was added dropwise, after being refluxed for 4 h. The mixture was filtered, concentrated, and a colorless oil **1** was obtained by distillation under reduced pressure, b.p. $54^{\circ}C/1.33kP$, yield 56%. ^1H NMR (δ, ppm) 1.62 (s, 1H, NH), 2.61 (m, 4H $SeCH_2$), 3.22 (m, 4H, NCH_2); MS (m/z, %): 151 (M^+, 74.0)

Compounds **2** and **3** were prepared according to literature.[23]

O,O-Diphenyl 2-Chloroacetylaminoalkyl Phosphonates 4

To a stirred solution of O,O-diphenyl 2-aminoalkyl phosphonates (10 mmol), triethylamine (11 mmol) and 15 mL solvent chloroform at $5^{\circ}C$, a mixture of chloroacetyl chloride (10 mmol) and 5 mL chloroform was added dropwise, then the mixture was stirred at $40^{\circ}C$ for 2 h. The resulting mixture was quenched with water and the organic layer was dried by sodium sulfate. The solvent was removed under reduced pressure to give a light yellowish syrup, TLC found the compound have high purity, yield: 76–92%. Typical compound **4a**: yield: 89%, ^1H NMR (δ, ppm) 3.69 (s, 2H, CH_2CO), 4.90 (dd, 1H, PCH, $^3J_{HH} = 10.0Hz$, $^2J_{PH} = 20.0Hz$), 6.73–7.14 (m, 15H, Ph), 8.05 (d, 1H, NH, $^3J_{HH} = 10.0Hz$); IR (cm^{-1}) 1637 ($\nu_{C=O}$), 1259 ($\nu_{P=O}$), 935 (δ_{P-C}), MS (EI, 70eV) m/z: 384.5 (M^+, 9.5), 302.5(15.7), 164(100), 292(56.8), 77(100), $^{31}PNMR$ δ, ppm: 10.52.

O,O-Diphenyl [substituted-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonates 5

O,O-diphenyl 2-chloroacetylaminoalkyl phosphonate (10 mmol), selenomorpholine (11 mmol), triethylamine (11 mmol) and 15 mL solvent acetone were added into a 50 mL reaction flask. The mixture was then stirred at reflux for 2–3 h. The resulting mixture was quenched with water and the solvent was removed under reduced pressure, the residue was dissolved in choloroform, and organic layer was washed with H_2O

(60 mL), dried by sodium sulfate, and evaporated to give a crude oil. Chromatography on silica gel using petromeum ether and acetone (5:1) as eluent gave product **5**.

O,O-Diphenyl [Phenyl-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5a)

Yield: 63%, m.p. 134–137°C.

^{1}H NMR (δ, ppm): 2.60~2.67 (m, 4H $SeCH_2$), 2.72~2.76 (m, 4H, NCH_2), 2.92 (s, 2H, CH_2CO), 5.90 (dd, 1H, PCH, $^3J_{HH} = 10.0$Hz, $^2J_{PH} = 20.0$Hz), 6.80–7.45 (m, 15H, Ph), 8.23 (d, 1H, NH, $^3J_{HH} = 10.0$ Hz)

IR (cm^{-1}) 1673 ($\nu_{C=O}$), 1264 ($\nu_{P=O}$), 937 (δ_{P-C})

MS (EI, 70eV) m/z: 530 (M^+, 0.15), 182 (6.38), 164 (100), 150 (27.70), 136 (53.42), 108 (18.24), 93 (50.86)

^{31}PNMR (δ, ppm): 13.83

Anal. Calcd for $C_{25}H_{27}N_2O_4PSe$ (530): C, 56.72; H, 5.14; N, 5.29; found, C, 56.48; H, 5.38; N, 5.41

O,O-Diphenyl [2-Chlorophenylphenyl-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5b)

Yield: 45%, m.p. 113–115°C.

^{1}H NMR (δ, ppm): 2.62~2.84 (m, 8H $SeCH_2$, NCH_2), 2.94 (s, 2H, CH_2CO), 6.45 (dd, 1H, PCH, $^3J_{HH} = 10.0$Hz, $^2J_{PH} = 22.0$Hz), 6.80–7.53 (m, 14H, Ph), 8.25 (d, 1H, NH, $^3J_{HH} = 10.0$Hz)

IR (cm^{-1}) 1684 ($\nu_{C=O}$), 1269 ($\nu_{P=O}$), 937 (δ_{P-C})

MS (EI,70eV) m/z: 565 (M^+,1.12), 164 (100), 150 (36.70), 136 (40.74), 94 (60.54)

^{31}PNMR (δ, ppm): 12.97

Anal. Calcd for $C_{25}H_{26}ClN_2O_4PSe$ (564.5): C, 53.26; H, 4.65; N, 4.97; found, C, 52.93; H, 4.49; N, 5.04

O,O-Diphenyl [3-Chlorophenyl-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5c)

Yield: 49%, m.p. 122–123°C

^{1}H NMR (δ, ppm): 2.59~2.69 (m, 4H $SeCH_2$), 2.74~2.86 (m, 4H, NCH_2), 2.96 (s, 2H, CH_2CO), 5.85 (dd, 1H, PCH, $^3J_{HH} = 10.0$Hz, $^2J_{PH} = 20.0$Hz), 6.86–7.41 (m, 14H, Ph), 8.13 (d, 1H, NH, $^3J_{HH} = 10.0$Hz)

IR (cm^{-1}) 1688 ($\nu_{C=O}$), 1271 (ν_{P-O}), 937 (δ_{P-C})

MS (El, 70eV) m/z: 565 (M^+, 0.23), 164 (100), 150 (27.67), 136 (42.94), 93 (37.96)

^{31}PNMR (δ, ppm): 13.21

Anal. Calcd for $C_{25}H_{26}ClN_2O_4PSe$ (564.5): C, 53.26; H, 4.65; N, 4.97; found, C, 53.04; H, 4.72; N, 4.83.

O,O-Diphenyl [4-Chlorophenyl-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5d)

Yield: 56%, m.p. 89–93°C

^{1}H NMR (δ, ppm): 2.63∼2.68 (m, 4H $SeCH_2$), 2.74∼2.78 (m, 4H, NCH_2), 2.97 (s, 2H, CH_2 CO), 5.84 (dd, 1H, PCH, $^3J_{HH}$ = 10.0Hz, $^2J_{PH}$ = 22.0Hz), 6.84–7.43 (m, 14H, Ph), 8.15 (d, 1H, NH, $^3J_{HH}$ = 10.0Hz)

IR (cm^{-1}) 1654 ($\nu_{C=O}$), 1278 ($\nu_{P=O}$), 932 (δ_{P-C})

MS (El, 70eV)m/z: 565 (M^+, 0.63), 164 (100), 150 (18.62), 136 (32.97), 93 (42.50)

^{31}PNMR (δ, ppm): 13.28

Anal. Calcd for $C_{25}H_{26}ClN_2O_4PSe$ (564.5): C, 53.26; H, 4.65; N, 4.97; found, C, 53.12; H, 4.53; N, 4.89.

O,O-Diphenyl [3,4-Dichlorophenyl-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5e)

Yield: 54%, m.p. 105–107°C

^{1}H NMR (δ, ppm): 2.64∼2.68 (m, 4H, $SeCH_2$), 2.75∼2.78 (m, 4H, NCH_2), 2.98 (s, 2H, CH_2CO), 5.81 (dd, 1H, PCH, $^3J_{HH}$ = 10.0Hz, $^2J_{PH}$ = 20.0Hz), 6.75∼7.51 (m, 13H, Ph), 8.17 (d, 1H, NH, $^3J_{HH}$ = 10.0Hz)

IR (cm^{-1}) 1669 ($\nu_{C=O}$), 1275 ($\nu_{P=O}$), 932 (δ_{P-C})

MS (El, 70eV)m/z: 599 (M^+, 0.24), 164 (100), 150 (24.76), 136 (42.35), 93 (54.62)

^{31}PNMR (δ, ppm): 12.67

Anal. Calcd for $C_{25}H_{25}Cl_2N_2O_4PSe$ (599): C, 50.19; H, 4.21; N, 4.68; found, C, 51.07; H, 4.13; N, 4.56.

O,O-Diphenyl [4-Methoxyphenyl-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5f)

Yield: 76%, m.p. 81–83°C

^{1}H NMR (δ, ppm): 2.59∼2.66 (m, 4H $SeCH_2$), 2.71∼2.79 (m, 4H, NCH_2), 2.94 (s, 2H, CH_2CO), 3.76 (s, 3H, CH_3O), 5.86 (dd, 1H, PCH, $^3J_{HH}$ = 10.0Hz, $^2J_{PH}$ = 20.0Hz)

IR (cm^{-1}) 1682 ($\nu_{C=O}$), 1267 ($\nu_{P=O}$), 940 (δ_{P-C})

MS (El,70eV) m/z: 599 (M^+, 0.24), 164 (100), 150 (24.76), 136 (42.35), 93 (54.62)

^{31}P NMR (δ, ppm): 12.67

Anal. Calcd for $C_{26}H_{29}N_2O_5PSe$ (560): C, 55.83; H, 5.23; N, 5.01; found, C, 55.68; H, 5.18; N, 4.89.

O,O-Diphenyl [1,3-Dihydro-isobenzofuran-5-yl)-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5g)

Yield: 72%, m.p. 81–83°C

^{1}H NMR (δ, ppm): 2.56∼2.67 (m, 4H $SeCH_2$), 2.72∼2.84 (m, 4H, NCH_2), 2.93 (s, 2H, CH_2CO), 5.77 (dd, 1H, PCH, $^3J_{HH} = 10.0$Hz, $^2J_{PH} = 22.0$Hz), 5.92 (s, 2H, OCH_2O), 6.72–7.31 (m, 13H, Ph), 8.10 (d, 1H, NH, $^3J_{HH} = 10.0$Hz)

IR (cm^{-1}) 1673 ($\nu_{C=O}$), 1263 ($\nu_{P=O}$), 937 (δ_{P-C})

MS (El, 70eV) m/z: 574 (M^+, 0.36), 164 (100), 150 (46.50), 136 (24.53), 93 (62.31)

^{31}P NMR (δ, ppm): 13.62

Anal. Calcd for $C_{26}H_{29}N_2O_6PSe$ (574): C, 54.46; H, 4.75; N, 4.89; found, C, 54.82; H, 4.63; N, 4.92.

O,O-Diphenyl [2,4-Dichlorophenyl-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5h)

Yield: 61%, m.p. 123–125°C

^{1}H NMR (δ, ppm): 2.56∼2.76 (m, 8H $SeCH_2$, NCH_2), 2.93 (s, 2H, CH_2 CO), 6.37 (dd, 1H, PCH, $^3J_{HH} = 10.0$Hz, $^2J_{PH} = 22.0$Hz), 6.86–7.48 (m, 13H, Ph), 8.22 (d, 1H, NH, $^3J_{HH} = 10.0$Hz)

IR (cm^{-1}) 1685 ($\nu_{C=O}$), 1274 ($\delta_{P=O}$), 956 (ν_{P-C})

MS (EI, 70eV) m/z: 599 (M^+, 0.27), 164 (100), 150 (32.62), 136 (34.75), 93 (63.72)

^{31}P NMR (δ, ppm): 12.85

Anal. Calcd for $C_{25}H_{25}Cl_2N_2O_4PSe$ (599): C, 50.19; H, 4.21; N, 4.58; found, C, 49.84; H, 4.36; N, 4.53.

O,O-Diphenyl [3-Bromophenyl-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5i)

Yield: 59%, m.p. 86–89°C

^{1}H NMR (δ, ppm): 2.65∼2.68 (m, 4H $SeCH_2$), 2.75∼2.77 (m, 4H NCH_2), 2.97 (s, 2H, CH_2CO), 5.84 (dd, 1H, PCH, $^3J_{HH} = 10.0$Hz, $^2J_{PH} = 22.0$Hz), 6.73–7.56 (m, 14H, Ph), 8.20 (d, 1H, NH,$^3J_{HH} = 10.0$Hz)

IR (cm^{-1}) 1683 ($\delta_{C=O}$), 1280 ($\nu_{P=O}$), 939 (δ_{P-C})

MS (EI,70eV) m/z: 609 (M^+, 0.15), 164 (100), 150 (57.21), 136 (43.40), 93 (48.50)

^{31}PNMR (δ, ppm): 12.75

Anal. Calcd for $C_{25}H_{26}BrN_2O_4PSe$ (609): C, 49.37; H, 4.31; N, 4.61; found, C, 48.93; H, 4.26; N, 4.59.

O,O-Diphenyl [Furan-2-yl-(2-selenomorpholin-4-yl-acetylamino)methyl] Phosphonate (5j)

Yield: 70%, m.p. 68–69°C

^{1}H NMR (δ, ppm): 2.60∼2.66 (m, 4H $SeCH_2$), 2.73∼2.76 (m, 4H NCH_2), 2.97 (d, 2H, CH_2 CO), 6.04 (dd, 1H, PCH, $^3J_{HH} = 10.0$Hz, $^2J_{PH} = 22.0$Hz), 6.34–7.37 (m, 3H, Furyl), 6.97–7.32 (m, 10H, Ph), 7.96 (d, 1H, NH, $^3J_{HH} = 10.0$Hz)

IR (cm^{-1}) 1669 ($\nu_{C=O}$), 1265 ($\nu_{P=O}$), 937 (δ_{P-C})

MS (EI,70eV) m/z: 520 (M^+, 3.54), 164 (100), 150 (67.80), 136 (47.50), 93 (73.20)

^{31}P NMR (δ, ppm): 11.05

Anal. Calcd for $C_{23}H_{25}N_2O_5PSe$ (520): C, 53.19; H, 4.85; N, 5.39; found, C, 52.98; H, 4.76; N, 5.43.

O,O-Diphenyl [1-(2-selenomorpholin-4-yl-acetylamino)] Ethyl Phosphonate (5k)

Yield: 65%, m.p. 62–64°C

^1H NMR (δ, ppm): 1.53 (d, 3H, CH_3), 2.64~2.68 (m, 4H $SeCH_2$), 2.75~2.79 (m, 4H NCH_2), 2.86 (d, 2H, CH_2CO), 5.13 (m, 1H, PCH), 7.07–7.46 (m, 10H, Ph), 8.25 (d, 1H, NH, $^3J_{HH} = 10.0$Hz)

IR (cm^{-1}) 1654 ($\nu_{C=O}$), 1255 ($\nu_{P=O}$), 934 (δ_{P-C})

MS (EI,70eV) m/z: 468 (M^+, 4.80), 164 (100), 150 (46.53), 136 (61.42), 93 (53.14)

^{31}P NMR (δ, ppm): 15.38

Anal. Calcd for $C_{20}H_{25}N_2O_4PSe$ (468): C, 51.41; H, 5.39; N, 5.99; found, C, 51.26; H, 5.51; N, 5.84.

O,O-Diphenyl [1-(2-selenomorpholin-4-yl-acetyl-amino)] Propyl Phosphonate (5l)

Yield: 68%, m.p. 79–82°C

^1H NMR (δ, ppm): 0.97 (t, 3H, CH_3, $^3J_{HH} = 7.6$Hz), 1.63 (m, 2H, $\underline{CH_2}CH_3$), 2.67~2.71 (m, 4H, $SeCH_2$), 2.77~2.83 (m, 4H NCH_2), 2.89 (d, 2H, CH_2CO), 5.26 (m, 1H, PCH), 7.03–7.41 (m, 10H, Ph), 8.18 (d, 1H, NH, $^3J_{HH} = 10.0$Hz)

IR (cm^{-1}) 1658 ($\nu_{C=O}$), 1250 ($\nu_{P=O}$), 937 (δ_{P-C})

MS (EI,70eV) m/z: 482 (M^+, 3.77), 164 (100), 150 (51.53), 136 (47.39), 93 (29.61)

^{31}P NMR (δ, ppm): 14.79

Anal. Calcd for $C_{21}H_{27}N_2O_4PSe$ (482): C, 52.40; H, 5.65; N, 5.82; found, C, 52.28; H, 5.51; N, 5.76.

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