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One-pot synthesis of 4-Aminobicyclo[2.2.2]octan-2-ones

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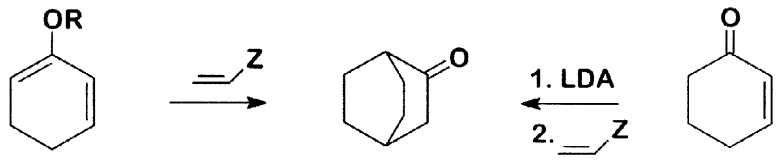
Abstract

Dialkylammonium rhodanides and benzylidene acetone give racemic (6*RS*,7*RS*)-4-dialkylamino-bicyclo[2.2.2]octan-2-ones in a one-pot reaction in good yields. The mechanism of the reaction includes a Diels-Alder step. The structures are established by NMR spectra and a single crystal structure analysis. The compounds consist of cations of racemates of optically active (6*R*,7*R*)- and (6*S*,7*S*)-4-dialkylamino-6,7-diphenylbicyclo[2.2.2]octan-2-ones and isothiocyanate anions.

Keywords: Bicyclic aliphatic compounds; Diels-Alder reactions

Introduction

Bicyclo[2.2.2]octanones **1** are important intermediates in the synthesis of natural substances such as sesquiterpenes [1-6], diterpenes [7-11] and alkaloids [12]. Usually they are prepared from electron-deficient alkenes by Diels-Alder reactions [13-17] with cyclohexa-1,3-dienes **2** or by tandem Michael additions [3-8, 18-23] with deprotonated cyclohexenones **3** (Scheme 1).



2 **1** **3**

Scheme 1

The corresponding 4-amino compounds **5** are available by intramolecular cyclization of 1-(4-dialkylaminocyclohex-3-en-1-yl)-ethanones **4** [24, 25] (Scheme 2). This paper reports the first

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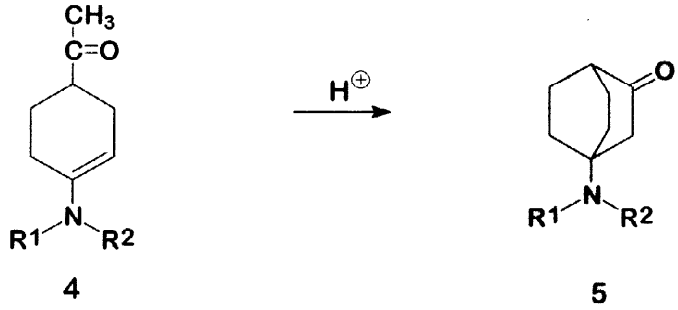
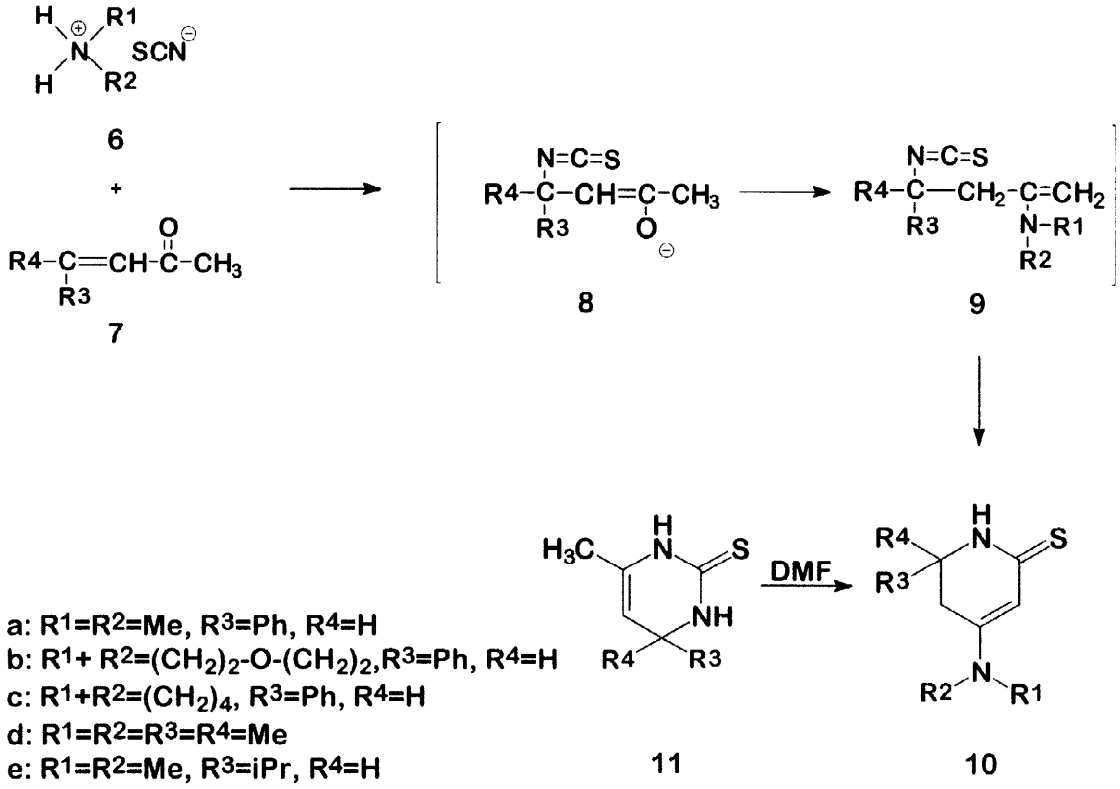
one-pot synthesis of 4-dialkylaminobicyclo[2.2.2]octan-2-ones from acyclic starting materials.



Scheme 2

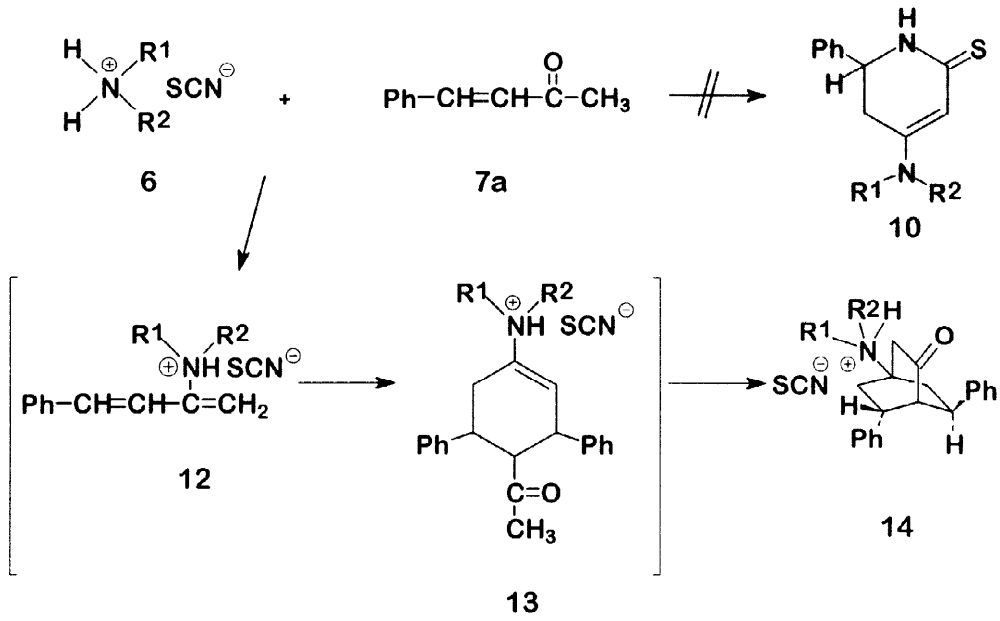
Results and Discussion

When the α,β-unsaturated ketones **7d,e** are refluxed at a water separator with dimethylammonium isothiocyanates **6d**, the rhodanide ion is usually added to the β-carbon in the initial step. The formed enolates **8d,e** are converted to enamines **9d,e**, which cyclize to 4-dimethylamino-5,6-dihydropyridine-2(1H)-thiones **10d,e** in good yields [26] (Scheme 3). The 5,6-dihydropyridine-2(1H)-thiones **10a,d** are available by treatment on 6-methyl-3,4-dihydropyrimidine-2(1H)-thiones **11a,d** with dimethylformamide at 230°C in poor yields [27].



Scheme 3

Our attempts to synthesize **10a-c** directly from benzylidene acetone **7a** and dialkylammonium rhodanides **6a-c** failed. We assume that the nucleophilic attack of the isothiocyanate ion at the β-carbon must be prevented for sterical or electronical reasons, because not even a small amount of dihydropyridin-2(1H)-thiones **10a-c** could be isolated from the mother liquor after separation of the major product. 4-Dialkylaminobicyclo[2.2.2]octan-2-ones **14a-c** were formed instead. Most likely the carbonyl carbon of **7a** reacts with dialkylamines to form enamines **12a-c**, followed by a Diels-Alder addition of unchanged benzylidene acetone. Finally the formed 4-acetylcyclohex-1-en-1-ylammonium salts **13a-c** cyclize to compounds **14a-c** (Scheme 4) and are identified as hydroisothiocyanates of racemic (6*RS*,7*RS*)-4-dimethylamino-6,7-diphenyl-bicyclo[2.2.2]octan-2-ones. The carbonyl absorptions of the cyclization products **14a-c** at 1725 cm^{-1} in I.R. spectra correlate with those of comparable compounds in ref. [24, 25].



Scheme 4

The resolution of the signals of ^{1}H NMR spectra for the rhodanides **14a-c** was poor. But when we measured the corresponding bases, we were even able to determine the coupling constants for some w-couplings. Most of the signals in ^{1}H and ^{13}C NMR spectra were assigned by means of two dimensional NMR experiments (gCOSY, gHSQC, gHMQC optimized on 10 Hz). Both the aromatic substituted chains have analogous configurations. Therefore the signals in NMR spectra are different for corresponding protons due to their unequal electronic environment. The discrimination between the two similar chains required the correlation of NOE spectra and w-couplings. Two methylene protons, H-8 and H-5', show interaction by a w-coupling. From a

molecular model it was obvious that only one of these protons (H-8) might give a NOE to aromatic ortho protons (Figure 1).

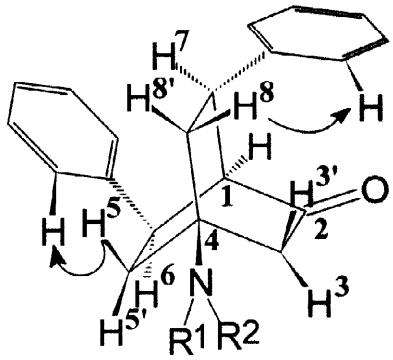


Figure 1

This was true for the proton resonating at higher field, which is understandably due to shielding by the aromatic ring. This assignment was established by a w-coupling between H-5 and H-3' and a NOE measurement from H-5 to aromatic ortho protons (Figure 1).

The X-ray diffraction analysis of the ionic compound **14a** (Figure 2) shows that the centrosymmetric structure consists of racemic cations of optically active (6*R*,7*R*)- and (6*S*,7*S*)-4-(dimethylamino)-6,7-diphenyl-bicyclo[2.2.2]octan-2-one besides the isothiocyanate anions. The two other possible isomers of the cation, the (6*R*,7*S*) and the (6*S*,7*R*) isomer are optically inactive due to a mirror plane through the atoms C1, C2, O2, C3, C4, N4 if the bicyclo[2.2.2]octane skeleton is not twisted around the C1·····C4 connecting line.

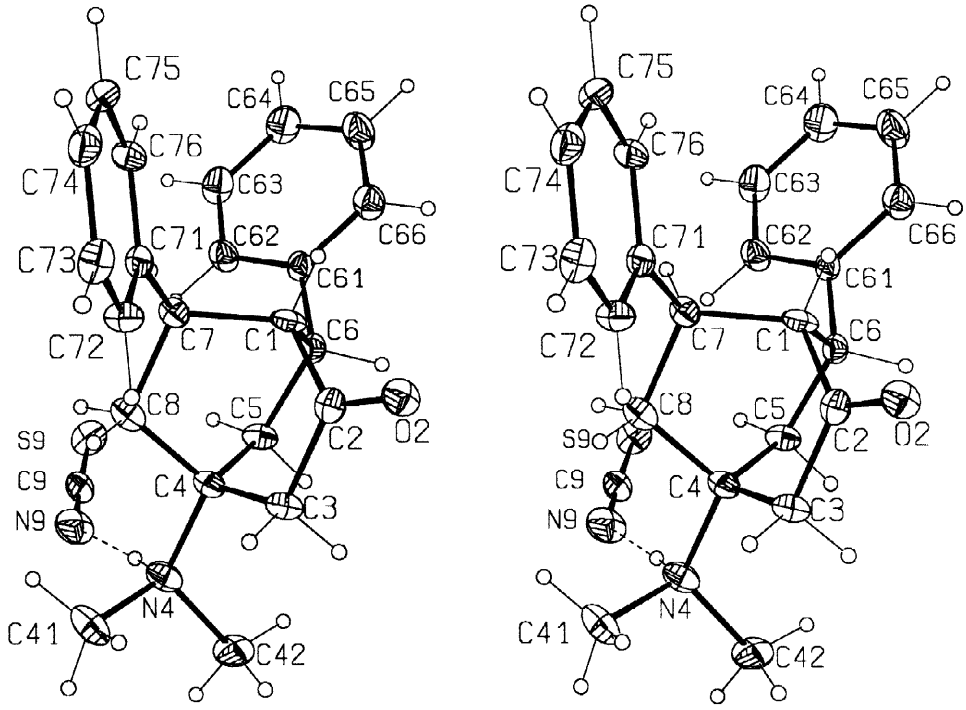


Figure 2 Stereoscopic plot of the asymmetric unit of **14a**. The ellipsoids are drawn at the 50% probability level.

This problem of twisting in bicyclo[2.2.2]octane was discussed in detail [28] as only two crystal structures were determined so far and D_{3h} symmetry was postulated.

The results of semi-empirical MNDO [29] and AM1 [30] calculations of bicyclo[2.2.2]octane show no twisting from the fully eclipsed D_{3h} symmetry to D_3 symmetry. Using the AM1 parameters ΔH_f° the values of 0.85, 3.91, 11.75, 32.08, 80.57kJ/mol larger than the minimum (-150.82kJ/mol) were obtained if the C1-C2-C3-C4 torsion angles τ and their equivalents were fixed at 5°, 10°, 15°, 20°, 25°, respectively. Evidently by the flat minimum, which has been confirmed by the calculated complete set of harmonic vibrational frequencies, a slight twisting must be taken into account especially in the presence of larger substituents at the bridging C atoms.

The crystal structure of the unsubstituted hydrocarbon could not be determined due to disorder [31, 32] the interpretation of electron diffraction data obtained from the molecule in the gas phase led to different values of the torsion angles τ of 0° or 12° [28]. A search in the Crystallographic Structural Database (CSD [33]) for structures of bicyclo[2.2.2]octane derivatives yielded 12 examples. Due to the constraints in the molecules the difference between the three torsion angles τ in the bridging chains is not larger than 8.2° [34]. The twists τ (maximum value 23.0° [35]) scarcely depend on the substituents: Substitution only in position 1 and / or 4 lead to values of $\tau \leq 1.1°$ [28, 36], $4.7° \leq \tau \leq 5.4°$ [37], $15.6° \leq \tau \leq 18.4°$ [38]. In general the presence of a keto-group diminishes τ, but values in the range $11.4° \leq \tau \leq 15.6°$ are observed [35, 39, 40]. In compound **14a** τ is smaller [1.6(4)°] in the chain containing the keto group than in the two other chains bearing the phenyl groups [7.9(4)°, 8.6(4)°].

All the bond lengths determined in both ions agree well with the corresponding interatomic distances found in organic compounds [41]. The phenyl groups are oriented such as the torsion angles C1-C6-C61-C62 and C1-C7-C71-C72 became about 90° [99.0(3)°, 84.7(3)°]. There is one presumably strong hydrogen bond between the atom H4 of the cation and the nitrogen atom N9 of the SCN^- group [N4···N9 2.749(4)Å, N4–H4···N9 174(3)°].

Experimental

Melting points: Melting point apparatus Dr.Tottoli, uncorrected. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer). NMR spectra: Varian Inova 400 (297 K) 5 mm tubes, solvent as internal standard. Elementary analyses: Laboratory for Microanalysis, Institute of Physical Chemistry of the University in Vienna.

Preparation of (6RS,7RS)-(±)-6,7-diphenylbicyclo[2.2.2]octan-2-ones

In a round-bottomed flask the corresponding ammonium isothiocyanate (0.1mol) and

benzylidene acetone (0.2 mol) are suspended in dimethylformamide (120 ml). The mixture is refluxed at a water separator for 6 hours and thereupon the solvent removed in vacuo. The residue is triturated with ethanol, filtered with suction and recrystallized from ethanol. For NMR measurements the bases were set free with 1*M* NaOH and extracted with ether. The organic phase was dried over sodium sulphate, filtered and the solvent evaporated yielding colourless oils.

(6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-one x HNCS **(14a)**
Reaction of dimethylammonium rhodanide with benzylidene acetone yielded 32.7 g (86 %) white crystals, mp 196°C; IR (KBr) 2364, 2043, 1725, 1498, 1465, 757, 701 cm^{-1}; ^1H NMR (base, 400 MHz, $CDCl_3$) δ 7.40-7.07 (m, 10H, aromatic H), 3.39-3.34 (m, 2H, 6-H, 7-H), 2.70 (t, *J*=1.5 Hz, 1H, 1-H), 2.57 (dd, *J*=18.4, 3.4 Hz, 1H, 3-H), 2.45 (dd, J=18.4, 2.7 Hz, 1H, 3'-H), 2.44-2.37 (m, 1H, 8'-H), 2.38 (s, 6H, $N(CH_3)_2$), 2.32 (ddd, J=13.3, 10.2, 3.1 Hz, 1H, 5'-H), 2.12 (ddd, J=13.3, 8.4, 2.7 Hz, 1H, 5-H), 1.69 (ddd, J=13.0, 8.2, 3.1 Hz, 1H, 8-H); ^{13}C NMR (base, 100 MHz, $CDCl_3$) δ 213.17 (C-2), 144.22, 141.18, 128.72, 128.65, 127.46, 126.94, 126.86, 126.51 (aromatic C), 57.92 (C-4), 53.72 (C-1), 44.20 (C-3), 38.51 ($N(CH_3)_2$), 38.21 (C-6), 36.85 (C-8), 35.60 (C-7), 31.69 (C-5), Anal. Calcd. for $C_{23}H_{26}N_2OS$: C, 72.98; H, 6.92; N, 7.40; S, 8.47. Found: C, 73.29; H, 7.26; N, 7.53; S, 8.49.

Crystal Structure Analysis of **14a**
A colourless single crystal (0.40 × 0.28 × 0.24 mm) was immersed in oil and suddenly cooled to 93K: $C_{22}H_{26}NO^+SCN^-$, monoclinic, P $2_1/c$, a = 12.994(3), b = 17.407(4), c = 9.440(2)Å, β = 106.76(2)°, V = 2044.5(8)$Å^3$, Z = 4, d_x = 1.230 g/cm^3, F(000) = 808. All the measurements were performed on a modified STOE four-circle diffractometer (graphite monochromator, MoK_α radiation, λ = 0.71069Å). The unit-cell parameters were determined from a least-squares fitting to the diffractometer angles of 50 well refined reflections (2Θ range 20-36°). The intensities of three standard reflections remeasured every 100 reflections during data collection (ω-scans, scan range 1.4°, 2Θ < 48°) indicated no decay. The intensities of the 4089 reflections were corrected for Lp effects. An absorption correction was not applied because of the low absorption coefficient (μ = 0.173 mm^{-1}). The structure was solved by direct methods [42]. The non-hydrogen atoms were refined [43] with anisotropic displacement parameters, the phenyl groups were refined as regular hexagons (C-C 1.390Å), the hydrogen atoms at calculated positions (C-H 1.000Å) with common isotropic displacement parameters for atoms attached to the same C atom or to the same phenyl group, respectively. The hydrogen atom H4 involved in the hydrogen bond was refined without any constraints. The final cycle of full-matrix least-squares refinement {$w = 1/[\sigma^2(F_o^2)+(0.0298*P)^2]$, $P = (F_o^2 + 2F_c^2)/3$} was based on 240

parameters and 3193 unique reflections, 1734 were observed with $I > 2\sigma(I)$. The refinement converged with agreement factors of R = 0.0548 for the observed and wR2 = 0.1098 for all data. The final atomic parameters, as well as bond lengths and angles are deposited at the Cambridge Crystallographic Data Centre. Computer programs used: SHELXS-86 [42], SHELXL-97 [43], ORTEP [44], AMPAC [45].

(6RS,7RS)-(±)-4-Morpholino-6,7-diphenylbicyclo[2.2.2]octan-2-one x HNCS **(14b)**
Reaction of morpholinium rhodanide with benzylidene acetone yielded 35.3 g (84 %) white crystalls, mp 208°C; IR (KBr) 2371, 2042, 1725, 1499, 1462, 757, 701 cm^{-1}; ^1H NMR (base, 400 MHz, $CDCl_3$) δ 7.41-7.04 (m, 10H, aromatic H), 3.75 (t, *J*= 4.6 Hz, 4H, $O(CH_2)_2$), 3.37-3.32 (m, 2H, 6-H, 7-H), 2.73-2.62 (m, 5H, 1-H, $N(CH_2)_2$), 2.56 (dd, *J*=18.2, 3.2 Hz, 1H, 3-H), 2.43 (dd, J=18.2, 2.5 Hz, 1H, 3'-H), 2.43-2.36 (m, 1H, 8'-H), 2.30 (ddd, J=13.1, 10.3, 2.9 Hz, 1H, 5'-H), 2.11 (ddd, J=13.1, 8.4, 2.5 Hz, 1H, 5-H), 1.67 (ddd, J=13.0, 8.2, 2.9 Hz, 1H, 8-H); ^{13}C NMR (base, 100 MHz, $CDCl_3$) δ 212.83 (C-2), 144.09, 141.04, 128.76, 128.69, 128.31, 127.44, 126.93, 126.58 (aromatic C), 67.49 ($O(CH_2)_2$), 58.15 (C-4), 53.75 (C-1), 46.32 ($N(CH_2)_2$), 44.65 (C-3), 38.07 (C-6), 37.19 (C-8), 35.50 (C-7), 31.75 (C-5), Anal. Calcd. for $C_{25}H_{28}N_2O_2S$: C, 71.40; H, 6.71; N, 6.66; S, 7.62. Found: C, 70.95; H, 6.74; N, 6.63; S, 7.53.

(6RS,7RS)-(±)-4-Pyrrolidino-6,7-diphenylbicyclo[2.2.2]octan-2-one x HNCS **(14c)**
Reaction of pyrrolidinium rhodanide with benzylidene acetone yielded 28.9 g (71 %) white crystalls, mp 202°C; IR (KBr) 2043, 1729, 1499, 1450, 752, 699 cm-1; ^1H NMR (base, 400 MHz, $CDCl_3$) δ 7.40-7.04 (m, 10H, aromatic H), 3.40-3.34 (m, 2H, 6-H, 7-H), 2.79-2.70 (m, 4H, $N(CH_2)_2$), 2.67 (t, *J*=1.6 Hz, 1H, 1-H), 2.62 (dd, *J*=18.4, 3.5 Hz, 1H, 3-H), 2.46 (dd, J=18.4, 2.5 Hz, 1H, 3'-H), 2.46-2.39 (m, 1H, 8'-H), 2.32 (ddd, J=13.3, 10.6, 2.8 Hz, 1H, 5'-H), 2.18 (ddd, J=13.3, 8.3, 2.5 Hz, 1H, 5-H), 1.84-1.79 (m, 4H, $(CH_2)_2$), 1.77 (ddd, J=12.8, 8.3, 2.8 Hz, 1H, 8-H); ^{13}C NMR (base, 100 MHz, $CDCl_3$) δ 213.49 (C-2), 144.35, 141.28, 128.72, 128.63, 128.32, 127.57, 126.99, 126.48 (aromatic C), 56.66 (C-4), 54.14 (C-1), 45.69 ($N(CH_2)_2$), 44.76 (C-3), 38.35 (C-6), 37.73 (C-8), 35.57 (C-7), 32.65 (C-5), 23.58 $(CH_2)_2$, Anal. Calcd. for $C_{25}H_{28}N_2OS$: C, 74.22; H, 6.98; N, 6.92; S, 7.93. Found: C, 73.98; H, 7.11; N, 7.03; S, 7.85.

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