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THE SYNTHESIS OF SUBSTITUTED ADAMANTANES FROM DEHYDROADAMANTANE

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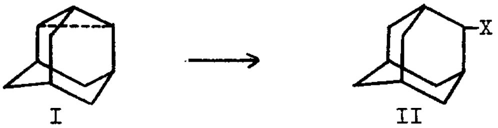
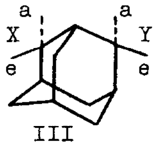
A large number of bridgehead substituted adamantanes are known (1). The number of secondary substituted adamantanes however is limited since their synthesis could formerly only be achieved by low yield ring-closure reactions (1).

Recently some high yield ring-closure reactions for the preparation of polyfunctional secondary substituted adamantanes have been described (2,3). In addition the reported syntheses of a 1,2-substituted adamantane (4) and of adamantanone (5) offer a good route to 2-substituted adamantanes.

Dehydroadamantane (tetracyclo[3,3,1,$1^{3,7}$,$0^{2,4}$]decane) I, prepared in our laboratory (6), proved to be a very useful source for the synthesis of 2-substituted and 2,4-disubstituted adamantanes (II and III).



I II



III

The cyclopropane ring in the strained hydrocarbon I can easily be opened by a variety of electrophilic reagents (7). In all cases only the adamantane system was formed, showing the strong preference for this nearly strain-free system (8).

A. <u>2-Substituted Adamantanes</u>

a) <u>Concentrated halogen acids</u> in ether caused ring-opening of I giving the known 2-chloro- and 2-bromoadamantane (9) and the hitherto unknown 2-iodoadamantane.

The yields were low (± 25%) because of the concomittant formation of the known 2-hydroxyadamantane (10) in about 40% yield.

b) Sulfuric acid in acetic acid gave ring-opening of I with formation of 2-acetoxyadamantane.

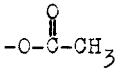
c) Methanol containing borontrifluoride etherate yielded 2-methoxyadamantane.

d) Aluminium chloride or borontrifluoride etherate in benzene reacted with I at roomtemperature to give 2-phenyladamantane. When we carried out the reaction in toluene or anisole we obtained mixtures of two isomeric (adamantyl-2)toluenes and (adamantyl-2)anisoles. These meta-para mixtures were not separated. With borontrifluoride etherate the same isomer mixtures were obtained, though the ratio of isomers differed from the reaction with aluminium chloride.

When dehydroadamantane (I) reacted with aluminium chloride in boiling benzene only the known 1-phenyladamantane (11) was isolated. It could be shown that 2-phenyladamantane rearranged to 1-phenyladamantane in boiling benzene under the influence of aluminium chloride.

TABLE I*

New 2-Substituted Adamantanes

X	yield %	phys.const.	τ value of CHX (CCl$_4$) (1H)	others (14H)
I	24	m.p. 46-48°	5,10	7,3-8,6
 $-O-\overset{O}{\overset{\|}{C}}-CH_3$	94	b.p. 125°/14 mm	5,15	7,5-8,8
$-O-CH_3$	80	b.p. 47°/12 mm	6,70	7,7-8,8
C_6H_5	70	m.p. 28-30°	7,05	7,8-8,8
$C_6H_4CH_3$ (m+p)	50	oil*	7,07	7,9-8,6
$C_6H_4OCH_3$ (m+p)	86	m.p. 60-107°	6,82	7,5-8,5

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* All new compounds gave satisfactory elemental analyses and the expected infrared spectra.

B. 2,4-Disubstituted Adamantanes

a) Chlorine and dehydroadamantane (I) in equimolecular amounts in carbontetrachloride solution at 0 yielded a complex reaction mixture, from which we isolated in low yield 2-chloroadamantane and $2^e,4^a$-dichloroadamantane.

b) Bromine added to I in carbontetrachloride solution at roomtemperature to give 2,4-dibromoadamantane and a small amount of 2-bromoadamantane. Formula III shows that three different isomers of the former are possible: one trans form (with the substituents axial and equatorial with respect to the ring bearing both substituents) and two cis forms (diequatorial or diaxial substituents). With the aid of G.L.C. and NMR analyses* we found that the 2,4-dibromoadamantane consisted of two isomers e.g. 40% $2^e,4^e$-dibromoadamantane and 60% $2^e,4^a$-dibromoadamantane. These could be separated by chromatography on alumina.

c) Addition of iodine to I in carbontetrachloride solution yielded a mixture of 69% $2^e,4^e$-diiodoadamantane and 31% $2^a,4^e$-diiodoadamantane. In order to prove the adamantane structure of the diiodoadamantanes we carried out a lithium aluminium hydride reduction of both isomers in ether. Surprisingly in both cases a mixture of hydrocarbons resulted in 70-80% yield, consisting of about 30% adamantane and 70% dehydroadamantane (I). There are only a few examples of cyclopropane formation from α,γ-dihalogeno compounds by LAH reported in the literature (12,13,14).

d) Reaction of the halogens with I in the presence of acetonitrile. When chlorine reacted with I in acetonitrile, containing some water 2^e-acetamido-4^e-chloroadamantane was formed. This coupled addition has been described for olefins (15). Dehydroadamantane (I) reacted with bromine and iodine in the presence of an equimolecular amount of silverperchlorate in acetonitrile to give 2^e-acetamido-4^e-bromoadamantane and 2^e-acetamido-4^e-diiodoadamantane in

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* The NMR spectra of the 2,4-substituted adamantanes in relation to their stereochemical configuration will be discussed in a separate paper.

good yield. This reaction is only known for some olefins and gives stereospecific *trans* addition with cyclohexene and 2-cholestene (16).

It turned out that the above mentioned coupled additions were stereospecific. Only the diequatorially 2,4-substituted adamantanes were formed. Other *cis* additions to cyclopropanes have only been reported for the strained bicyclo[1,1,0]butane system (12,13,17). The halogeno amides could be converted into the amines using boiling concentrated hydrochloric acid.

e) The coupled addition of *chlorine and water* to I in dioxane gave 2^e-chloro-4^e-hydroxyadamantane. The addition was stereospecific *cis*. Oxidation of the chloro alcohol with chromiumtrioxide in acetic acid yielded 4^e-chloroadamantanone, while reaction with phosphorus pentachloride gave a mixture of 31% $2^e,4^e$-dichloro- and 69% $2^e,4^a$-dichloroadamantane. The pure isomers could be obtained by chromatography on alumina.

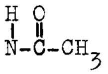
f) *N-bromosuccinimide in wet DMSO* (known to give *trans* addition with olefins resulting in bromohydrins) (18,19) reacted with I to give 2^e-bromo-4^e-hydroxyadamantane in good yield. Again the addition was stereospecific *cis*. Oxidation of the bromohydrin with chromiumtrioxide in acetic acid gave 4^e-bromoadamantanone. With silver nitrate in ethanol-water mixture 2,4-dihydroxyadamantane was formed (mixture of 61% diequatorial and 39% axial-equatorial isomer, that was not separated). The diol was oxidised to adamantane-2,4-dione by chromiumtrioxide in acetic acid. Reaction of I with NBS in DMSO containing methanol instead of water gave 2-bromo-4-methoxyadamantane.

g) The known reaction of cyclopropanes with *mercuric diacetate* (7) was applied to I giving 2-hydroxy-4-mercuryacetoxyadamantane that was characterised as 2-hydroxy-4-mercurychloroadamantane by reaction with aqueous potassium chloride. Since its NMR spectrum was complex, no stereochemical assignments could be made. Its reduction to the known 2-hydroxyadamantane (10) using sodium borohydride served as structure proof.

h) *Nitrosyl chloride* in chloroform, a well-known reagent for double bonds, reacted with I to give in 38% yield the oxime of 4^a-chloroadamantanone. The latter was probably formed from the primary addition product 2-chloro-4-nitrosoadamantane or its dimer. This seems to be the first addition of nitrosyl chloride to a cyclopropane.

TABLE II

2,4-Disubstituted Adamantanes

X	Y	yield%	m.p.	X	Y	yield%	m.p.
Cl	Cl	77 dieq.	120-122	I	NH_3Cl	90	234-235 (dec.)
		ax.eq.	170-175	Cl	OH	71	214-216
Br	Br	86 dieq.	115-117	Cl	=O	81	201-203
		ax.eq.	120-122	Br	OH	83	167-168
I	I	100 dieq.	109-110	Br	=O	84	156-159
		ax.eq.	63-64	OH	OH	50	286-297 (mixt.)
Cl	 $\overset{H}{\underset{}{N}}-\overset{O}{\overset{\|}{C}}-CH_3$	76	163-166	=O	=O	71	280-282
Br	"	78	174-177	Br	OCH_3	23	b.p. 145°/12 mm
I	"	81	176-180 (dec.)	OH	HgCl	95	209-213 (dec.)
Cl	NH_3Cl	90	290-292 (dec.)	Cl	=NOH	38	198-199
Br	"	63	266-269 (dec.)				

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