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Synthesis and Reactivity of Aldehydes of the Adamantane Series

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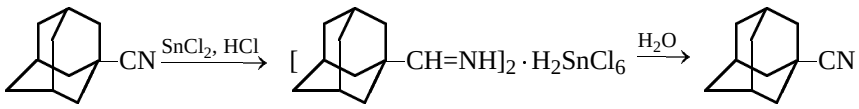
Abstract — 1-Adamantanecarbonitriles are very active in the Stephen reaction, which allows synthesis of the corresponding aldehydes in high yields. Electron-acceptor substituents in the 3 position of the adamantine nucleus exert almost no effect on the yield of aldehydes. Separation of the nitrile group and the adamantane nucleus by one methylene group results in a complete loss of reactivity. A quantitative study of the reactivity of the synthesized aldehydes in the oximation reaction was performed.

Stephen and Sonn–Möller reductions of aromatic and certain aliphatic nitriles and imidoyl chlorides with tin(II) chloride, followed by hydrolysis of the reduction products, gives rise to the corresponding aldehydes [1]. Reduction and hydrolysis of nitriles and imidoyl chlorides, containing an adamantlyl fragment, may prove a convenient synthetic route to hardly available adamantanecarbaldehydes.

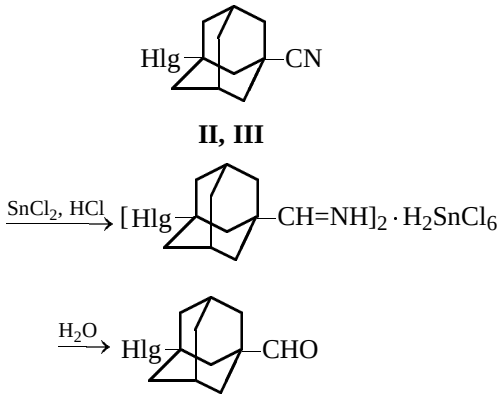
For the objects for study we used 1-adamantanecarbonitrile (**I**), 3-bromo-1-adamantanecarbonitrile (**II**), 3-chloro-1-adamantanecarbonitrile (**III**), 3-hydroxy-1-adamantanecarbonitrile (**I**–**IV**), 1,3-adamantanedicarbonitrile (**V**), 1-adamantylacetonitrile (**VI**), and *N*-phenyl1-adamantanecarboximidoyl chloride (**VII**) [2].

It is khown that the Stephen reduction of aliphatic nitriles most frequently provides low yields of the corresproding aldehydes because of the side formation of iminoesters [3] and *N*,*N*'-diacyl-1,1-diaminoalkanes [4]. We found that the Stephen reduction of nitrile **V** occurs fast and gives 1-adamantanecarbaldehyde (**VIII**) in high yield.



I **VIII**

Similar results were obtained with nitriles **II** and **III**.



II, III

IX, X

Hlg = Br (**II, IX**), Cl (**III, X**).

It should be noted that the reduction of nitrile **II** involves no substitution of bromine by chlorine. This was shown by mass spectral studies of the reaction products.

It can be supposed that the high reactivity of 1-adamantanecarbonitriles derives from the considerable electron-donor effect of the adamantyl group, which is obviously not wiped out by the electron-acceptor effect of the 3-substituents in the adamantane nucleus.

The reduction of nitrile **IV** involves two concurrent reactions.

The fraction of aldehyde **X** in the reaction products depends on reaction conditions and varies from 5 to 18%. Increased reaction temperature and $SnCl_2$: nitrile **IV** molar ratio increase the fraction of aldehyde **X**.

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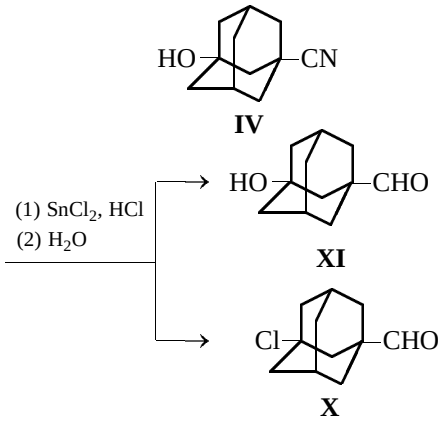
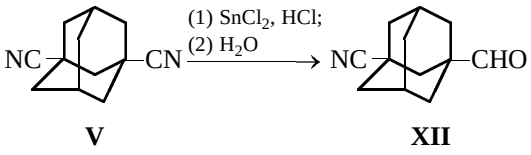


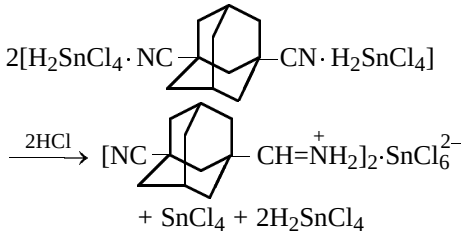
It is known that aliphatic dicarbonitriles fail to undergo Stephen reduction, and the reaction gives nitrilium salts [5] or cyclization products [6, 7]. In this connection we considered it of interest to bring into the Stephen reaction dinitrile **V** which, having a rigid carcass, does not tend to cyclization.

At the $SnCl_2$: dinitrile **V** molar ratio of 2 : 1, only one nitrile group could be selectively reduced. Subsequent hydrolysis of the reduction products gave 3-cyano-1-adamantanecarbaldehyde (**XII**) in 83–87% yield.



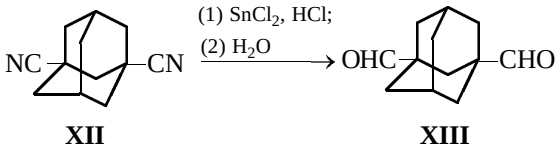
The fraction of 1,3-adamantanedicarbaldehyde (**XIII**) in the reaction products normally does not exceed 3%. To direct the reaction to dialdehyde **XIII** formation, we used an excess of tin(II) chloride (up to 5 mol of $SnCl_2$ per 1 mol of dinitrile **V**). However, the fraction of dialdehyde **XIII** could not be increased in this way.

The observed reaction direction can be explained by the strong deficit of electron density on the aldimine carbon atom, which is produced by the positive charge generated by protonation of the adjacent nitrogen atom in the course of reduction of the first nitrile group.



The cage effect resulting from the overlap of orbital backsides of bridgehead atoms of the adamantane nucleus [8] favors partial transfer of the deficit of electron density from the aldimine carbon on the 3-CN group, making the latter less reactive.

The above reasoning led us to expect that the Stephen reaction of aldehyde **XII** followed by hydrolysis of the reduction products would allow synthesis of dialdehyde **XIII**. We succeded in effecting this reaction sequence to obtain dialdedyde **XIII** in 60–66% yield.



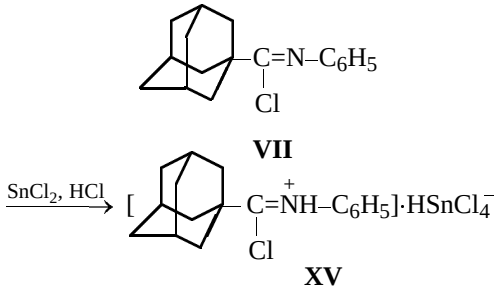
The fraction of dialdehyde **XIII** in the reduction products is 92–94%; the moderate isolable yield of dialdehyde **XIII** can be explained by its partial solution in water.

Aldehyde **VIII** readily trimerizes [9], which makes it difficult to operate. The synthesized 3-substituted adamantanecarbaldehydes are not prone to spontaneous polymerization, most probably, on account of disturbed symmetry of the molecule and increased vibrational and rotational mobility of its units. Evidence for this assumption was obtained from analysis of the Stewart–Briegleb models.

To obtain 1-adamantylethanal **XIV**, we tried to effect the Stephen reaction–hydrolysis sequence with nitrile **VI**. However, aldehyde **XIV** was not found even if the reaction mixture was allowed to stand for 4 days. This result can be explained both by different inductive effects of the 1-$AdCH_2$ and 1-Ad groups on the reaction center ($\sigma^*_{1\text{-Ad}}$ –0.26, $\sigma^*_{1\text{-AdCH}_2}$ –0.10) [10] and by different steric effects of these groups. According to [10], the 1-$AdCH_2$ group exerts a stronger steric effect than 1-Ad. The steric constants (E_s) of the 1-$AdCH_2$ and 1-Ad groups are –2.00 and –1.51, respectively.

The yields, constants, spectra, and elemental analyses of aldehydes **VIII**–**XIII** are listed in Table 1.

Compound **VII** under conditions of the Sonn–Möller reaction converts into *N*-phenyl-(1-adamantyl)chloromethaniminium tetrachlorostannite (**XV**).



Treatment of complex **XV** with water yields *N*-phenyl-1-adamantanecarboxamide.

To assess the effect of the 3-substituents in the adamantane nucleus on the reactivity of the carbonyl group of the synthesized adamantanecarbaldehydes, we performed a quantitative study of the reactivity of the latter in the oximation reaction. The objects for study were aldehydes **VIII**–**XII**.

The rate constants of oxime formation were estimated based on the concentrations of unreacted hydroxylamine, which were measured by iodometric titration [11]. It was found that the oximation reaction is an irreversible second-order reaction. The reaction order in each reagent is one. Table 2 lists the mean rate constants of oximation of aldehydes **VIII**–**XII**. The conversions are all higher than 70%. The decomposition of the oximes during kinetic measurements was inconsiderable, and we did not take it into account in calculating the rate constants.

It follows from data in Table 2 that substituents in the 3 position of the adamantane nucleus appreciably affect the reactivity of the carbonyl group. The reactivity increases with the inductive constant σ^* [12].

Treatment of the resulting data in terms of the Taft equation [13] with exception of compound **I** showed that the logarithms of the rate constants correlate well with the inductive constants of the substituents; the correlation coefficient is 0.992.

The high correlation coefficient is likely to suggest that the 3-substituents exert an only slight steric effect on the reactivity of the carbonyl group and that the rate constants are controlled exclusively by the inductive constants of the substituents.

Table 1. Yields, melting points, IR, ^{1}H NMR, and mass spectra, and elemental analyses of aldehydes **VIII**–**XIII**

Comp. no.	Yield, %	mp, °C, (solvent for crystallization)	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm	Mass spectrum, *m/z* (I_{rel}, %)
VIII	95	125–128 (hexane)	2686 (C–H in CHO), 1700 (C=O), 1340, 1100, 990 (Ad)	1.66 m ($H^{4,6,10}$), 1.73 m ($H^{3,5,7}$), 2.05 m ($H^{2,8,9}$), 8.86 s (CHO)	164 (11.3), 136 (18.1), 135 (100), 106 (13.4), 93 (25.2), 91 (14.5), 81 (8.3), 79 (21.0), 77 (11.7), 67 (14.0), 65 (4.2), 55 (8.3), 53 (4.8), 44 (7.6), 41 (14.4), 29 (18.8)
IX	91	104–106 (hexane)	2666 (C–H in CHO), 1700 (C=O), 1340, 1104, 968 (Ad), 692 (C–Br)	1.60 d ($H^{8,9}$), 2.04 m ($H^{4,6,10}$), 2.08 m ($H^{5,7}$), 2.13 s (H^2), 9.16 s (CHO)	242/244 (14.4/14.1), 214/216 (10.7/0.5), 163 (80.1), 135 (100), 107 (8.9), 93 (26.0), 92 (7.6), 91 (9.4), 81 (18.3), 79 (25.6), 67 (20.5), 65 (13.1), 56 (8.8), 55 (4.9), 53 (2.6), 44 (2.9), 42 (9.6), 41 (11.0), 29 (19.6)
X	88	114–116 (hexane)	2666 (C–H in CHO), 1700 (C=O), 1340, 1100, 968 (Ad), 788 (C–Cl)	1.63 d ($H^{8,9}$), 2.02 m ($H^{4,6,10}$), 2.10 m ($H^{5,7}$), 2.17 s (H^2), 9.16 s (CHO)	198/200 (16.3/5.3), 170/172 (5.1/1.6), 163 (79.6), 135 (100), 107 (10.4), 93 (28.8), 92 (4.9), 91 (8.3), 81 (20.4), 79 (19.0), 67 (32.3), 65 (15.4), 56 (7.1), 55 (5.5), 53 (4.7), 44 (1.8), 42 (30.9), 41 (24.6), 35 (11.4), 37 (3.7), 9 (17.8)
XI	66	200–202 (toluene–hexane, 1 : 1)	2668 (C–H in CHO), 1700 (C=O), 3420 (O–H), 1340, 1100, 968 (Ad)	1.57 d ($H^{8,9}$), 1.68 m ($H^{4,6,10}$), 2.01 m ($H^{5,7}$), 2.09 s (H^2), 3.65 s (OH), 9.02 s (CHO)	180 (10.2), 152 (100), 151 (31.0), 96 (8.7), 95 (4.1), 94 (63.2), 42 (39.5), 41 (19.4), 29 (13.6)
XII	87	169–171 (benzene)	2660 (C–H in CHO), 2232 (CN), 1720 (C=O), 1348, 1100, 976 (Ad)	1.67 d ($H^{8,9}$), 1.98 m ($H^{4,6,10}$), 2.12 m ($H^{5,7}$), 2.24 s (H^2), 9.24 s (CHO)	189 (10.7), 163 (83.1), 161 (20.3), 147 (13.3), 135 (100), 107 (17.8), 93 (74.1), 81 (21.4), 79 (20.6), 67 (32.6), 65 (13.8), 56 (11.9), 53 (9.4), 44 (3.2), 42 (19.6), 41 (18.3), 40 (18.3), 29 (17.4)
XIII	65	[a]	2682 (C–H in CHO), 1700 (C=O), 1340, 1104, 968 (Ad)	1.66 m ($H^{4,6,8,9,10}$), 2.11 m ($H^{5,7}$), 2.19 s (H^2), 9.09 s (CHO)	192 (11.1), 163 (73.5), 135 (100), 107 (19.4), 93 (64.8), 81 (19.6), 79 (19.8), 67 (41.0), 65 (11.7), 56 (13.4), 53 (8.3), 44 (3.1), 42 (15.5), 41 (18.6), 40 (18.0), 29 (16.4)

Table 1. (Contd.)

Compound no.	Found, %			Formula	Calculated, %		
	C	H	Hlg		C	H	Hlg
VIII	79.88	10.0	–	$C_{11}H_{16}O$	80.48	9.75	–
IX	54.09	6.6	32.60	$C_{11}H_{15}BrO$	54.53	6.17	32.92
X	66.19	8.10	17.64	$C_{11}H_{15}ClO$	66.49	7.55	17.88
XI	73.41	9.08	–	$C_{11}H_{16}O_2$	73.33	8.88	–
XII	75.19	8.10	–	$C_{12}H_{15}NO$	76.19	7.93	–
XIII	74.42	8.51	–	$C_{12}H_{16}O_2$	75.00	8.33	–

[a] bp 143°C (1 mm), d_4^{20} 1.0960, n_D^{20} 1.5132.

Table 2. Oximation of aldehydes **I**–**V**

Product no.	k, l mol^{-1} s^{-1}			$-\Delta S^{\neq}$, J mol^{-1} K^{-1}	$\Delta H^{\neq}$, kJ/mol	$\Delta G^{\neq}$, kJ/mol
	0°C	10°C	20°C			
VIII	0.7317	1.0848	1.6240	0.2961	24.19	24.27
IX	0.7702	1.1441	1.7246	0.2957	24.48	24.57
X	0.7832	1.1619	1.7520	0.2957	24.45	24.54
XI	0.7406	1.1201	1.6540	0.2954	24.37	24.45
XII	0.8119	1.1789	1.8107	0.2954	24.57	24.47

As seen from data in Table 2, the activation parameters of the reaction are almost independent of the structure of the aldehyde. Thus, the substituents in the 3 position of the adamantane nucleus all only slightly increase the activation parameters. The activation entropies for the aldehydes in study are small negative values, which is accounted for by the high reactivity of the carbonyl group.

EXPERIMENTAL

The IR spectra were obtained on a Specord M-82 instrument in Vaseline oil. The ^{1}H NMR spectra were measured on a Tesla BS-567A spectrometer (100 MHz), internal reference HMDS, solvent carbon tetrachloride. The mass spectra were obtained on a Varian MAT-111 instrument with direct inlet, ionizing voltage 70 V, emission current 240 μA. Chromatographic analysis of the reaction mixtures was performed on a Perkin–Elmer LC-1022 Plus chromatograph with diode array at 25°C, steel column (250 × 4 mm), sorbent Ultrasphere ODS (5 μm), eluent acetonitrile–water, 85 : 15, flow rate 1 ml/min.

All experiments were peformed in moisture-proof conditions.

1-Adamantanecarbaldehyde (VIII). A mixture of 40 ml of absolute diethyl ether and 23.5 g of tin(II) chloride was saturated with stirring at 0–5°C with hydrogen chloride until a real solution, after which 10 g of nitrile **I** was added in portions so that the temperature of the reaction mixture did not rise above 5°C. The mixture was stirred at 0–5°C for 2 h and then left to stand without stirring for 20 h at 20–25°C. Within this time, 1-adamantylmethanimine hexachlorostannate precipitated. The reaction mixture was added to 200 ml of water and slowly heated to evaporate the diethyl ether. Heating was discontinued, when the temperature reached 60°C. At this moment, 1-adamantylmethanimine had completely hydrolyzed to aldehyde **VIII**. The suspension of the aldehyde in water was cooled 20–25°C, the precipitate was filtered off, washed with water (2 × 20 ml), dried, and recrystallized. Aldehydes **IX**–**XIII** were obtained in a similar way.

***N*-Phenyl-(1-adamantyl)chloromethaniminium tetrachlorostannite (XV).** A mixture of 30 ml of absolute diethyl ether and 13.8 of tin(II) chloride was saturated with stirring at 0–5°C with hydrogen chloride until a real solution, after which a solution of 10 g of carboximidoyl chloride **VII** in 20 ml of absolute diethyl ether was added dropwise. During the addition, crystals formed and were filtered off, washed

with absolute diethyl ether and saturated hydrogen chloride, and dried in a vacuum dessicator over $CaCl_2$ to obtain 19.3 g (98%) of compound **XV** as a colorless hygroscopic powder. The product slowly decomposed on handling with hydrogen chloride evolution. Found, %: Cl 34.4; Sn 20.7. $C_{17}H_{22}Cl_5NSn$. Calculated, %: Cl 33.1; Sn 22.1.

Kinetic measurements. Aldehydes **VIII**–**XII** in a buffer solution [0.04 M CH_3COONa and 0.04 M CH_3COOH in 75% (v/v) ethanol, pH 6.5] were placed in a temperature-controlled volumetric flask. Another volumetric flask was charged with a solution of hydroxylamine hydrochloride in the same buffer. After the required temperature had been attained, the aldehyde solution was added to the hydroxylamine hydrochloride solution, and the reaction onset time was marked. Samples (10 ml) were taken in a flask containing an excess of a 0.04 M solution of iodine in aqueous potassium iodide, cooled to 0–5°C, after which an excess of a standard 0.04 M solution of sodium thiosulfate was added. The excess sodium thiosulfate was titrated with a standard solution of iodine in aqueous potassium iodide in the presence of starch.

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