2-Oxaadamantane-1-N,N,N-trimethylmethanaminium Iodide:[1] Synthesis and Potential for Muscarinic Activity*

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The synthesis of the title compound from adamantanone is described. The series of steps include ring expansion and hydrolysis to *endo*-7-hydroxy-*exo*-3-bicyclo(3.3.1)nonane carboxylic acid, followed by oxidative ring closure using lead tetraacetate. The final substituted oxaadamantane incorporates the key functional group elements known to be necessary for useful muscarinic activity into a molecular geometry not present in acetylcholine agonists or antagonists previously prepared.

INTRODUCTION

The human autonomic nervous system is usually divided into two units the names of which relate to the types of natural chemical transmitters that stimulate them.[5] The sympathetic or adrenergic one responds to treatment with adrenalin; the parasympathetic or cholinergic unit functions when in contact with acetylcholine (ACh, *Ia*). The characteristics of interneuron membranes have been subclassified further from observations of the effect that nicotine or muscarine (*IIa*) has on them. The latter compound is the parent to which a number of synthetic chemicals called »muscarines« are compared both with respect to potency as well as chemical structure.
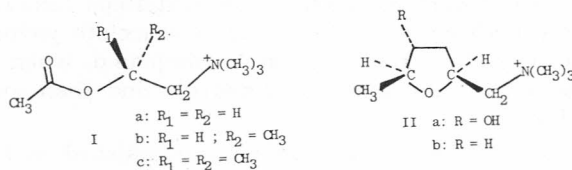
There is a need for the development of more efficient drugs for use in the chemical treatment of nerve diseases, a problem that becomes more prevalent as the human life-span increases. To be effective, a drug must bind to a membrane. Only a few of the large number of synthetic materials tested for cholinergic activity meet this requirement. The basis for most structural

modification studies has been to divide ACh into three fragments as follows: the oxygen containing or ester portion, the ethano carbon skeleton, and the quaternary ammonium group. To learn how the lipoprotein molecules of the membranes, the receptors, might be stereochemically structured both at rest and when binding to a transmitter, model compounds similar to but more conformationally rigid than *I* and *IIa* have been prepared. Productive structure-activity relationship data has been obtained from evaluation of the cyclic examples *IIb-VI*.[6]
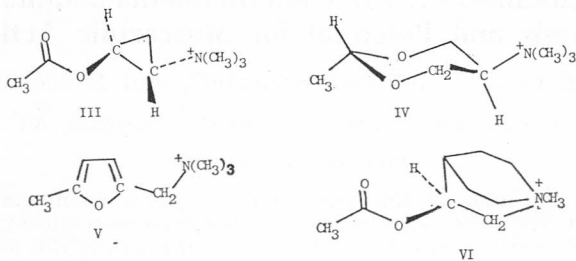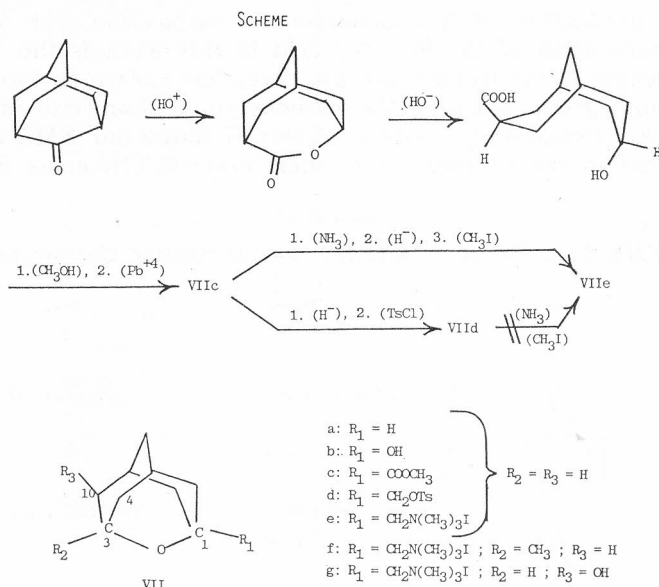

The present paper contains information on the synthesis of the first in a new series of potential muscarine-like compounds. The unique structure of 2-oxaadamantane-1-*N,N,N*-trimethylmethanaminium iodide (*VIIe*) contains the three fragments considered necessary for the neurotransmitter activity, but they are incorporated into a more rigid and hydrophobic molecular composite than in previously studied compounds. The synthesis is facilitated by the ability of lead tetraacetate to convert alcohols to cyclic ethers.[7]

<div align="center">SYNTHESIS CONSIDERATIONS</div>

The Scheme shows the series of steps that result in the synthesis of *VIIe*. Adamantanone readily undergoes a Baeyer-Villiger reaction with peroxytrifluoracetic acid to yield the expected lactone. The latter can be made to ring open with concomitant epimerization of the carboxylate moiety to give *endo*-7-hydroxy-*exo*-3-bicyclo(3.3.1)nonane carboxylic acid. Esterification of the acid group to prevent decarboxylation in the next step,[8] followed by oxidative ring closure of the hydroxy ester with lead tetraacetate yields methyl-2-oxaadamantane-1-carboxylate (*VIIc*). This latter compound, when treated sequentially with ammonia, lithium aluminum hydride and then iodomethane provides the desired *VIIe*.

The preparation of the lactone can be accomplished in high yield using the general procedures published for the oxidation reaction.[9] It proved reluctant to undergo hydrolysis, however, unless concentrated base and extended reflux times were used. High yields of the corresponding hydroxy acid can be obtained using 25% sodium hydroxide in water-methanol. In more dilute base the unreacted lactone is recovered.

The hydroxy acid shown in the Scheme is a 3,7-disubstituted bicyclo(3.3.1)-nonane derivative and, as such, has several stereochemical properties that merit evaluation. First, the flexibility of the two rings allows for both chair-chair and chair-boat geometries to exist. For the parent hydrocarbon, as well as for several derivatives, various authors have used numerous experimental

SCHEME

a: R_1 = H
b: R_1 = OH
c: R_1 = COOCH$_3$ R_2 = R_3 = H
d: R_1 = CH$_2$OTs
e: R_1 = CH$_2$N(CH$_3$)$_3$I
f: R_1 = CH$_2$N(CH$_3$)$_3$I ; R_2 = CH$_3$; R_3 = H
g: R_1 = CH$_2$N(CH$_3$)$_3$I ; R_2 = H ; R_3 = OH

VII

techniques to achieve understanding of the forces that dictate conformation preferences.[10] All agree that several can coexist and that their relative concentration in any given situation will depend on the position, type and stereochemistry of attached substituents. Furthermore, the bicyclic structure prefers a flattened chair-chair or chair-boat conformation any time there is a group other than hydrogen in the *endo*-3 and/or -7 position.[10] Second, as with cyclohexane examples, substituents prefer to occupy an equational position unless two having similarly disposed dipoles are in close proximity. Table I shows data for mixtures of isomers known to exist under equilibrating conditions.
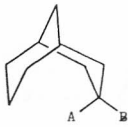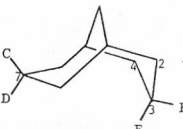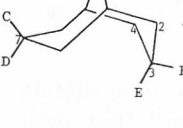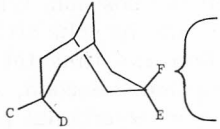
TABLE I
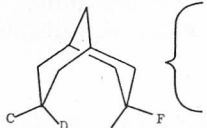
Preferred Stereochemistry in Bicyclo(3.3.1)nonane Derivatives

Substituent	Equatorial (%)	Ref.
2-OH	69	11
3-OH	97	11
3-COOCH$_3$	99	12

The lactone formed in the present synthesis would yield an *endo*-3, *endo*-7, diaxially substituted bicyclo(3.3.1)nonane if the generally accepted mechanism of hydrolysis were followed and no competing processes occurred. A number of analogies from the literature can be advantageously called upon to explain the need for the strongly basic conditions described above for the hydrolysis. In general, two compatible groups will react with each other if they are in the *endo*-3 and *endo*-7 positions. Hence, the degenerate pair of chair-boat conformers of *endo*, *endo*-3,7-bicyclo(3.3.1)nonandiol react in sulfuric acid to form oxaadamantane (*VIIa*),[13] *endo*-7-hydroxybicyclo(3.3.1)nonane-3--one exists in the ring closed form *VIIb*,[14] and, when *endo*,*endo*-3,7-bicyclo--(3.3.1)nonane dicarboxylic acid or its dimethyl ester is treated with base,

quantitative cyclization to 2-adamantanone-1-carboxylic acid occurs.[15] The successful preparation of the hydroxy acid in this work is the result of not only ring opening of the lactone but also reversible carbanion formation *alpha* to the carbonyl group allowing the carboxylate to isomerize *in situ* to the more stable *exo* (equatorial) position.[16] Table II shows our NMR data in comparison to that in the literature for other bicyclo(3.3.1)nonane derivatives.

TABLE II

NMR Data For Bicyclo(3.3.1)nonane Derivative Conformers

| Conformer	Proton/δ(ppm)	Ref.
	A=H/4.25; B=OH	10a, 11, 17
	A=H/2.25; B=COOCH$_3$	11,15
	VIII C=H/3.80; D=OH; E=F=H	10a, 11, 17
	IX C=H/4.00; E=H/3.36; D=OH; F=COOCH$_3$	This Work
	C=H/4.18; D=OH; E=COOCH$_3$; F=H	18
	D=H/4.20; E=H/2.65; C=OH; F=COOCH$_3$	18

Compounds containing an oxaadamantane moiety have been prepared from several different cyclization procedures applied to bicyclo(3.3.1)nonane derivatives. Two examples have already been mentioned.[13,14] Moon, *et al.* have utilized a two-fold oxymercuration reaction on several bicyclo(3.3.1)nona-2,6-dienes, followed by sodium borohydride reduction, to prepare 6-substituted--2-oxaadamantane compounds.[19] Bicyclo(3.3.1)nonan-3,7-dione has been shown to react with nitromethane to give 1,3-disubstituted-2-oxaadamantanes.[20]

Pertinent to the present study is the conversion of *VIII*, which is in equilibrium with the chair-chair conformer, into *VIIa* using lead tetraacetate.[8b,17] The ability of the latter metal ion oxidant to convert alcohols to tetrahydrofuran and tetrahydropyran derivatives has been most extensively studied in Yugoslavia under the direction of Mihailović.[21] The mechanism of cyclic ether formation involves both free radical and ionic species. The oxidant is considered to first form an alkoxylead triacetate intermediate which undergoes homolytic cleavage to generate an alkoxy free radical. The latter may abstract

a hydrogen atom from a proximal carbon if structural and experimental conditions are right. The carbon-centered free radical is then most likely oxidized to a carbonium ion which captures the previously formed neighboring hydroxyl group.

The relationship of alcohol structural features to the ratio of oxidation products that can be obtained from reaction with lead tetraacetate is well known. In general, a 1,5-hydrogen atom shift leading subsequently to a tetrahydrofuran product will predominate if allowed by the stereochemistry of the carbon skeleton. Only when an *epsilon* carbon-hydrogen bond in an alicyclic alcohol is activated by an adjacent π-bond or heteroatom will a tetrahydropyran product become important. Ester functional groups do not interfere with some types of intramolecular oxidation reactions but no studies designed to evaluate their effect on the ether-forming reaction have been reported.[22] That is, no examples of alcohols having a carboalkoxy group attached to a *delta* or *epsilon* carbon have been previously treated with lead tetraacetate. It is precisely such a positioning that exists in the key molecule being utilized for the synthesis of *VIIc-e* in this work.

When the present work was initiated it was considered that the electronic nature of the *exo*-3 ester group in *IX* (Table II) could inhibit the formation of a carbocation at C3 subsequent to intramolecular abstraction of the *endo*-3 hydrogen. In the higher energy chair-boat conformer of *IX* not shown in Table II, but certainly present in the hot reaction medium, the *endo*-7 alkoxy radical would be within bonding distance of the two equivalent axial hydrogen atoms at C2 and C4. Carbocation formation at one of these latter centers would not be influenced by the C3 ester group and it was predicted that oxidation of *IX* could produce *X* rather than the more strain-free tetrahydropyran, *VIIc*.

X   XI
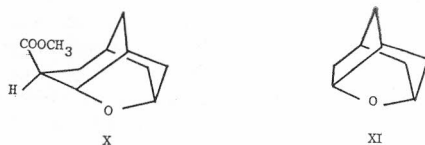
Analogy for the possible formation of *X* comes from the example of Brun, *et al*. who report that lead tetraacetate oxidation of *endo*-bicyclo(3.2.1)--octan-3-ol yields tricyclic ether *XI*.[23] Our results indicate, however, that even though the electronic influence of the ester group probably inhibits carbocation formation *alpha* to the ester group, the high energy chair-boat conformation of *IX* is not influencial in the ether forming reaction. No detectable amount of *X* was formed as evidenced by the lack of NMR signal for a C—H proton *alpha* to the ester carbonyl and the simplicity of the ^{13}C spectrum of the product.

The final three steps in the overall synthesis of (*VIIe*) followed standard reaction procedures. However, an alternative synthesis sequence (Scheme) merits a brief comment. 1-Carbomethoxy-2-oxaadamantane was reduced to the corresponding 1-hydroxymethyl derivative with lithium aluminum hydride. The tosylate *VIId* was prepared and treated with ammonia in methanol at

elevated temperature and pressure in an attempt to form 2-oxaadamantane-1-methanamine. The tosylate was consistently recovered unchanged, which reflects its neopentyl-like nature and lack of SN_2 reactivity.[24]

CONCLUSION

Lead tetraacetate can be used to prepare oxaadamantane derivatives structurally related to compounds capable of controlling neuron impulses. The availability of the parent compound in the new series of molecularly compact substrates will allow more information to be gained on the nature of muscarinic chemicals and how they interact with receptor membranes.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and have not been corrected. IR spectra were determined using a Perkin Elmer 1340 spectrophotometer, and ^1H NMR spectra were recorded on a Hitachi-Perkin Elmer R-24B instrument using tetramethylsilane (TMS) as an internal standard; shifts are given in ppm values downfield from TMS. The ^{13}C NMR spectrum of *VIIc* was recorded on a Varian instrument using benzene as an internal standard. Gas-liquid chromatography (GLC) was performed on a Perkin Elmer Sigma 2000 Mod. with flame ionization detector, using column 2×0.002 m with $3^0/_0$ Silicone OV-17 on Gas Chrom D and nitrogen as carrier gas. Electron impact mass spectrometry was performed on a Dupont 21-490 instrument at 70 ev. Thin layer chromatography (TLC) was performed on Eastman Kodak silica gel coated plastic plates with fluorescent indicator. Column chromatography was run over silica gel 40—140 mesh (Baker). Organic extracts were regularly dried over $MgSO_4$ and evaporated *in vacuo*. Commercially available adamantanone from Aldrich Chemical Company was used as starting material.

2-Oxatricyclo(4.3.1.1$^{4.8}$)undecane-3-one (Lactone)

Trifluoroacetic anhydride (29.7 g, 0.14 mol) was dissolved in 30 mL methylene chloride and cooled in an ice bath. To this solution was added, dropwise, $50^0/_0$ hydrogen peroxide (3.0 mL, 0.053 mol) with vigorous stirring for 10—15 minutes. The resulting solution was added over a 20 minute period to a stirred suspension of anhydrous Na_2HPO_4 (35.9 g, 0.25 mol) in methilene chloride (250 mL) and 2-adamantanone (7.50 g, 0.050 mol). The mixture was refluxed for 24 hours, cooled and filtered to remove the insoluble salts, which were washed repeatedly with methylene chloride. The washes were combined with the original filtrate, and the total solution was washed with saturated sodium bicarbonate solution (125 mL). The organic layer was then dried and evaporated, giving 7.79 g (0.47 mol, 93.9$^0/_0$ yield) of the lactone, m. p. 288—289 °C (lit. 285—287 °C)[9], 100$^0/_0$ pure by GLC. IR (KBr): 2910 (s), 2850 (m), 1715 (vs), 1165 (s) cm^{-1}. ^1H NMR (CDCl$_3$): 4.45 (M, 1H, H-1), 3.05 (m, 1H, H-4), 2.5—1.3 (m, 12H) ppm.

endo-7-Hydroxy-exo-3-bicyclo(3.3.1)nonane Carboxylic Acid (Hydroxy-acid)

Lactone (7.50 g, 0.045 mol) was stirred and refluxed with 250 mL of a 25$^0/_0$ sodium hydroxide solution in water : methanol (3 : 1) for 24 hours. The methanol was removed *in vacuo*, the mixture cooled, diluted with 250 mL ice water and washed with methylene chloride (2 × 125 mL) to remove any unhydrolyzed lactone. The basic aqueous layer was then cooled in an ice bath and made acidic with concentrated hydrochloric acid (pH monitored with VWR Scientific universal pH paper). The acidified reaction mixture was extracted with methylene chloride (3 × 250 mL), dried, and evaporated to leave 7.03 g (0.038 mol, 83.6$^0/_0$ yield) of the hydroxy-acid. The product was recrystallized from methylene chloride (appr. 75 mL/g); m. p. 151—152 °C (lit. 150 °C)[25], 100$^0/_0$ pure by GLC. IR (KBr): 3450 (s),

3200—2500 (broad, s), 1710 (vs) cm^{-1}. ^{1}H NMR (DMSO): 5.7—5.0 (broad s, 2H, OH, COOH), 3.90 (quintet, 1H, H-7), 3.40 (sextet, 1H, H-3), 2.5—1.0 (m, 12H) ppm.

Anal. $C_{10}H_{16}O_3$ (184.24) calc'd.: C 65.19; H 8.76%
found: C 65.46; H 8.90%.

Methyl endo-7-hydroxy-exo-3-bicyclo(3.3.1)nonane Carboxylate (IX)

Hydroxy-acid (5.01 g, 0.027 mol) was added to 100 mL of dry methanol with stirring. Once dissolved, BF$_3$:2 CH$_3$OH (2.0 mL; Aldrich) was added quickly with stirring. This solution was refluxed for one hour and then cooled to room temperature. The cooled solution was made basic with saturated sodium bicarbonate solution, and the methanol was removed *in vacuo*. Water (50 mL) was added and then the basic aqueous layer was extracted with methylene chloride (4 × 60 mL). The organic layer was dried and evaporated to yield 5.05 g of a clear yellow oil containing two fractions according to TLC. Column chromatography (methylene chloride-ethyl acetate eluent, 5 : 1) yielded 4.74 g (0.024 mol, 88%) of the hydroxy--ester as a white solid, m. p. 50.5—51.5 °C, 100% pure by GLC. IR (crystalline film): 3220 (s, broad), 1720 (s), 1440 (s) cm^{-1}. ^{1}H NMR (CDCl$_3$): 4.1—3.8 (quintet, 1H, H-7), 3.60 (s, 3H, OCH$_3$), 3.5—3.0 (m, 1H, H-3), 2.45 (s, 1H, OH), 2.3—1.1 (m, 12H) ppm.

The other fraction, present in about 3—5%, appeared to be the ene-ester resulting from dehydration of the desired product. IR (neat liquid): 1750 (s) cm^{-1}. ^{1}H NMR (CDCl$_3$): 5.82 (m, 2H, HC=CH), 3.63 (s, 3H, OCH$_3$), 3.0—1.5 (broad, m, 11H).

Methyl 2-Oxaadamantane-1-carboxylate (VIIc)

Hydroxy-ester (*IX*, 2.86 g, 0.014 mol) was dissolved in dry, distilled benzene (230 mL) and the solution was purged with dry nitrogen for 15 minutes. Then, lead tetraacetate ([CH$_3$COO]$_4$Pb, 6.75 g, 0.015 mol; dried in vacuum desiccator over KOH to remove excess acetic acid) was added and dry nitrogen was bubbled through the mixture for an additional ten minutes. After the mixture was refluxed for 15 hours, it was cooled and filtered to remove the lead diacetate precipitate which was the thoroughly washed with benzene. The benzene solution was washed with saturated sodium bicarbonate solution (2 × 100 mL) and water (100 mL), dried and evaporated to leave a pale yellow oil (2.85 g, approximately 80% of the ring-closed product, and 7% starting material according to GLC). Column chromatography (petroleum ether-ethyl acetate eluent, 4 : 1) followed by sublimation (30—35 °C/1.2 torr) yielded 2.20 g (0.011 mol, 78.4%) of the oxaadamantane ester (*VIIc*) as colorless prisms, m. p. 39—40 °C, >99% purity by GLC. IR (KBr): 1730 (s), 1440 (m), 1270 (s), 1200 (s), 1100 (s) 1090 (s) cm^{-1}. ^{1}H NMR (CDCl$_3$): 4.27 (m, 1H, H-3), 3.75 (s, 3H, OCH$_3$), 2.5—1.2 (m, 12H) ppm. ^{13}C NMR (C$_6$H$_6$, 0.00): —44.49 (s, COOCH$_3$), 55.38 (s, C$_1$), 60.20 (d, C$_3$), 77.39 (q, CH$_3$), 90.88 and 93.39 (t, t; C$_4$, C$_8$, C$_9$, C$_{10}$), 101.65 (d, C$_5$, C$_7$), 128.60 (q, C$_6$) ppm.

2-Oxaadamantane-1-carbonxamide

Oxaadamantane ester (*VIIc*, 1.50 g, 7.6 mmol) was added to concentrated ammonium hydroxide (6.0 mL, 0.089 mol) and stirred for 15 hours. The white precipitate was vacuum filtered and washed with water (4 × 5 mL). Air drying yielded 0.86 g of a white powder, m. p. 177—179 °C. This was combined with the methylene chloride extracts (3 × 15 mL) of the aqueous filtrate, dried and precipitated with petroleum ether to yield 1.02 g (5.6 mmol, 73.6%) of the amide as white needles, m. p. 179—180 °C, >99% purity by GLC. IR (KBr): 3440 (s), 3260 (w), 3200 (m), 1650 (s) cm^{-1}. ^{1}H NMR: 6.60 (broad s, 1H, NH), 5.80 (broad s, 1H, NH), 4.19 (broad s, 1H, H-3), 2.7—113 (m, 12H) ppm.

A colorless crystalline mass (0.18 g) resulted from evaporation of the aqueous filtrate, m. p. 211 °C. On the basis of melting point, IR data [3500—2500 (broad, strong, 1570 (strong)], and its mass this was determined to be ammonium 2-oxa-adamantane-1-carboxylate. Acidification with 5% HCl followed by etxtraction with methylene chloride yielded 0.13 g (0.71 mmol, 9.33%) of 2-oxaadamantane-1-carboxylic acid, m. p. 75 °C.

2-Oxaadamantane-1-methanamine

A THF solution of borane monomer (10 mL of 1 M solution, approximately 10 mmol) (or lithium aluminum hydride) was added to a 50 mL round botton flask with reflux condenser and drying tube, pressure equalizing addition funnel, dry nitrogen gas line, and magnetic stir bar. After 15 minute nitrogen purge, the solution was cooled to 0 °C, and carboxamide (0.60 g, 3.31 mmol) dissolved in THF (15 mL, dried, distilled over LAH) was added through addition funnel over 15 minutes with stirring. After warming to room temperature, the solution was refluxed for two hours under a nitrogen blanket, and then cooled overnight. Hydrochloric acid (6 M, 2 mL) was added slowly and then the THF was removed by distillation at atmospheric pressure. The residue was washed with methylene chloride (3 × 15 mL) to remove unreacted amide (0.085 g, 0.46 mmol). The aqueous layer was made basic with 5% sodium hydroxide solution and extracted with methylene chloride (3 × 15 mL) to yield free amine as a pale yellow oil which crystallized (carbonate?) to waxen solid upon cooling, m. p. approx. 100 °C (0.41 g; 90% pure by GLC, 77.6% yield based on converted amide). IR (neat oil): 3380, 3300, 2920, 2840, 1600, 1445, 1010 cm^{-1}. ^{1}H NMR (CDCl$_3$): 4 : 00 (broad s, 1H, H-3), 2.45 (s, 2H, CH$_2$N), 2.30—1.40 (m, 12H), 1.30 (s, 2H, NH$_2$) ppm. MS: M$^+$ 167 (100), 96 (69), 30 (69), 150 (39).

2-Oxaadamantane-1-N,N,N-trimethylmethanaminium Iodide (VIIe)

Methanamine (0.79 g, 3.88 mmol) was added to a 50 mL round bottom flask fitted with a reflux condenser and addition funnel. After cooling in an ice-water bath, methyl iodide (2.54 g, 17.9 mmol) was added slowly through the funnel. After 5 minutes of mixing at 0 °C, the solution was allowed to warm to room temperature, gently refluxed for an additional fifteen minutes, and cooled in an ice-water bath. The white precipitate was collected by filtration and washed with cold ether to quantitatively yield the methiodide, recrystallized from ethyl acetate--ethanol, m. p. 181—183 °C, soluble in water, ethanol and acetone. IR (KBr): 3500 (broad, H$_2$O), 2940, 1630, 1520, 1010 cm^{-1}. ^{1}H NMR (D$_2$O): 4.15 (broad, 1H, H-3), 3.14 (s, CH$_2$—N$^+$), 2.98 (s, CH$_3$—N$^+$), 2.40—1.80 (broad m). The mass spectrum (probe, 300 °C) did not show a molecular ion: 58 [100, CH$_2$ = $^+$N(CH$_3$)$_2$], (23), 181 (13), 95 (12), 195 (10).

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SAŽETAK

2-Oksoadamantan-1-*N,N,N*-trimetilmetanium iodid. Sinteza i muskarinska aktivnost

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Opisana je priprava 2-oksoadamantan-1,*N,N,N*-trimetilmetanium iodida (*1*) iz adamantanona. Ključni stupnjevi sinteze jesu proširenje prstena polaznog spoja u biciklo(3.3.1)nonaski derivat i njegova oksidativna ciklizacija u odgovarajuću okso-adamantanski prekursor u prisustvu olovnog tetraacetata. Po svojima strukturnim karakteristikama *1* je predstavnik skupine muskarinskih spojeva.