Synthesis of Novel 1,3-Dithiolan-2-one Derivatives

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Novel 1,3-dithiolan-2-one derivatives were prepared starting from α,β- or β,γ-dichlorinated carboxylic esters and potassium *O*-ethyl dithiocarbonate. The scope and the mechanism of this reaction were investigated. The biological uses of the compounds obtained here were examined.

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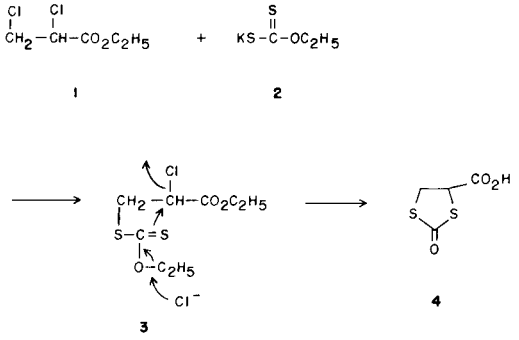
Dithiolane derivatives have been known to exhibit biological activities [1a-c]. During the course of our studies on the synthesis of biologically active organic sulfur compounds, we found a novel synthetic method for 1,3-dithiolan-2-one derivatives. The parent compound itself had been previously prepared by several procedures [2a-b]. However reports regarding 1,3-dithiolan-2-one derivatives substituted at the 4 and/or 5 position have been rarely found. This report describes that novel 1,3-dithiolan-2-one derivatives having substituents are accessible from α,β- or β,γ-dichlorinated carboxylic ester derivatives and potassium *O*-ethyl dithiocarbonate (**2**).

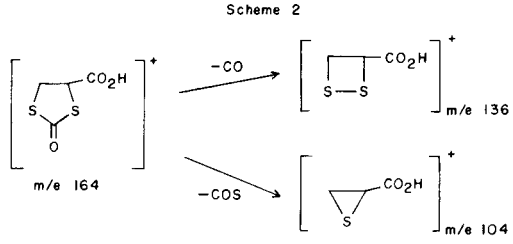
When ethyl α,β-dichloropropionate (**1**) was treated with **2** in ethanol for 2 days at room temperature followed by removal of potassium chloride and evaporation, a reaction intermediate was obtained as a residual oil. Without further purification this was heated in a mixture of concentrated hydrochloric acid and acetic acid at 100° for 8 hours to give crystalline 4-carboxy-1,3-dithiolan-2-one (**4**) in 57% yield (Scheme 1).

Scheme 1



The structural assignment of **4** was based on the elemental analyses and the spectroscopic data. The ir spectrum exhibits ν CO at 1705 cm^{-1} and 1645 cm^{-1} due to carboxyl group and dithiocarbonate group respectively. The nmr signals due to the ring protons showed a typical ABX type pattern with δ 3.70 to 4.11 (AB) and δ 4.77 (X). The mass spectrum exhibits a molecular ion at m/e = 164 and fragment ions at m/e = 136 and 104. They can be interpreted by the following fragmentation scheme (Scheme 2).

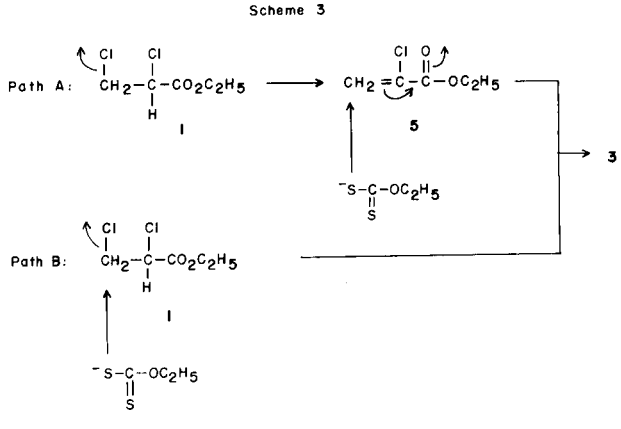
Scheme 2



This is a novel reaction for preparing 1,3-dithiolan-2-one derivative and therefore the mechanism of the formation of **4** was investigated. The reaction intermediate obtained at the first step of the reaction could not be purified by distillation without decomposition. The nmr spectrum of the intermediate showed two types of ethyl signals and an ABX pattern in which the AB type protons were observed at higher field compared with starting material **1**. This indicates that the structure of the intermediate is **3** as shown in Scheme 1, together with the probable reaction pathway to afford **4**.

Two routes for producing **3** can be considered as shown in Scheme 3. Path A is the 1,4-addition to the acrylic ester derivative **5** initially generated and path B is the direct substitution of β-chlorine atom. In order to confirm which route is possible, the following experiments were performed.

Scheme 3

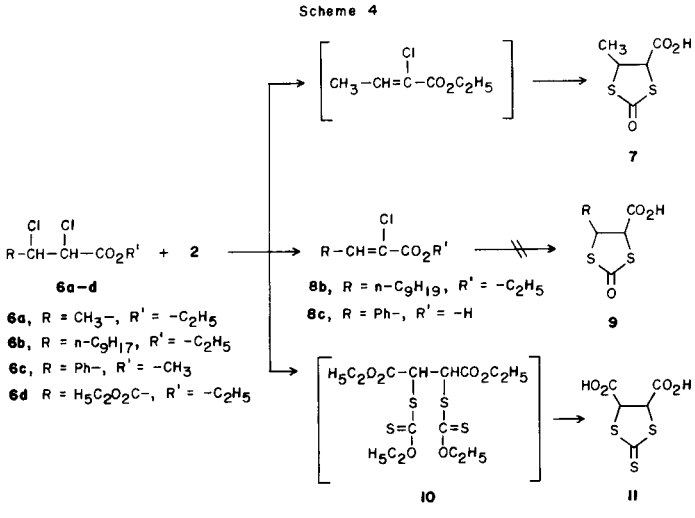


A treatment of ethyl α-chloroacrylate (**5**) with **2** resulted in the quantitative formation of **3**. Similarly ethyl α,β-dichloro-α-methylpropionate and 1,2-dichlorobutane were

treated with **2**. The former does not have an α-hydrogen atom of a carboxylic ester and the latter does not have the electron-withdrawing carboxyl group. In both cases the corresponding reaction did not proceed. These results suggest that path A is reasonable.

Furthermore we investigated the application of this procedure to prepare 5-substituted 4-carboxy-1,3-dithiolan-2-one according to the scheme as described below (Scheme 4). The same procedure with **6a** gave the desired product (**7**) in 18% yield. This product was proven to be a mixture of *cis* and *trans* isomers, as the presence of two types of methyl signals were observed in the nmr spectrum. However when the compounds **6b** and **6c** were treated with **2**, the desired products **9** were not obtained and only α-chloro-β-substituted acrylic acid derivatives **8b** and **8c** were isolated respectively. These results suggest that 1,4-addition of **2** to acrylic ester derivatives are inhibited by

Scheme 4

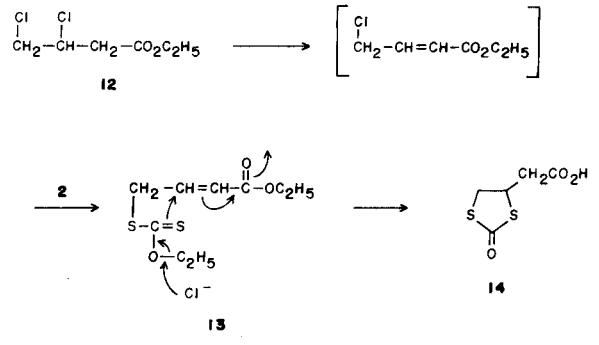


steric hindrance of bulky β-substituents, such as the *n*-nonyl group and the phenyl group. This is supported by the fact that the yield of **7** is lower than that of **4**. In the case of **6c**, the stabilization of **8c** by conjugation with phenyl group also may inhibit the addition reaction.

The same treatment of diethyl dichlorosuccinate (**6d**) with **2** gave 4,5-dicarboxy-1,3-dithiolane-2-thione (**11**) in 30% yield. The structure of **11** was confirmed by elemental analyses and the nmr spectrum. The intermediate of this reaction is presumed to be the compound **10**. As a similar example, Frassetti has reported that 1,3-dithiolane-2-thione could be prepared in quantitative yield by treating diethyl ethylene xanthogenate with potassium hydroxide [3]. The nmr spectrum of **11** exhibits a singlet signal of methine protons at δ 5.5. This indicates that either one of *cis* or *trans* isomer was isolated.

Furthermore, this reaction could be extended to β,γ-dichlorinated carboxylic ester. The same treatment of ethyl β,γ-dichlorobutyrate (**12**) with **2** gave 4-carboxymethyl-1,3-dithiolan-2-one (**14**) in 10% yield. The intermediate of this reaction was isolated by column chromatography on silica gel and the structure was identified as **13** by spectroscopic data. In the nmr spectrum two kinds of ethyl signals are observed and the signals at δ 6.26 and 7.18, which are similar to the signals of olefinic part of ethyl crotonate, indicate the presence of β-alkylated acrylic acid ester. Thus the following scheme illustrates the synthetic sequence of **14** (Scheme 5).

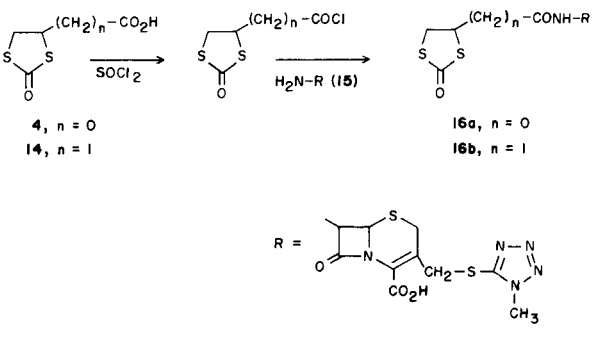
Scheme 5



The novel 1,3-dithiolan-2-one derivatives obtained here were tested for their preventive effect on cucumber anthracnose. The acitivity against *Colletotoricum Lagenarium* is slightly lower than that of a control substance Zineb [4].

In addition we examined the utilization of them for the side chain of the cephalosporin nucleus. The compounds **4** and **14** were condensed to 7-amino-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid (**15**) by the acid chloride method to afford **16a** and **16b** respectively as shown in the following scheme (Scheme 6). The novel cephalosporins **16a** and **16b** show the same level of *in vitro* antibacterial activity as cephalotin.

Scheme 6



EXPERIMENTAL

Melting points (uncorrected) were determined on a Yanaco micro melting point apparatus. Infrared spectra were recorded on a Shimadzu IR-430 spectrophotometer. Proton nuclear magnetic resonance spectra were taken on a Varian EM-390 (90 MHz) or T-60 (60 MHz) spectrometer using TMS or DSS as an internal reference. Mass spectra were measured on a JEOL DX-300 mass spectrometer.

The starting materials, α,β-dichlorocarboxylic esters were prepared by the reaction of the corresponding α,β-unsaturated carboxylic ester with an equimolecular amount of chlorine in the presence of 0.04 equivalent of dimethylformamide at 40° for 2-5 hours. The structure of the products was confirmed by the nmr spectrum and by comparison with the physical data reported in the literature [5a-e]. Other starting materials were commercially available or prepared by the reported methods.

4-Carboxy-1,3-dithiolan-2-one (**4**).

To a solution of potassium hydroxide (20.2 g, 0.36 mole) in ethanol (700 ml), carbon disulfide (34.3 g, 0.45 mole) was added. After addition of ethyl α,β-dichloropropionate (51.3 g, 0.3 mole), the mixture was allowed to stand for 2 days at room temperature. The potassium chloride generated was removed by filtration and the filtrate was concentrated *in vacuo* to yield 74.8 g of *S*-(β-ethoxycarbonyl-β-chloroethyl)-*O*-ethyl dithiocarbonate (**3**) as a residual yellow liquid, nmr (deuteriochloroform): δ 1.30 (t, 3H, -$CO_2CH_2CH_3$), 1.40 (t, 3H, -C(=S)OCH_2CH_3), 3.63 (AB part of ABX, 2H, -S-CH_2-), 4.23 (q, 2H, -$CO_2CH_2CH_3$), 4.47 (X part of ABX, 1H, -CHCl-), 4.63 (q, 2H, -C(=S)OCH_2CH_3).

To the residual liquid **3**, acetic acid (200 ml) and concentrated hydrochloric acid (200 ml) was added. The mixture was heated under reflux for 8 hours and evaporated *in vacuo*. Benzene was added to a residue and the mixture was evaporated to dryness *in vacuo*. The residual solid was recrystallized from chloroform to give 28.2 g (57%) of **4** as pale yellow needles, mp 78-80°; ir (Nujol): ν max 1700 (-COOH), 1640 cm^{-1} (-S-C(=O)-S-); nmr (deuteriochloroform): δ 3.70-4.11 (AB part of ABX, 2H, -CH_2-), 4.77 (X part of ABX, 1H, -CH-COOH), 10.30 (s, 1H, -COOH).

Anal. Calcd. for $C_4H_4O_3S_2$: C, 29.26; H, 2.45; S, 39.05. Found: C, 29.38; H, 2.45; S, 38.84.

4-Carboxy-5-methyl-1,3-dithiolan-2-one (**7**).

By a procedure analogous to that used for **4**, ethyl α,β-dichlorobutylate (46.3 g, 0.25 mole), prepared by the chlorination of ethyl crotonate, was allowed to react with 1.2 molar equivalents of potassium *O*-ethyl dithiocarbonate (**2**) in ethanol. After heating in acetic acid and concentrated hydrochloric acid, the mixture was evaporated *in vacuo* to give 30 g of a reddish oil. After washing with petroleum ether, the oil was dissolved in ether and dicyclohexylamine (28 g, 0.15 mole) was added. A dicyclohexylamine salt of **7** precipitated and was collected by filtration. The salt thus obtained was dissolved in 1*N* hydrochloric acid (250 ml) and extracted with ethyl acetate several times. The combined extracts were dried and evaporated *in vacuo* to give 6.2 g (18%) of **7** as a brown oil; ir (neat): ν max 1710 (-COOH), 1630 cm^{-1} (-S-C(=O)-S-); nmr (deuteriochloroform): δ 1.60, 1.66 (two types of doublets, 3H, CH_3-), 4.10-4.70 (m, 2H, -CH-CH-).

The elemental analysis was performed in the form of the dicyclohexylamine salt.

Anal. Calcd. for $C_5H_6O_3S_2 \cdot C_{12}H_{23}N$: C, 56.79; H, 8.13; N, 3.90; S, 17.83. Found: C, 56.88; H, 8.21; N, 3.86; S, 17.80.

4,5-Dicarboxy-1,3-dithiolane-2-thione (**11**).

Similarly, diethyl α,β-dichlorosuccinate (36.5 g, 0.15 mole), prepared by the chlorination of diethyl fumarate, was allowed to react with 3 molar equivalents of **2** in ethanol. After heating in acetic acid and concentrated hydrochloric acid, the mixture was evaporated *in vacuo*. The residual oil was treated with ether and the ether layer was separated and concentrated *in vacuo* to dryness. The residual solid was recrystallized from water to give 9.8 g (30%) of **11**, mp 218°; ir (nujol): ν max 1690 cm^{-1} (-COOH); nmr (DMSO-d_6): δ 5.50 (s, 2H, -CH-CH-).

Anal. Calcd. for $C_5H_4O_4S_3$: C, 26.78; H, 1.80; S, 42.89. Found: C, 27.22; H, 1.92; S, 43.10.

4-Carboxymethyl-1,3-dithiolan-2-one (**14**).

Similarly, ethyl β,γ-dichlorobutyrate [6] (18.5 g, 0.1 mole) was allowed to react with 1.5 molar equivalents of **2** in ethanol. After removal of potassium chloride, the reaction mixture was concentrated *in vacuo* to yield 20.8 g of *S*-(3-ethoxycarbonylallyl)-*O*-ethyl dithiocarbonate (**13**) as a residual brown liquid [7], nmr (deuteriochloroform): δ 1.27 (t, 3H, -COO-CH_2CH_3), 1.40 (t, 3H, -C(=S)OCH_2CH_3), 3.90 (d of d, 2H, -S-CH_2-CH=), 4.20 (q, 2H, -$COOCH_2CH_3$), 4.66 (q, 2H, -C(=S)-OCH_2CH_3), 5.92 (t of d, 1H, -CH=CH-COO-), 6.83 (t of d, 1H, -CH=CH-COO-).

The mixture of crude **13**, acetic acid (70 ml) and concentrated hydrochloric acid (70 ml) was heated under reflux for 8 hours. After evaporation, the residue was extracted with hot benzene and the benzene extract was evaporated *in vacuo* to give 7.2 g of a residual syrup. The syrup was dissolved in ethanol and dicyclohexylamine (7.3 g, 0.04 mole) was added. By addition of petroleum ether to the mixture, a dicyclohexylamine salt of **14** was precipitated. The salt was collected by filtration and dissolved in 5% sodium bicarbonate. After washing with ethyl acetate, the aqueous solution was acidified to *p*H 1 with concentrated hydrochloric acid, followed by extraction with ethyl acetate. The ethyl acetate phase was dried and evaporated *in vacuo* to give 1.7 g (10%) of **14** as a brown oil; ir (neat): ν max 1705 (-COOH), 1635 cm^{-1} (-S-C(=O)-S-); nmr (deuteriochloroform): δ 3.02 (d, 2H, -CH_2COOH), 3.73 (m, 2H, -S-CH_2-), 4.47 (m, 1H, -CH-).

Elemental analysis was performed in the form of the dicyclohexylamine salt.

Anal. Calcd. for $C_5H_6O_3S_2 \cdot C_{12}H_{23}N$: C, 56.79; H, 8.13; N, 3.90; S, 17.83. Found: C, 56.94; H, 8.10; N, 3.81; S, 17.70.

Reaction of Ethyl α-Chloroacrylate With **2**.

A mixture of ethyl α-chloroacrylate [8] (1.2 g, 0.01 mole) and 1.2 molar equivalents of **2** in ethanol were allowed to stand for 3 days at room temperature. After evaporation, the residual oil was treated with ether. The ether extract was evaporated *in vacuo* to yield 1.6 g (67%) of a residual yellow liquid, which was identified as **3** by the nmr spectrum.

Reaction of Ethyl α,β-Dichloro-α-methylpropionate With **2**.

Ethyl α,β-dichloro-α-methylpropionate (37.8 g, 0.2 mole) was treated with 1.2 molar equivalents of **2**, followed by heating in a mixture of acetic acid and concentrated hydrochloric acid. The mixture was evaporated to yield 17 g (54%) of a residual liquid, which was identified as α,β-dichloro-α-methylpropionic acid by comparison of ir spectrum with that of the authentic sample.

Reaction of 1,2-Dichlorobutane With **2**.

A mixture of 1,2-dichlorobutane and 1.2 molar equivalents of **2** in ethanol was allowed to stand for a week at room temperature. After acidification by hydrochloric acid, the mixture was analyzed by gas chromatography, which showed 90% of 1,2-dichlorobutane was recovered.

Reaction of Ethyl α,β-Dichlorododecanate With **2**.

A mixture of ethyl α,β-dichlorododecanate (16 g, 0.04 mole) and 1.2 molar equivalents of **2** in ethanol was allowed to stand for a week at room temperature. After addition of water (100 ml), the mixture was brought to *p*H 5 with hydrochloric acid and extracted with ether. The ether phase was dried and evaporated *in vacuo* to give 14.5 g of a reddish liquid, which was identified as ethyl 2-chloro-2-dodecanate (**8b**) by the nmr spectrum; nmr (deuteriochloroform): δ 0.86 (m, 3H, CH_3CH_2-), 1.10-1.90 (m, 17H, -(CH_2-), and -$CO_2CH_2CH_3$), 2.18-2.50 (m, 2H, -CH_2-CH=), 4.25 (q, 2H, -$CO_2CH_2CH_3$), 7.00 (t, 1H, -CH=C).

Reaction of Methyl α,β-Dichloro-β-phenylpropionate With **2**.

Methyl α,β-dichloro-β-phenylpropionate (16.8 g, 0.07 mole) was treated with 1.2 molar equivalents of **2**, followed by heating a mixture of acetic acid and concentrated hydrochloric acid. After cooling, a precipitate was collected by filtration to give 10.5 g (80%) of α-chlorocinnamic acid (**8c**), mp 142-143° (lit [9] 137-138°); nmr (deuteriochloroform): δ 7.23-7.50 (m, 3H, Ph-H), 7.70-7.92 (m, 2H, Ph-H), 7.96 (s, 1H, -CH=C).

Sodium 7β-(1,3-Dithiolan-2-one-4-carboxamido)-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylate (**16a**).

A mixture of 4-carboxy-1,3-dithiolan-2-one (0.99 g, 6 mmoles) and thionyl chloride (5 ml) was stirred at 60° for 2 hours. After evaporation, dry benzene (10 ml) was added and the mixture was concentrated *in vacuo* to

give the corresponding acid chloride as a residual syrup. It was dissolved in dry acetone (10 ml). 7β-Amino-3-[(1-methyl-1*H*-tetracol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid (**15**) (1.64 g, 5 mmoles) and sodium bicarbonate (5.04 g) were dissolved in a mixture of water (25 ml) and acetone (15 ml). To this solution, the acid chloride solution previously prepared was added dropwise with stirring and ice-cooling. Subsequently, the solution was stirred for 30 minutes with ice-cooling and for 30 minutes at room temperature. During the reaction, the *p*H of the mixture was kept at 7-8 with saturated sodium bicarbonate. The solution was covered with ethyl acetate (70 ml) and the aqueous phase was acidified to *p*H 1.0 with 6% hydrochloric acid. After removal of a precipitated solid, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (70 ml). The combined organic layers were washed with water, dried and evaporated *in vacuo*. A residual solid was triturated with ether and collected by filtration. To a solution of the solid thus obtained in a mixture of methanol (5 ml) and ethyl acetate (5 ml), 0.65 ml of 33% 1-butanol solution of sodium 2-ethylhexanoate was added with stirring. After stirring for 10 minutes, dry ether (90 ml) was added with stirring with ice-cooling. The precipitate was collected by filtration and dried to give 0.49 g (20%) of **16a**, mp 150° dec; ir (nujol): ν max 1765 (β- lactam), 1640 cm^{-1} (-S(C=O)-S-); nmr (deuteriochloroform): δ 3.50 (m, 2H, C_2-H), 3.93 (s, 3H, tetrazole N-CH_3), 4.00 (m, 2H, -SCH_2-), 4.10 (m, 2H, C_3-CH_2-), 4.80-5.20 (m, 2H, C_6-H + -CH-S-), 5.50 (m, 1H, C_7-H); FAB-ms: $(M + H)^+$ at m/z 497 (mw, 496, monosodium salt).

Anal. Calcd. for $C_{14}H_{13}N_6S_4O_5Na \cdot 1.9H_2O$: C, 31.68; H, 3.20; N, 15.84; Na, 4.33. Found: C, 32.02; H, 3.26; N, 15.45; Na, 4.11.

Sodium 7β-[2-(1,3-Dithiolan-2-on-4-yl)acetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylate (**16b**).

By a similar procedure to that used for compound **16a**, 4-carboxymethyl-1,3-dithiolan-2-one (1.07 g, 6 mmoles) was allowed to react with **15** (1.64 g, 5 mmoles) to give 0.62 g (24%) of **16b**, mp 140° dec; ir (nujol): ν max 1765 (β-lactam), 1640 cm^{-1} (-S-C(=O)-S-); nmr (deuterium oxide): δ 2.90 (m, 2H, -S-CH-CH_2-CO-), 3.60 (m, 2H, C_2-H), 4.00 (m, 5H, tetrazole N-CH_3 and -S-CH_2-CH-), 4.20 (m, 2H, C_3-CH_2-), 4.45 (m, 1H, -CH_2C*H*-S-), 5.06 (d, 1H, C_6-H), 5.60 (d, 1H, C_7-H); FAB-ms: $(M + H)^+$ at m/z 511 and $(M^{\cdot} + Na)^+$ at m/z 533 (mw, 510, monosodium salt).

Anal. Calcd. for $C_{15}H_{15}N_6S_4O_5Na \cdot 0.25H_2O$: C, 34.93; H, 3.04; N, 16.32; Na, 4.46. Found: C, 34.53; H, 3.08; N, 16.79; Na, 4.11.

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