Journal of Organometallic Chemistry, 253 (1983) 31–37
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

ALKYL TELLURAALKANOATES $C_nH_{2n+1}Te(CH_2)_mCOOR$ ($R = CH_3$, C_2H_5 OR H) *

ROBERT A. GRIGSBY, Jr., KURT J. IRGOLIC **
Department of Chemistry, Texas A&M University, College Station, Texas 77843-1243 (U.S.A.)

and FURN F. KNAPP, Jr.,
Nuclear Medicine Group, Health and Safety Research Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830 (U.S.A.)

(Received February 9th, 1983)

Summary

Methyl telluraalkanoates, $C_nH_{2n+1}Te(CH_2)_mCOOR$ (n, m: 4, 7; 6, 4; 6, 7; 6, 9; 7, 4; 8, 7; 11, 2; 11, 5; 18, 11) were synthesized in yields ranging from 33 to 82 percent based on the quantities of the methyl ω-bromoalkanoates substrates. Disodium ditelluride was obtained from tellurium and sodium in ethylenediamine and was treated with alkyl bromides to give dialkyl ditellurides. The crude ditellurides were reduced with $NaBH_4$ to the alkane tellurolates which were coupled with methyl ω-bromoalkanoates to give the methyl telluraalkanoates. Ethyl 4-tellurapentadecanoate was prepared similarly from ethyl 3-bromopropanoate. The telluraalkanoates were characterized by elemental analyses, mass spectrometry, NMR spectrometry, and UV and IR spectrophotometry. Telluraalkanoates radiolabeled with ^{123m}Te or other radioisotopes have been reported elsewhere to be preferentially taken up by the heart and promise to be useful as myocardial imaging agents.

Introduction

Alkyl telluraalkanoates, $C_nH_{2n+1}Te(CH_2)_mCOOR$ belong to the class of unsymmetric tellurides, R′–Te–R″, which cannot be prepared efficiently by stepwise alkylation from disodium telluride. However, methods are available which employ diorganyl ditellurides as starting materials in the synthesis of unsymmetric tellurides [1]. Symmetric diorganyl ditellurides react with reducing agents in appropriate media to form tellurols, RTeH, or tellurolates, RTeM (M = Li, Na, K). The addition of

---

* By acceptance of this article, the publisher or recipient acknowledges the U.S. Government's right to retain a nonexclusive, royalty-free license in and to any copyright covering the article.

** Author to whom all correspondence should be addressed.

alkyl halides to these solutions yields unsymmetric diorganyl tellurides [2,3].

Several telluraalkanoic acids and esters of the general formula $RTeCH_2COOR'$ (R, R′: C_4H_9, C_2H_5; C_4H_9, *l*-menthyl [4]; C_5H_{11}, H [5]) are reported in the literature. These compounds were obtained through a rather involved sequence of reactions not well suited for general application and for the synthesis of telluraalkanoates labeled with the ^{123m}Te radioisotope.

Initial experiments with ^{123m}Te telluraalkanoates suggested that these compounds might be attractive as agents for myocardial imaging [6]. This finding led to the search for simple, high yield reactions which could be employed for the preparation of ^{123m}Te labeled telluraalkanoates. The investigations reported in this paper describe a simple method which has been used to prepare telluraalkanoates of various chain lengths with the tellurium atom in either the 4, 6, 7, 9, 11 or 13 position. Compounds of this type are now being investigated as myocardial imaging agents [7,8]. The most thoroughly evaluated analog is 9-telluraheptadecanoic acid, which shows high uptake and prolonged retention by the heart and high heart/blood ratios in dogs. The concentration of this compound in the heart muscle is directly related to the regional blood flow. The retention of the telluraalkanoate in the heart is probably associated with the conversion of the compound to a telluroxide with subsequent formation of an insoluble polymer via the interaction of the TeO group with the carboxyl group [9]. The corresponding selenium analog, 9-selenaheptadecanoic acid, shows much lower heart uptake and shorter myocardial retention [10].

As described in this paper, the methyl or ethyl telluraalkanoates are prepared by condensation of a tellurolate with an ω-bromoalkanoate. The esters are readily purified by column chromatography, and can be stored with only minimal decomposition. For biological evaluation, the radiolabeled esters are readily hydrolyzed with base to the free acids just prior to administration to laboratory animals.

Experimental

Materials. Tellurium powder (99.9%), Noranda Brand, was obtained as a gift from Canadian Copper Refiners Limited. Ethylenediamine, sodium borohydride, and anhydrous calcium chloride were supplied by Fisher Scientific. The alkyl bromides, $n\text{-}C_nH_{2n+1}Br$, were obtained from Eastman Organic Chemicals ($n = 4$), J.T. Baker Chemical Co. ($n = 6$, 8), and Fluka AG($n = 7$, 11, 18). The ω-bromoalkanoic acids, $Br(CH_2)_nCOOH$, and ethyl 3-bromopropanoate were supplied by Aldrich Chemical Co. ($n = 5$), Fluka AG ($n = 4$) and K&K Laboratories ($n = 7$, 9, 11). Diazald® was also purchased from Aldrich and petroleum ether (b.p. 35–60°C) and anhydrous diethyl ether came from Malinckrodt Chemical Works. Reagent grade benzene, ethanol and hexane were supplied by MCB Manufacturing Chemists, Inc.

Instrumentation and analysis. The mass spectra were obtained with a CEC 21-110B spectrometer. Infrared spectra were recorded on a Beckman IR-8 or a Perkin–Elmer 297 IR spectrometer in the range 4000 to 625 cm^{-1} with the neat compounds between NaCl windows. The UV-visible spectra were obtained with a Cary-14 or Cary-219 spectrophotometer. Proton nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc. of Knoxville, Tennessee and by Chemalytics, Inc. of Tempe, Arizona.

Disodium ditelluride. The quantities in brackets are for the large-batch preparation of disodium ditelluride.

A dry, nitrogen-purged 100-ml [500-ml], two-necked, round bottom flask fitted with a condenser, a magnetic stirring bar and a nitrogen inlet and one neck closed with a rubber septum was charged with tellurium powder (0.51 g, 0.004 mol) [15.0 g, 0.12 mol], ethylenediamine (25 ml) [250 ml] and clean sodium (0.092 g, 0.004 mol) [2.76 g, 0.12 mol]. The stirred reaction mixture was slowly heated with a heating mantle to the reflux temperature (116°C) and kept at this temperature for 2 h. The deep-purple reaction mixture was then allowed to cool to room temperature.

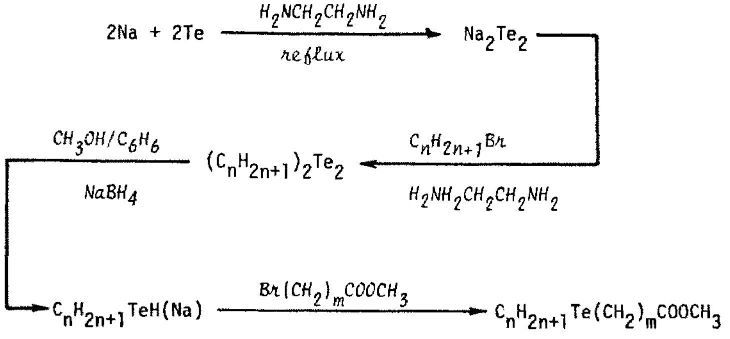
Dialkyl ditellurides. For the preparation of dialkyl ditellurides the solution from the small-scale synthesis of sodium ditelluride can be used. Alternately, an aliquot (8.4 ml) of the large-batch disodium ditelluride solution (containing theoretically 0.002 mol Na_2Te_2) was transferred to a 100-ml, nitrogen-purged, two-necked, round-bottom flask equipped with a reflux condenser and a magnetic stirring bar. One side-arm was capped with a rubber septum. The solution was heated to reflux temperature. The alkyl bromide, $C_nH_{2n+1}Br$ ($n = 4, 6, 7, 8, 11, 18$) (0.004 mol) was added slowly to the refluxing solution by means of a syringe. After all the halide had been added, heating was discontinued and the stirred mixture was allowed to cool to room temperature. Water (25 ml) was then slowly added to the flask. The mixture was transferred to a 100-ml separation funnel and extracted twice with hexane (25 ml each). The combined hexane extracts were washed with water (25 ml) and then dried over anhydrous magnesium sulfate. The filtered solution was kept under aspirator vacuum until all the solvent had evaporated. The crude dialkyl ditellurides, which were obtained as orange to dark-red oils or low melting solids in yields ranging from 66 to 91%, were not purified.

Methyl ω-bromoalkanoates. Diazomethane (approximately 0.02 mol) was generated from Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) (6 g, 0.028 mol) according to the instructions supplied with the compound in an efficient hood behind a safety shield. The yellow solution of diazomethane in diethyl ether (~ 80 ml) was kept at 0°C. This diazomethane solution was added dropwise via a pipette to the solution of the bromoalkanoic acid, $Br(CH_2)_nCOOH$ ($n = 3, 5, 6, 8, 10, 12$), (0.002 mol) in diethyl ether (10 ml) until the ether remained yellow. The ether and the slight excess of diazomethane were removed under an aspirator vacuum. The methyl alkanoates were obtained as oily liquids and were used without further purification. Small volumes of diazomethane solutions not used in the reactions were slowly evaporated under a stream of nitrogen in a well ventilated hood.

Methyl telluraalkanoates. The crude dialkyl ditelluride (0.0013 mol) was dissolved in a mixture of ethanol (20 ml) and benzene (20 ml) and placed in a nitrogen-purged, 100-ml flask equipped with a stirring bar and a nitrogen inlet. Sodium borohydride was added in small portions to the stirred solution until the red color had disappeared. The methyl ω-bromoalkanoate (0.001 mol) was added dropwise from a pipette into the reaction mixture. After all the alkanoate had been added, the mixture was stirred at room temperature for 30 min and then poured into a 250-ml separatory funnel containing water (40 ml) and diethyl ether (25 ml). After thorough shaking the organic phase was separated, washed three times with 25-ml portions of water, dried over anhydrous calcium chloride and filtered. The solvent was removed from the filtrate under an aspirator vacuum. The residue was placed on a silicic acid column (25 g Sil-A-200 packed into a 2 cm × 55 cm column with petroleum ether). The excess orange-red dialkyl ditelluride was washed from the column with petroleum ether. The telluraalkanoate was collected as a yellow solution with diethyl ether/petroleum ether (2/98 v/v) as the mobile phase. After evaporation of the solvent under an aspirator vacuum at 40°C the telluraalkanoate remained as an analytically pure, yellow oil.

Results and discussion

Methyl telluraalkanoates, $C_nH_{2n+1}Te(CH_2)_mCOOCH_3$ (n, m: 4, 7; 6, 4; 6, 7; 6, 9; 7, 4; 8, 7; 11, 2; 11, 5; 18, 11) were prepared from alkane tellurolates and methyl ω-bromoalkanoates in yields ranging from 33 to 82 percent according to the sequence of reactions summarized in Scheme 1. Disodium ditelluride has been obtained from equimolar amounts of sodium and tellurium in liquid ammonia [11], ethylenediamine [12] or dimethylformamide [13]; from tellurium, sodium borohydride and sodium in absolute ethanol [14], and from tellurium (1 mol) and sodium hydride (1 mol) in dimethylformamide [12]. When hexyl bromide reacted with these disodium ditelluride solutions the yields of crude dihexyl ditelluride were 94% (liquid ammonia reactions), 78% (ethylenediamine), 70% (sodium borohydride/ethanol) and 62% (sodium hydride/DMF) [12]. Although the highest yields were obtained in the liquid ammonia reactions, working with this solvent is inconvenient. Alkyl halides with more than ten carbon atoms freeze at liquid ammonia temperatures. To obtain dialkyl tellurides from such halides, the ammonia must be evaporated and replaced by a higher boiling solvent. Ethylenediamine is much easier to handle than ammonia. Reactions between disodium ditelluride and alkyl bromides produced dialkyl ditellurides in good yields when the halides were added to the refluxing solution of disodium ditelluride. All of the ditellurides were therefore prepared with ethylenediamine as the reaction medium. The water-soluble ethylenediamine is easily separated which simplifies the isolation of the dialkyl ditellurides. The only impurity identified in the ditellurides prepared in this manner are varying amounts of the symmetric tellurides.



SCHEME 1

Since the methyl telluraalkanoates are purified by column chromatography, pure dialkyl ditellurides are not necessary for the synthesis of these compounds. Any symmetric telluride impurity will be removed in the initial column wash (vide ante). The crude ditellurides were reduced to alkane tellurolates with sodium borohydride

TABLE 1. ALKYL CHALCOGENAALKANOATES, $C_nH_{2n+1}X(CH_2)_mCOOR$

$C_nH_{2n+1}X(CH_2)_mCOOR$				Analysis found (calcd.)		Yield (%)[a]	Molecular mass[b] Mass spec.
n	X	*m*	R	C	H		
4	Te	7	CH_3	45.62 (45.66)	7.72 (7.66)	33	344.0999 (.0986)
6	Te	4	CH_3	43.85 (43.95)	6.29 (7.38)	67	330.0843 (.0854)
6	Te	7	CH_3	48.86 (48.69)	7.31 (8.17)	82	372.1313 (.1304)
6	Te	9	CH_3	51.40 (51.30)	8.41 (8.61)	65	400.1625 (.1621)
7	Te	4	CH_3	45.34 (45.66)	6.65 (7.66)	56	344.0999 (.1011)
8	Se[c]	7	CH_3	58.67 (58.43)	9.89 (9.81)	56	350.1724 (.1714)
8	Se[c]	7	H	57.26 (57.30)	9.30 (9.62)	79	336.1567 (.1577)
8	Te	7	CH_3	51.00 (51.30)	8.40 (8.61)	78	400.1625 (.1621)
11	Te	2	C_2H_5[d]	50.13 (50.04)	7.32 (8.40)	43	386.1469 (.1455)
11	Te	5	CH_3	52.67 (52.46)	8.05 (8.81)	51	414.1782 (.1795)
18	Te	11	CH_3	62.79 (62.64)	9.98 (10.51)	44	596.3817 (.3819)

[a] Yields of purified product based on alkyl ω-bromoalkanoate. [b] The first number represents the theoretical molecular mass based on $^{12}C = 12.0000$, $^{1}H = 1.007825$, $^{16}O = 15.994915$, $^{130}Te = 129.9067$ and $Se = 79.9165$; the digits in parantheses give the decimals of the experimental molecular mass. [c] Prepared according to the procedure in ref. 10. [d] Prepared from ethyl propanoate.

TABLE 2. PROTON NMR, UV AND IR DATA FOR ALKYL CHALCOGENAALKANOATES, $C_nH_{2n+1}X(CH_2)_mCOOR$

$C_nH_{2n+1}X(CH_2)_mCOOR$				NMR ($CDCl_3$, 0.5 *M*, TMS int.)					IR (cm^{-1}) ν(CO)	UV λ max (log ε)
n	X	*m*	R	R(s)	CH_2COO(t)[a]	CH_2XCH_2(t)[a]	other CH_2(m)	CH_3[b]		
4	Te	7	CH_3	3.70	2.33 (7)	2.67 (7)	1.1–1.8	0.88	1750	233.0 (3.71)
6	Te	4	CH_3	3.68	2.37 (6)	2.67 (7)	1.1–2.0	0.92	1735	233.0 (3.68)
6	Te	7	CH_3	3.65	2.30 (7)	2.62 (7)	1.1–2.0	0.90	1735	233.0 (3.66)
6	Te	9	CH_3	3.78	2.33 (6)	2.65 (7)	1.1–2.0	0.90	1730	235.0 (3.72)
7	Te	4	CH_3	3.65	2.33 (6)	2.68 (7)	1.1–2.0	0.90	1735	232.0 (3.68)
8	Se	7	H	10.63	2.35 (6)	2.56 (7)	1.1–2.0	0.88	–	–
8	Se	7	CH_3	3.67	2.38 (6)	2.57 (7)	1.1–2.0	0.90	1730	216.0 (3.45)
8	Te	7	CH_3	3.70	2.35 (7)	2.68 (7)	1.1–2.0	0.92	1740	233.0 (3.64)
11	Te	2	C_2H_5	[c]	2.68 (7)	2.82 (7)	1.2–2.1	0.88	1730	233.0 (3.59)
11	Te	5	CH_3	3.70	2.33 (6)	2.67 (7)	1.1–1.8	0.88	1750	233.0 (3.71)
18	Te	11	CH_3	3.62	2.30 (6)	2.67 (7)	1.1–2.0	0.88	1730	233.0 (3.45)

[a] *J*(HH) given in parentheses. [b] Poorly resolved triplet. [c] $R = C_2H_5$: 4.17(q), 1.23(t).

in methanol/benzene [2, 3, 15–17]. To assure that the methyl ω-bromoalkanoates were completely used in the reactions with tellurolates, an approximately two-fold excess of the alkane tellurolates was employed. After the reagents had been combined, the almost colorless mixtures were stirred for 30 min at room temperature. Treatment with water and extraction with diethyl ether, produced an orange-colored organic phase. The orange oil obtained after evaporation of the ether was chromatographed on silica gel. The unreacted excess symmetric ditelluride was removed in the initial column wash. Further elution provided pure methyl telluraalkanoates (Table 1).

When a series of dialkyl ditellurides and telluraalkanoates must be prepared, a large batch of disodium ditelluride can be made from tellurium and sodium in ethylenediamine. The concentration of disodium ditelluride solution is calculated from the amounts of the reagents and the volume of solvent used, and the appropriate aliquots are measured in a graduated cylinder or syringe for quick transfer. Although disodium ditelluride solutions are sensitive to oxygen, aliquots can be transferred quickly in air with only negligible deposition of tellurium on the surface of the solution.

Although the alkyl telluraalkanoates can be handled in air, prolonged exposure to light and the atmosphere should be avoided to prevent oxidation and decomposition. With exception of ethyl 4-tellurapentadecanoate all of the esters prepared in this study were stable when stored in sealed vials under nitrogen in a freezer. Ethyl 4-tellurapentadecanoate deposited tellurium after a few days even under these conditions.

The alkyl telluraalkanoates were characterized by mass spectrometry, proton NMR spectrometry, and UV-visible and IR spectrophotometry. These data are summarized in Tables 1 and 2.

All of the mass spectra of the telluraalkanoates contained molecular ions. Exact mass measurements on the molecular ion peaks containing the ^{1}H, ^{12}C, ^{16}O and ^{130}Te isotopes agreed well with the calculated molecular mass values (Table 1).

The proton NMR data (Table 2) illustrate that the CH_2Te triplets are found in the 2.62 to 2.82 ppm range which is approximately 0.3 ppm upfield from the corresponding CH_2Te resonances in the spectra of the dialkyl ditellurides [12]. The poorly resolved triplets of the terminal methyl groups in the alkyl chains are located between 0.88 and 0.92 ppm. The CH_2COO protons have chemical shifts of approximately 2.33 ppm, which is similar to those found for methyl alkanoates at 2.23 ppm [18]. However, in ethyl 4-telluropentadecanoate the CH_2COO resonance is at 2.68 ppm. Protons on the carbon atom in the α, β or γ-position to the tellurium atom are also deshielded compared to similar protons in compounds not containing a heteroatom. The deshielding effect decreases with increasing distance from the tellurium atom and does not extend beyond three carbon atoms. The ROOC-resonances in the 3.65 to 3.78 ppm range are similar to those of the chalcogen-free compounds [19]. The other methylene groups exhibit multiplets over the 1.0 to 2.0 ppm range.

The IR spectra of the neat alkyl telluraalkanoates exhibit carbonyl absorptions at approximately 1735 cm^{-1} (Table 2). Methanolic solutions of the compounds absorbed ultraviolet radiation at 233 nm with log ε values between 3.71 and 3.42 (Table 2). This band can be assigned to the C–Te–C groups. Diethyl telluride has an absorption maximum at 235 nm (log $\varepsilon = 3.84$). Methyl 9-selenaheptadecanoate absorbed at 216 nm (log ε = 3.45). Diethyl selenide is reported to have a band at 250 nm (log ε = 1.70) [20]. The selenaalkanoate does not absorb at all at 250 nm suggesting that the reported diethyl selenide absorption is erroneous.

Acknowledgements

The financial support of these investigations by the Office of Health and Environmental Research, U.S. Department of Energy under contract W-7405-eng-26 with the Union Carbide Corporation through a subcontract with The Texas A&M Research Foundation, the Selenium–Tellurium Development Foundation, and the Robert A. Welch Foundation of Houston, Texas is greatly appreciated.

References

1 K.J. Irgolic, The Organic Chemistry of Tellurium, Gordon and Breach Science Pubishers, Inc., New York, N.Y., 1974, p. 121.
2 J.L. Piette and M. Renson, Bull. Soc. Chim. Belges, 79 (1970) 353.
3 J.L. Piette and M. Renson, Bull. Soc. Chim. Belges, 79 (1970) 367.
4 M.P. Balfe and K.N. Nandi, J. Chem. Soc., (1941) 70.
5 M.P. Balfe, C.A. Chaplin and H. Phillips, J. Chem. Soc., (1938) 341.
6 F.F. Knapp, Jr., K.R. Ambrose, R.A. Grigsby, A.P. Callahan and K. J. Irgolic, Proc. 2nd Int. Symp. Radiopharm., March, 1979, Seattle, Washington, p. 101.
7 F.F. Knapp, Jr., K.R. Ambrose, A.P. Callahan, L.A. Ferren, R.A. Grigsby and K.J. Irgolic, J. Nucl. Med., 22 (1981) 988.
8 R.D. Okada, F.F. Knapp, Jr., D.R. Elmaleh, T. Yasuda, C.A. Boucher and H.W. Strauss, Circulation, 65 (1982) 305.
9 G. Kirsch, M.M. Goodman, and F.F. Knapp, Jr., Organometallics, 2 (1983) 357.
10 F.F. Knapp, Jr., T.A. Butler, K.R. Ambrose, A.P. Callahan, C.E. Guyer, J.A. Roberts, C.A. Ferren, R.A. Grigsby, and K.J. Irgolic, Applications of Nuclear and Radiochemistry, Chapter 28, Pergamon Press, New York, 1982, p. 347–358.
11 M.T. Chen and J.W. George, J. Organomet. Chem., 12 (1968) 401.
12 R.A. Grigsby, Ph.D. Dissertation, Te-123m Labeled Fatty Acids and Barbiturates: Synthesis, Characterization and Use as Imaging Agents for the Myocardium and the Brain. Texas A&M University, August 1980.
13 D.J. Sandman, J.C. Stark and B.M. Foxman, Organometallics, 1 (1983) 739.
14 G.P. Basmadjian, G.R. Parker, A.S. Kirchner, R.D. Ice, R.A. Magarian and S.J. Mills, J. Nucl. Med., 19 (1978) 689.
15 J.L. Piette and M. Renson, Bull. Soc. Chim. Belges, 79 (1970) 33.
16 N. Dereu, J.L. Piette, J. Van Coppenolle and M. Renson, J. Heterocycl. Chem., 12 (1975) 423.
17 S.R. Buzilova, I.D. Sadekov, T.V. Lipovich, T.M. Filippova and L.I. Vereshagin, Zh. Obhsch. Khim., 47 (1977) 1999.
18 The Sadtler Standard Spectra, Sadtler Research Laboratories, Inc., NMR Spectrum No. 6790, 1964.
19 Ref. 18, NMR Spectra No. 6903, 10425, 10160, 10161.
20 D.L. Klayman and W.H.H. Gunther, Organic Selenium Compounds: Their Chemistry and Biology. John Wiley and Sons, Inc., New York, 1973, p. 867.