IMIDAZOLE-ASSISTED INTRAMOLECULAR PHENOXYTHIOCARBONYLATION OF TERTIARY ALCOHOLS. A KEY REACTION FOR THE DEOXYGENATION OF α-TRIFLUOROMETHYLARYLMETHYL ALCOHOLS ¥

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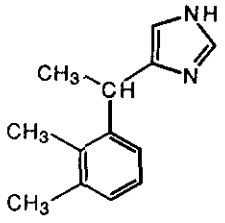
Abstract -- The deoxygenation of α-trifluoromethylarylmethyl alcohols failed under catalytic hydrogenation conditions. However, these alcohols can be deoxygenated *via* their thionocarbonate intermediates followed by homolytic reductive cleavage of the C–O bond. The formation of the phenyl thionocarbonate esters is sterically dependent. Consequently, secondary α-trifluoromethyl arylmethyl alcohols can be smoothly converted to thionocarbonates, but tertiary alcohols cannot. Exceptions to this lack of reactivity are the aryl 4-substituted imidazolyl trifluoromethyl carbinols, which do form the thionocarbonates under these conditions.

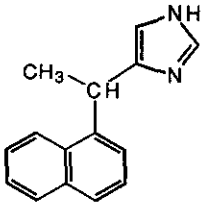
The benzylic or arylmethyl alcohol moiety is readily accessible *via* the reaction of aryl aldehydes or ketones with carbanion equivalent reagents or by the reaction of arylmetal reagents and carbonyl compounds. The combination of aryl and benzylic hydroxyl functionalities coupled with an amino group has become a major pharmacophore in many medicinal compounds. In addition, benzylic alcohols have been shown to be versatile *intermediates for the construction of larger, more complex molecules.*

¥ Dedicated to Dr. A. Brossi on the occasion of his 70th birthday.

The hydrogenolysis of benzylic alcohols using catalytic hydrogenation provides a mild and effective method to produce the corresponding deoxygenated product.[1,2] This procedure has been used for chemical manipulation and by medicinal chemists for structure-activity relationship (SAR) studies of biologically interesting molecules. In a study of α_2-adenergic agonists related to medetomidine (**1**), we recently prepared the naphthalene analog (**2**) and found it has α_2-adrenergic agonist activity similar to **1**.[3] Therefore, a series of naphthalene analogs was synthesized for SAR studies. One of the compounds we wanted to prepare is the trifluoromethyl analog (**3**). This paper discusses the preparation of **3** by deoxygenation of **4** *via* the homolytic cleavage of the C–O bond of the phenyl thionocarbonate ester and the study of the deoxygenation reaction of other aryl trifluoromethyl carbinols with and without an imidazole moiety at the benzylic carbon.



1



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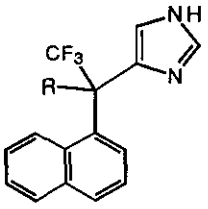


3 R = H

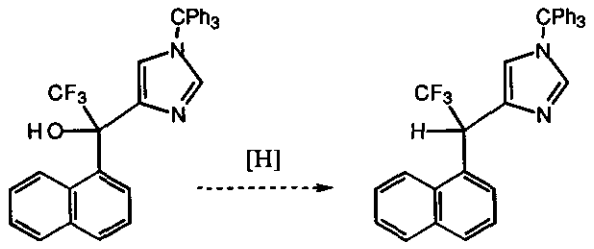
4 R = OH

CHEMISTRY

The development of trifluoromethyltrimethylsilane by Olah *et al.*[4] made trifluoromethyl carbinols readily accessible. Although the deoxygenation of benzylic alcohols is well documented,[1,2] the deoxygenation of aryl trifluoromethyl carbinols has not been reported. We were interested in this chemical transformation to prepare **3** from the alcohol (**5**) for biological evaluation in comparison with the parent compound (**2**). Several attempts to prepare **6** from **5** under a variety of hydrogenolysis conditions failed to produce the desired deoxygenation product as shown in **Scheme 1**. The hydrogenation of **5** in ethanol using a variety of catalysts gave only starting material, even when a small amount of hydrochloric acid was added. When trifluoroacetic acid or acetic acid was used as a solvent, partial ring reductions were observed. The difficulty encountered in effecting the transformation of **5** to **6** was attributed to the presence of the trifluoromethyl group. It is known that the rate of hydrogenolysis of benzyloxy compounds increases in the order OH < O-alkyl << O-aryl < OH^+–alkyl < OH_2^+ < OAc < $OCOCF_3$.[1] The ease of displacement parallels the leaving group ability of the substituents (the ability to bear a negative charge). Due to the inductive effect of the trifluoromethyl group, the protonation of

Scheme 1

Attempted Deoxygenation of **5**

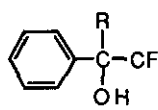


5 **6**

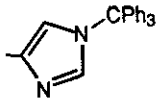
Reaction Conditions	Results
H_2, Pd/C CF_3COOH	No Reaction
H_2, Pd black CF_3COOH	N.R.
H_2/PtO_2 CF_3COOH	mixture
Et_3SiH CF_3COOH	N.R.
Li/NH_3	mixture

the benzyl alcohol functionality would be impeded and formation of a carbocation or carbocation-like intermediate would be unfavorable. Thus, catalytic reduction procedures fail to yield deoxygenated products. Therefore, a reductive deoxygenation procedure that proceeds through a free-radical mechanism was attempted.

Many reagents have been developed for such a homolytic cleavage of C–O bonds.[5] We chose the Robins procedure[6] for this study because of its mild conditions and effective conversion to the desired deoxygenated products. To study the homolytic cleavage of the C–O bond of **5**, model compounds (**7**) (a secondary alcohol), (**8**) and (**9**) (tertiary alcohols) were used. Compound (**7**) is the simplest benzyl alcohol and is commercially available. Compounds (**8** and **9**) were prepared from 2,2,2-trifluoroacetophenone and the corresponding methyl- or phenylmagnesium bromide.

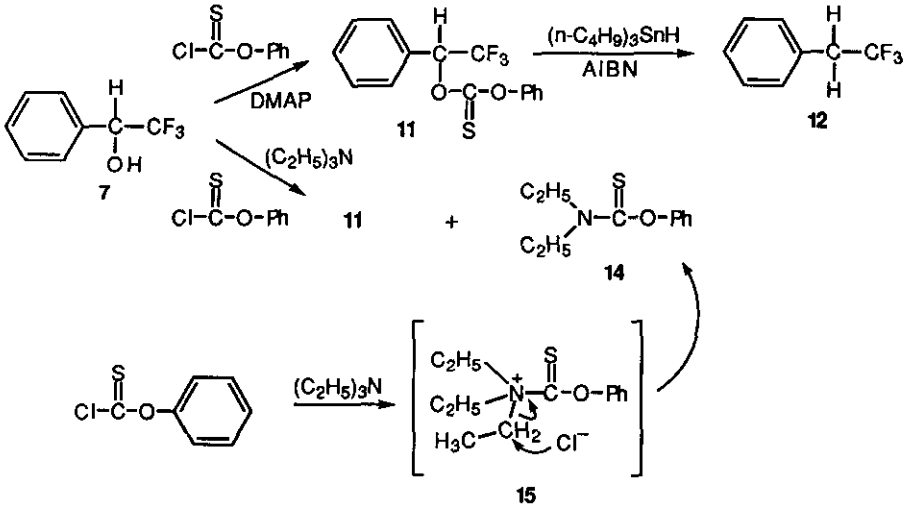


7 R = H
8 R = CH_3
9 R = C_6H_5

10 R = 

Compound (**7**) reacted with phenyl chlorothionoformate (PTC-Cl) and 4-dimethylaminopyridine (DMAP) in CH_3CN very smoothly to give **11** along with a small amount of the symmetrical diphenyl thionocarbonate (**13**) as a by-product. Interestingly, when triethylamine was used as the acid scavenger, in addition to the desired product (**11**), a major side product (**14**) was isolated in 53% yield. The mechanism of formation of **14** is proposed in **Scheme 2**. The formation of **14** must be derived from attack of the chloride ion at one of the ethyl

Scheme 2

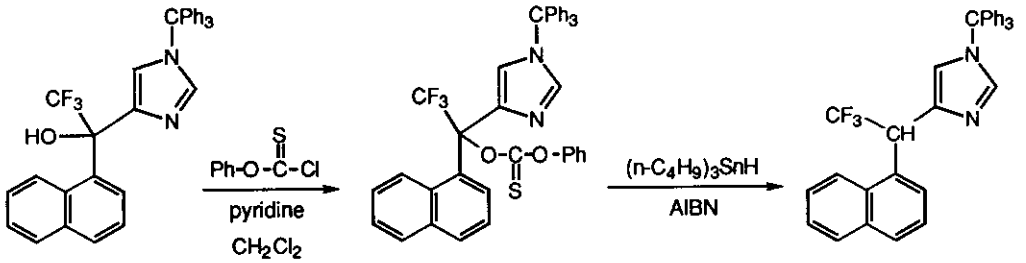


groups of the charged intermediate (**15**). Consequently, it is recommended that a pyridine-type amine be used as the base in this reaction. Compound (**11**) was then smoothly transformed to **12** using tributyltin hydride (n-Bu_3SnH) and 2,2'-azobisisobutyronitrile (AIBN) in toluene. We found ^{19}F Nmr spectroscopy was very useful for monitoring these reactions since the fluorine atom is present in the starting material and the product. Thus, the chemical shifts of the fluorine atom and the characteristic of H-F coupling become a very useful diagnostic tool for these chemical transformations. For instance, the fluorine signal of **7** is a doublet centered at –78.55 ppm due to coupling with the benzylic proton. After deoxygenation the fluorine signal becomes a triplet due to coupling with the two benzylic protons as observed in compound (**12**).

The reaction of **5** with PTC-Cl and pyridine in CH_2Cl_2 followed by reductive deoxygenation gave **6** in 66% yield (**Scheme 3**). To our surprise, the reaction of **8** or **9** with PTC-Cl and DMAP or pyridine in CH_3CN or CH_2Cl_2 gave only starting material and diphenyl thionocarbonate (**13**). Compound (**13**) was also formed

Scheme 3

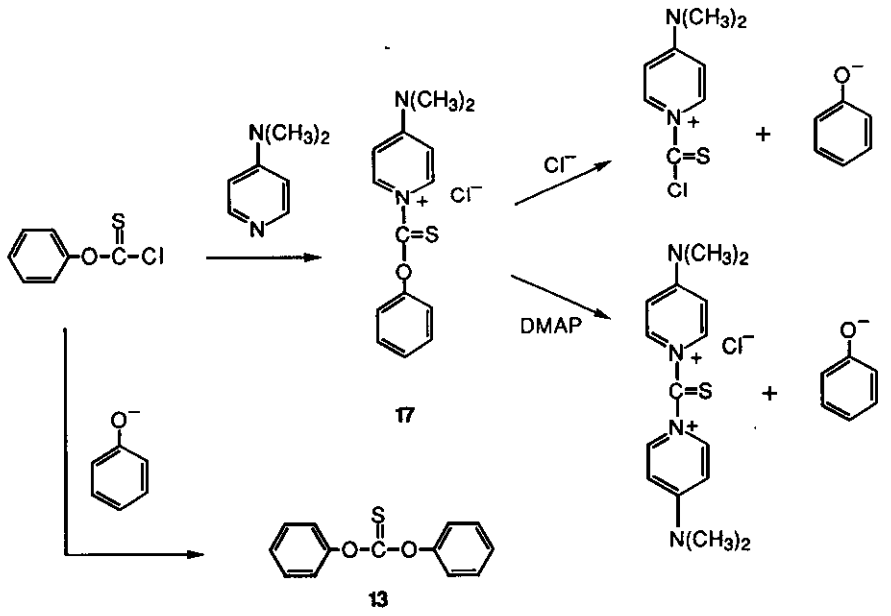
Free Radical Deoxygenation of **5**



without the presence of **8** or **9** under these conditions. It appears that the hindered alcohols (**8** and **9**) react either very slowly or do not react with the adduct of DMAP-(PTC-Cl) (**17**). Thus, intermediate (**17**) reacts with DMAP, or chloride ion, resulting in the release of phenolate ion which further reacts with PTC-Cl to produce **13** as shown in **Scheme 4**. To examine the possibility of any electronic factor being involved in this reaction,

Scheme 4

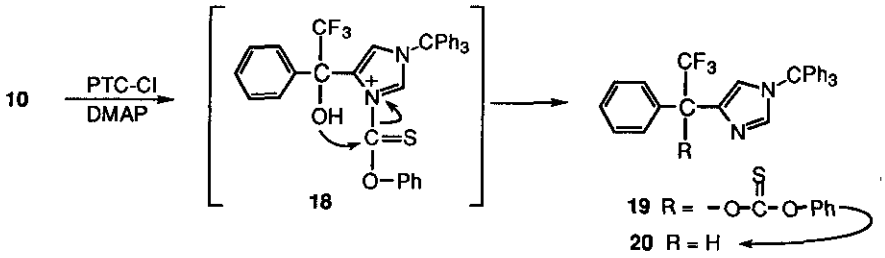
Proposed Mechanism for the Formation of Diphenyl Thionocarbonate (**13**)



we substituted **7** with 2-phenyl-2-propanol for phenoxythiocarbonylation. Under identical conditions, the destrifluoro tertiary alcohol did not react to produce any thionocarbonate ester. Thus, the difficulty of

converting the tertiary alcohols (**8** and **9**) to their phenyl thionocarbonate intermediates must be attributed to steric hindrance at the hydroxyl group. Interestingly, this steric factor was not observed in **5** and we suspected that the imidazole moiety might play a role in this transformation. Thus, model compound (**10**) was prepared from the reaction of 2,2,2-trifluoroacetophenone and 4-(1-tritylimidazolyl)magnesium halide.[7,8] Reaction of **10** with PTC-Cl in CH_2Cl_2 was smoothly converted to the phenyl thionocarbonate ester (**19**), which was subjected to deoxygenation to provide **20** (**Scheme 5**). These studies confirm the involvement of the imidazole moiety in the phenoxythiocarbonylation of arylmethyl alcohols. Based on these results, we proposed that the imidazole moiety in **5** and **10** reacted with PTC-Cl to form an acylimidazolium intermediate, such as **18**, which directed an intramolecular transacylation to the hydroxyl group to produce phenyl thionocarbonate esters.

Scheme 5



EXPERIMENTAL SECTION

Melting points were determined using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1420 spectrophotometer. ^{1}H-Nmr spectra were recorded with a Bruker 250 spectrometer using TMS as the internal standard. ^{19}F-Nmr spectra were referenced to $CFCl_3$. Chemical ionization (CI) mass spectra were obtained on a Finnigan 1015D spectrometer and high-resolution mass measurements (HRms) were obtained using a VG-Micro Mass 7070F mass spectrometer. Elemental analyses were performed at the Atlantic Microlab, Inc., Norcross, GA. The composition of the reaction mixtures from various runs was monitored by thin layer chromatography (tlc) on silica gel GF plates (Analtech, Inc., Newark, DE). Flash column chromatography was performed on Merck silica gel 60, 230-400 mesh ASTM. The solvent extracts during work-up were dried over anhydrous sodium sulfate or magnesium sulfate.

General Procedure for Phenyl Thionocarbonate Esters Synthesis

To a solution of the alcohol (1 mmol) and PTC-Cl (0.19 g, 1.1 mmol) in dry CH_3CN or CH_2Cl_2 (2.5 ml) was added DMAP (0.269 g, 2.2 mmol) or pyridine (0.18 ml, 2.2 mmol) at ice-bath temperature under nitrogen. The

mixture was stirred at room temperature for 16 h and tlc was used to monitor the reaction: silica gel, hexane/benzene = 8/3. After the reaction was complete, the precipitate was filtered and washed with the solvent. The solvent was removed and the residue was dissolved in $CHCl_3$, and the organic layer was washed with 1N HCl, saturated $NaHCO_3$, water, and dried. Evaporation of solvent gave the crude product which was purified by flash column chromatography (silica gel, eluted with hexane followed by benzene).

*1-Phenyl-2,2,2-trifluoroethyl Phenyl Thionocarbonate (**11**) and Phenyl N,N-Diethylthionocarbamate (**14**)*

Method 1. Compound (**11**) was prepared from **7** as a pale yellow oil: ^{1}H-Nmr ($CDCl_3$) δ 6.65 (q, 1H, benzylic-H, J = 6.5 Hz), 7.05-7.52 (m, 10H, ArH); ^{19}F-nmr ($CDCl_3$) –75.58 ppm (d, J = 5.0 Hz); ms (CI/NH_3) m/z 313 (MH^+, 50%), 159 (C_6H_5-CH-CF_3^+, 100%).

Method 2. Et_3N was used as the base instead of DMAP in *Method 1*. Compound (**11**) was isolated in 29% yield and the byproduct (**14**) was obtained in 53% yield as a brown oil: ^{1}H-Nmr ($CDCl_3$) δ 1.31 (t, 6H, $2CH_3$, J = 7.0 Hz), 3.67 (q, 2H, CH_2, J = 7.0 Hz), 3.89 (q, 2H, CH_2, J = 7.0 Hz), 7.06 (d, 2H, ArH, J = 8.0 Hz), 7.25 (dd, 1H, ArH, J = 7.5 , 7.5 Hz), 7.39 (d, 2H, ArH, J = 8.0 Hz).

*(2,2,2-Trifluoroethyl)benzene (**12**)*

To a solution of **11** (312 mg, 1 mmol) in toluene (15 ml) was added n-Bu_3SnH (0.4 ml, 437 mg, 1.5 mmol) and AIBN (32 mg, 0.2 mmol) at room temperature. The mixture was degassed with N_2 for 3 min, then heated in an oil bath at 75–80 °C for 3 h. The boiling point of **12** was estimated to be close to that of the solvent, toluene; therefore, the isolation of **12** was not attempted. ^{19}F-Nmr was used to determine the extent of the reaction. ^{19}F-Nmr (toluene, reaction mixture) showed that the signal at –75.58 ppm (starting material) had disappeared and a new signal at –66.1 ppm (t, J = 11.0 Hz) had appeared, consistent with the formation of **12**.

*1-Naphthalene-2,2,2-trifluoro-1-[4-(1-triphenylmethyl)imidazole]ethyl Phenyl Thionocarbonate (**16**)*

Compound (**16**) was obtained as the crude product (85% yield) from **5** in CH_2Cl_2 using pyridine as the base: Ir (KBr) 1751 cm^{-1} (thionocarbonate); ^{1}H-nmr ($CDCl_3$) δ 6.78–6.65 (m, 29H, ArH and Im-H); ^{19}F-nmr ($CDCl_3$) –67.58 ppm; ms (CI/NH_3) m/z 671 (MH^+, 100%), 243 (Ph_3C^+, 100%).

*4-[1-(1-Naphthalenyl)-2,2,2-trifluoroethyl]-[1-(triphenylmethyl)]imidazole (**6**)*

The crude phenyl thionocarbonate ester (**16**) (1.06 g, 1.5 mmol) was dissolved in benzene (15 ml) and treated with n-Bu_3SnH (0.6 ml, 2.3 mmol) and AIBN (48 mg, 0.3 mmol) at room temperature. The mixture was then

degassed with N_2 for 3 min, then heated in an oil bath at 75–80 °C for 3 h. The solvent was evaporated and the residue was chromatographed on silica gel (hexane/EtOAc = 4/1). The collected product was recrystallized from ether to afford **6**: (680.8 mg, 66% yield from **5**): mp 173–174 °C. Ir (KBr) 3062, 1492, 1147, 1103 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.62 (q, 1H, benzylic-H, J = 9.3 Hz), 6.81 (s, 1H, Im-H), 7.07–7.11 (m, 6H, ArH), 7.27–7.36 (m, 9H, ArH), 7.40 (d, 1H, J = 1.3 Hz), 7.45 (d, 1H, ArH, J = 7.6 Hz), 7.48–7.57 (m, 2H, ArH), 7.68 (d, 1H, J = 7.3 Hz), 7.79–7.88 (m, 2H, ArH), 8.10 (d, 1H, ArH, J = 8.1 Hz); HRms (m/z): calcd for $C_{34}H_{25}N_2F_3$ (M+): 518.1970. Found: 518.1954.

4-[1-(1-Naphthalenyl)-2,2,2-trifluoroethyl]-1H-imidazole (3)

To a suspension of **6** (700 mg, 1.35 mmol) was added 60% aqueous CF_3COOH (15 ml). The mixture was stirred for 16 h and the solvent was evaporated. The residue was partitioned between CH_2Cl_2 (15 ml) and 10% aqueous HCl (15 ml). The organic layer was then washed with 3x15 ml of 10% aqueous HCl. The combined acidic solution was neutralized to pH 10 and extracted with 4x75 ml of CH_2Cl_2. The combined organic layers were washed with brine, dried and concentrated to yield **3** (250 mg, 67% yield): mp 186–187 °C (recrystallized from CH_2Cl_2). Ir (KBr) 3417, 1463, 1251, 1153, 1097 cm^{-1}; ^{1}H-nmr (CD_3OD) δ 5.80 (q, 1H, benzylic-H, J = 9.5 Hz), 7.14 (s, 1H, Im-H), 7.43–7.68 (m, 5H, ArH), 7.87 (t, 2H, ArH, J = 8.8 Hz), 8.20 (d, 1H, ArH, J = 8.4 Hz); ^{19}F-nmr (CD_3OD) –66.35 ppm (d, J = 8.0 Hz); HRms (m/z): calcd for $C_{15}H_{11}N_2F_3$ (M^+): 276.0874. Found: 276.0873.

3·HCl: mp 106–108 °C. Anal. Calcd for $C_{15}H_{12}N_2ClF_3 \cdot H_2O$: C, 54.47; H, 4.27; N, 8.40. Found: C, 54.73, H, 3.88; N, 8.33.

4-[(1-Hydroxy-1-phenyl-2,2,2-trifluoro)ethyl]-N-triphenylmethylimidazole (10)

A solution of EtMgBr in ether (3M, 0.73 ml, 2.2 mmol) was added to a solution of 4-iodo-(1-triphenylmethyl)-imidazole[7,8] (873 mg, 2.0 mmol) in dry CH_2Cl_2 (8 ml) at room temperature under N_2. After 30 min 2,2,2-trifluoroacetophenone (0.31 ml, 2.2 mmol) was added and the resulting mixture was stirred for 16 h. The mixture was quenched with saturated NH_4Cl solution and the aqueous phase was separated and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude solid was recrystallized from CH_2Cl_2/hexane to yield **10** (904 mg, 93% yield): mp 163–164 °C. Ir (KBr) 3061, 1599, 1493, 1153, 1142 cm^{-1}; ^{1}H-nmr (CD_3OD) δ 6.96 (s, 1H), 7.14–7.17 (m, 8H), 7.30–7.52 (m, 13H); ^{19}F-nmr ($CDCl_3$) –78.3 ppm; ms (CI/NH_3) m/z 485 (MH^+).

1-Phenyl-2,2,2-trifluoro-1-[4-(1-triphenylmethyl)imidazole]ethyl Phenyl Thionocarbonate (19)

Compound (**19**) was prepared from **10** and PTC-Cl and purified by column chromatography (silica gel, CH_2Cl_2). Recrystallization from ether gave **19** (51% yield): mp 156–157 °C. Ir (KBr) 3059, 1741, 1147 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 6.82 (s, 1H), 6.99–7.05 (m, 2H), 7.12–7.17 (m, 7H), 7.27–7.34 (m, 14H); ^{19}F-nmr ($CDCl_3$) –67.58 ppm; ms (CI/NH_3) m/z 621 (MH^+).

4-(1-Phenyl-2,2,2-trifluoroethyl)-[1-(triphenylmethyl)]imidazole (20)

Compound (**20**) was prepared from **19** in 94% yield: mp 172–173 °C. Ir (KBr) 3063, 1494, 1263, 1141 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 4.69 (q, 1H, J = 9.6 Hz), 6.87 (s, 1H), 7.12–7.15 (m, 6H), 7.31–7.41 (m, 15H); ^{19}F-nmr ($CDCl_3$) –68.26 ppm; ms (CI/NH_3) m/z 469 (MH^+).

Anal. Calcd for $C_{30}H_{23}N_2F_3$: C, 76.91; H, 4.95; N, 5.98. Found: C, 76.75; H, 4.96, N, 5.89.

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