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REMARKABLE BEHAVIOUR IN ACID HYDROLYSIS OF THE CYCLOADDUCTS FORMED BETWEEN ALLYL BROMIDE AND 1,2,4-TRICHLORO-3,5,5-TRIMETHOXYCYCLOPENTADIENE

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Abstract—Two isomeric compounds (**2a** and **2b**) are formed on addition of allyl bromide to 1,2,4-trichloro-3,5,5-trimethoxycyclopentadiene (**1**). The striking difference in behaviour of these two isomers on acid catalysed solvent addition can be explained by assuming a stabilization of the intermediate carbenium ion by the near *endo*-CH_2Br group in **2a**. The stabilization of this cation from the *endo*-side forces subsequent nucleophiles to attack from the *exo*-direction, resulting in an overall *cis-exo* addition to **2a**. *trans*-Additions on the contrary are observed for **2b**. Screening by the bromomethyl grouping of the intermediate cation formed from **2a** gives a satisfactory explanation for the formation of the observed reaction products and for the sigmatropic rearrangement observed in poorly nucleophilic media. The structures of parent compounds **2a** and **2b** are confirmed from the different reaction products. The structure **4a**, as previously reported[4] to be formed under similar reaction circumstances, is revised and an alternative structure **4'a** is proposed.

INTRODUCTION

The Diels–Alder addition of allyl bromide to 1,2,4-trichloro-3,5,5-trimethoxycyclopentadiene (**1**), yields only two (**2a** and **2b**) out of four possible isomers, in a 75:25 ratio, with an overall yield of 77% (Scheme 1).

The two compounds formed are positional isomers, both possessing an *endo*-configuration, with the 5-*endo*-isomer, **2a**, being the major compound. It was impossible to identify **2a** and **2b** from spectral data alone, as these were too similar to yield conclusive evidence. ^{1}H NMR spectroscopy (CCl_4 at 300 MHz) suggested both isomers to be *endo*,[1] e.g. **2a**: $J(5x,6x) = 8.64$ Hz; $J(5x,6n) = 3.86$ Hz; **2b**: $J(5x,6x) = 8.50$ Hz; $J(5n,6x) = 4.02$ Hz. recent studies[2] however, incite us to be careful in handling presumed values for *exo–exo* coupling constants as a criterion for configurational assignments.

Selective acid-catalysed hydrolysis of the enol ether system in adducts of **1** yielding the *endo*-chloroketone **3** has been reported.[3] It has further been claimed[4] that the sulphuric acid catalyzed hydrolysis of the cyclopropene adduct of **1** results in the formation of the *endo*-chloroketone **4a**, while the *exo*-isomer **4b** would result from the same adduct during perchloric acid assisted hydrolysis.

The results we obtained from a hydrolysis study of the allyl bromide adducts, not only provide evidence for the structure of compounds **2a** and **2b** but also prompt us to suggest a revised structure for the compounds thought[4] to be **4a** and **4b**.

RESULTS AND DISCUSSION

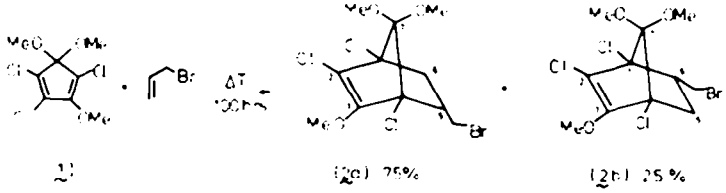
Acid hydrolysis of **2a** and **2b** was performed using perchloric acid in aqueous ethanol, and sulphuric acid (50% and 75%) in ether. Under these different circumstances the 6-*endo*-bromomethyl isomer **2b** invariably yields the expected 2-*endo*-chloroketone **5** (accompanied by the mixed acetal **6** in ethanol (Scheme 2).

The chloromethine proton at C_2 in **5** and **6** appears as a doublet in ^{1}H NMR spectrum (Table 1) due to the diagnostic and stereospecific W *exo–exo* long range coupling.[5,6] This observation establishes the configuration of both carbon centers involved (C_2 and C_6). Therefrom, the structure of **2b**, as proposed, is confirmed while **2a** possesses the bromomethylsubstituent at C_5.

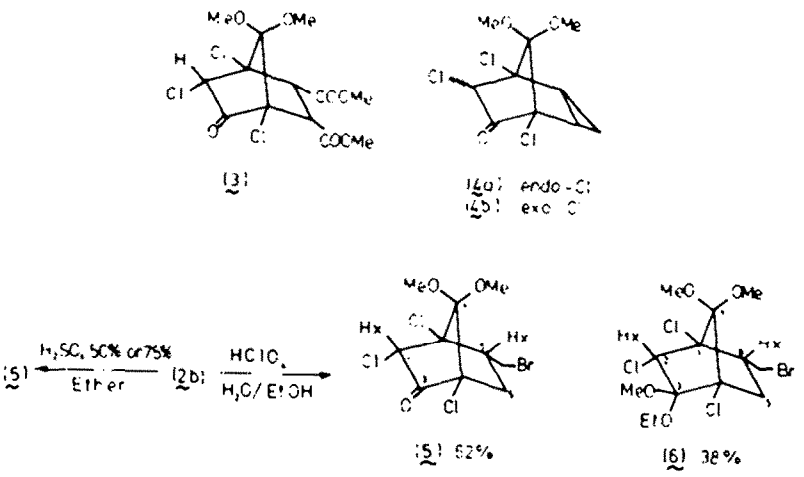
The behaviour of **2a** was found to be strikingly sensitive to the reaction circumstances, yielding a different compound **7**, **8** or **9** as the sole and almost quantitative reaction product under three different reaction conditions (Scheme 3).

Compounds **7** and **8** are 2-*endo*-chloroketones, since the chloromethine proton at C_2 each time appears as a doublet in the ^{1}H NMR spectrum (Table 1). This long range coupling involves the *exo*-methylene proton at C_6, hence the bromomethyl group has to be at position 5.

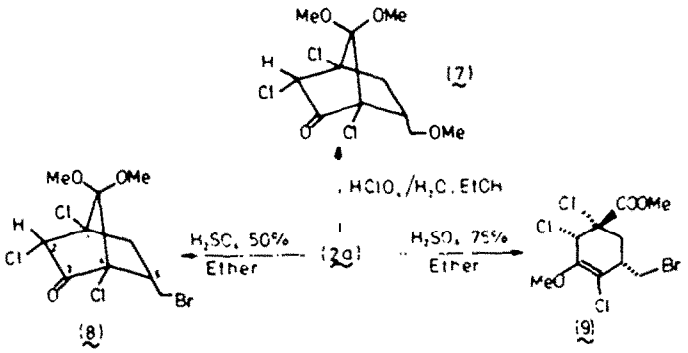
In fact, the formation of the unexpected compound **7** from **2a** (Scheme 3) gives definite proof to the structure assigned to **2a**. Compound **7** can only arise from an intramolecular nucleophilic displacement of bromine by a OMe group on C_3 as a result of an *endo*-(syn)-*endo*



Scheme 1.



Scheme 2.



Scheme 3.

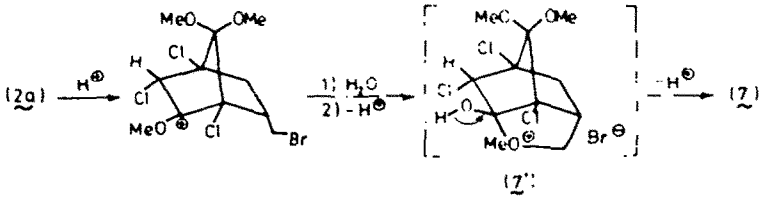
neighbouring group participation by the ether oxygen, that has come into the *endo* position during the formation of a hemiacetal derived from the intermediate carbenium ion. The appropriate geometry for MeO-5 participation[7,8] is thereby achieved, leading to the cyclic intermediate 7'. The formation of 7' from the hemiacetal is also favoured by the rather high reaction temperature and the polar medium in which the reaction takes place. Migration of one OMe group during acetal-OMe participation can be induced by Me–O bond breaking of the second geminal OMe bond,[9] resulting in the formation of a CO group (loss of $Me^{\oplus}$ from the cyclic oxonium ion). In the present case of a hemiacetal, OMe migration is accompanied by an even more facile loss of a proton (Scheme 4).

It is noteworthy that the sequence implies a *cis–exo* addition of water to the norbornene system.[10] IR data were of help in elucidating the structure of compound **9**: the absorption at 1740 cm^{-1} can hardly be assigned to a chloronorbornanone structure, which absorbs at higher wavenumbers (Table 1). The value (1740–1745 cm^{-1}) reported[4] for the proposed structure **4a** bears the same anomaly and a difference of 40 cm^{-1} between *exo*- and *endo*-chloroisomers **4a** and **4b** as is stated,[4] seems hard to explain. The IR data of **9** agree with the presence of a carbomethoxy group, from a structure formed on rearrangement of the norbornane system **2a** according to Scheme 5. These rearrangements are known in terpene chemistry[11] and are observed when a very stable cation is formed.[12]

Definite proof of structure **9** is obtained from IR, ^1H NMR and mass spectroscopy, and by chemical transformations (see section "structural assignment of 9"). We therefore propose **4a'** as an alternative structure for the product formed from **11** on acid treatment, in a similar way as **9** is formed from compound **2a** (Scheme 6).

Stereochemistry of acid-promoted solvent addition

As stated, the formation of **7** from **2a** by water addition can be satisfactory explained by an *exo–cis* addition



Scheme 4.

Table 1. ^{1}H NMR data of norbornane derivatives at 300 MHz, TMS internal. [a]In CCl_4. [b]In $CDCl_3$. [c]Ref. 3. (**10**): 1,2-*endo*,4-trichloro-7,7-dimethoxy-5-*endo*-methyl-3-norbornanone

	δ 2x	^4J(2x,6x)	ν CO(IR) cm^{-1}
5[a]	4.79	1.76 Hz	1780
6[a]	4.63	1.92 Hz	—
7[a]	4.52	2.25 Hz	1785
8[b]	4.70	2.23 Hz	1780
10[a]	4.56	2.10 Hz	1785
3[c]	4.8	3 Hz	1810

mechanism. *Exo* protonation of the enol ether double bond in **2a** and **2b** could be expected from the known behaviour of norbornene-7-one acetals on acid treatment.[13] This *exo-cis* addition is however only observed for **2a** and *not* for **2b**, even under identical reaction conditions. A crystallographic study[14] reveals that the addition product **6** has an *endo* OEt grouping and is therefore the result of a *trans*-addition of ethanol.

The difference in behaviour between **2a** and **2b** follows from a difference in participation ability of the *endo* bromomethyl group. Protonation of **2a** leads to a shielded and stabilized carbenium ion **12** where further *endo*-attack by a nucleophile (leading to *trans* addition) is rendered improbable (Scheme 7).

In the presence of low concentrations of nucleophile (e.g. in 75% sulphuric acid in ether) the cation **12** exists long enough to be able to rearrange, involving intramolecular *exo*-attack by the C_6–C_7 sigma bond, prior to the *exo*-addition of an external nucleophile. In dry trifluoroethanol (a poorly nucleophilic solvent) **2a** rearranges readily to **9** even with traces of sulphuric acid, while **2b** only yields a mixture of **5** and the mixed acetal **13**, presumably with the trifluoroethoxy group in *endo* position,[15] analogous to **6** (Scheme 8).

Sigmatropic rearrangement of **2b** was never observed, possibly because the carbenium ion formed from **2b** is always accessible to an externally attacking species, leaving no chance for rearrangements to occur.

Structural assignment of **9**.

In order to obtain additional proof of structure **9** a few chemical transformations were performed, and the reaction products were identified by ^{1}H NMR, IR, UV and mass-spectroscopy. (Experimental). After treatment of **9** with sodium ethoxide a substituted benzoic acid (**14**) is obtained, through elimination and subsequent aromatization (Scheme 9). Dehalogenation with zinc in acetic acid results in the formation of a mixture of *cis* (32%)- and *trans* (68%)-1-carbomethoxy-3-oxo-5-methyl-cyclohexane (**15**).

The relative position of the functional groups in **14** and **15** is consistent with the proposed structure for **9** and thus also corresponds to the structure of the parent norbornene (**2a**).

CONCLUSION

Whereas the isomeric adducts **2a** and **2b** are not distinguishable on spectroscopic grounds, they show a remarkable difference in chemical behaviour, determined by the possibility of neighbouring group participation by the bromomethyl substituent to occur. Making use of these differences (also noticed in other adducts and derivatives[15]) it has been possible to identify a series of isomeric compounds chemically, where spectroscopic methods failed. This also allowed to corroborate structural assignments for **2a** and **2b**.

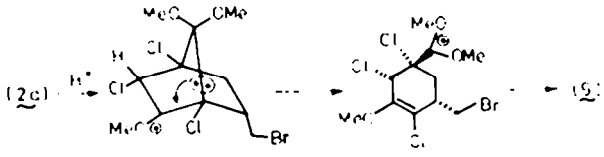
EXPERIMENTAL

1,2 - endo,4 - *Trichloro* - 7,7 - *dimethoxy* - 5 - endo - *methoxymethyl* - 3 - *norbornanone* (**7**)

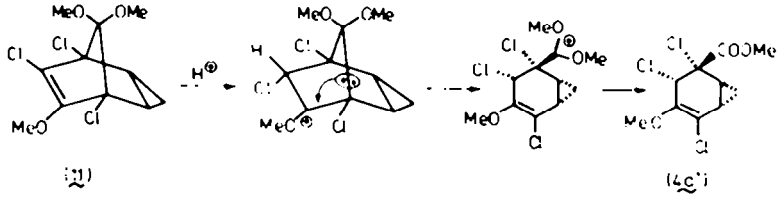
A soln of **2a** (1.5 g; 0.0039 mole) in 20 ml EtOH, to which 2 ml water and 1.2 ml 70% perchloric acid were added, was refluxed for 24 hr. After cooling and neutralization with $NaHCO_3$, the mixture was extracted with CH_2Cl_2 and the extract washed and dried over $MgSO_4$. Evaporation of the solvent yielded 1.2 g (0.0038 mole) of **7** as a colourless viscous oil (yield: 97%). IR: ν(C=O): 1785 cm^{-1} (s). Mass spectrum: M$^+$: 316 (Cl_3 isotope distribution). (Found: C, 41.65; H, 4.84; Cl, 33.40. Calc. for ($C_{11}H_{15}O_4Cl_3$): C, 41.60; H, 4.76; Cl, 33.49%).

1,2 - endo,4 - *Trichloro* - 7,7 - *dimethoxy* - 6 - endo - *bromomethyl* - 3 - *norbornanone* (**5**)

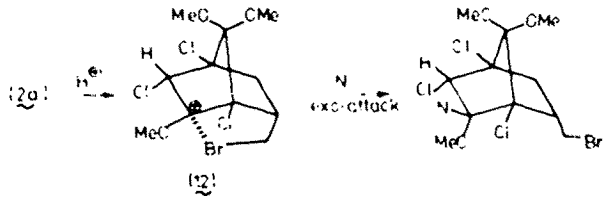
An isomeric mixture (1:1) of **2a** and **2b** was hydrolysed as described for the preparation of **7** from **2a**. After usual workup,



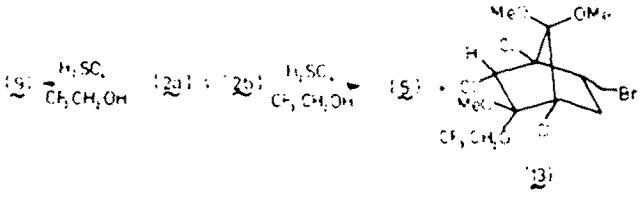
Scheme 5.



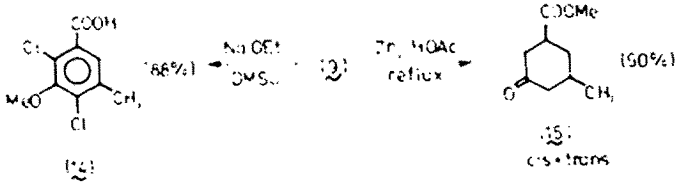
Scheme 6.



Scheme 7.



Scheme 8.



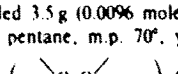
Scheme 9.

the mixture was analysed by GLC (SE30; 5 m; 210°) and pure samples of **5** and of the accompanying **6** were collected. (**5**): m.p.: 123°. IR: ν(C=O) 1780 cm^{-1} (s); Mass spectrum: M$^+$: 364 (Cl_3Br isotope distribution). (Found: C, 32.81; H, 3.41; Cl, 29.00. Calc. for ($C_{10}H_{12}O_3Cl_3Br$): C, 32.78; H, 3.39; Cl, 29.03%). (**6**): mass spectrum: M$^+$ 424 (Cl_3Br isotope distribution); *m/e* 393 (48%): M$^+$–MeO$^\cdot$; *m/e* 379 (10%): M$^+$–EtO$^\cdot$; *m/e* 331 (100%): M$^+$–CH_2Br.

1,2 - endo,4 - *Trichloro* - 7,7 - *dimethoxy* - 5 - *endo* - *bromomethyl* - 3 - *norbornanone* (**8**)

To a soln of **2a** (4 g; 0.0105 mole) in 50 ml ether, cooled in an ice salt bath, was added 40 ml of 50% H_2SO_4 (temp. < 5°). Following complete addition, the mixture was stirred vigorously for 60 hr at room temp. The ether layer is removed and the water phase is extracted repeatedly with ether. The extract is washed with a dil $NaHCO_3$ aq, then with water. Drying over $MgSO_4$ and evaporation of the solvent yields 3.6 g (0.0098 mole) of **8** purified by recrystallization from hexane, m.p.: 103°, yield: 93%. (**8**): IR: ν(C=O): 1780 cm^{-1} (s). Mass spectrum: M$^+$ 364 (Cl_3Br isotope distribution). (Found: C, 32.77; H, 3.39; Cl, 29.01. Calc. for ($C_{10}H_{12}O_3Cl_3Br$): C, 32.78; H, 3.39; Cl, 29.03%).

1,2,4 - *Trichloro* - 3 - *methoxy* - 5 - *bromomethylcyclohex* - 3 - *enecarboxylic acid methyl ester* (**9**)

(a) A soln of **2a** (4 g; 0.0105 mole) in 30 ml of ether was added slowly and under vigorous stirring to 25 ml cooled (−5°) 75% H_2SO_4 (temp. < + 5°). After complete addition, the mixture was allowed to warm up to room temp. and stirred for 1.5 hr. It was poured into 250 ml ice water and repeatedly extracted with ether, washed with $NaHCO_3$ aq and water, and dried over $MgSO_4$. Evaporation of the solvent afforded 3.5 g (0.0096 mole) of **9**, purified by recrystallization from pentane, m.p. 70°, yield: 91%. (**9**): IR: ν(C=O): 1740 cm^{-1} (s); ν(): 1645 cm^{-1} (m). Mass spectrum: M$^+$ 364 (Cl_3Br isotope distribution). (Found: C, 32.68; H, 3.36; Cl, 28.96. Calc. for ($C_{10}H_{12}O_3Cl_3Br$): C, 32.78; H, 3.39; Cl, 29.03%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.14 (d, H2); δ 2.68, δ 2.64 (m, H6, H6'); δ 3.04 (m, H5); δ 3.57, δ 3.67 (q, CH_2Br); δ 3.83, δ 3.84 (s, COOMe, OMe).

(b) Compound **2a** (4 g; 0.0105 mole) was dissolved in 30 ml dry CF_3CH_2OH. 2 ml of conc H_2SO_4 were added dropwise under cooling in a water bath. The mixture was stirred for 2 hr at room temp. The acid was then neutralized by addition of solid $NaHCO_3$ and the CF_3CH_2OH was evaporated. After the addition of water the mixture was extracted with $CHCl_3$, and dried over $MgSO_4$. Evaporation of the solvent yielded pure **9**, which recrystallized from pentane, yield: 85%.

1,2 - endo,4 - *Trichloro* - 7,7 - *dimethoxy* - 6 - endo - *bromomethyl* - 3 - *norbornanone* (**5**)

When an isomeric mixture (1:1) of **2a** and **2b** was subjected to hydrolysis in the same manner as described for the preparation of **9** from **2a**, a mixture of **5** and **9** was obtained.

2,4 - *Dichloro* - 3 - *methoxy* - 5 - *methylbenzoic acid* (**14**)

Sodium (0.5 g; 0.022 mole) was dissolved in 25 ml of EtOH. The soln was then concentrated to about 10 ml, and a soln of 300 mg (0.82 mmole) of **9** in 10 ml dry DMSO was added. The mixture was stirred for 24 hr at ambient temp. and then poured into 50 ml distilled water. The soln was acidified with 2N HCl to pH 2, and continuously extracted with chloroform. Evaporation of the solvent yielded 170 mg (0.73 mmole) of **14** as a white solid. Recrystallization from CCl_4 afforded very light white needles, m.p. 186°, yield: 88%; IR: ν(COOH): 2400 cm^{-1}–3200 cm^{-1} (s); ν(C=O): 1710 cm^{-1} (s); ν(C=C aromatic): 1580 cm^{-1} (m). Mass spectrum: M$^+$ 234 (Cl_2 isotope distribution) (100%); *m/e* 219 (36%): M$^+$ – CH_3. UV(EtOH) λ_{max}: 240 mμ, 287 mμ. ^{1}H NMR (DMSO-d_6, 90 MHz): δ 13.3 (s, COOH); δ 7.6 (s, ArH); δ 3.85 (s, $ArOCH_3$); δ 2.35 (s, $ArCH_3$).

cis- and trans - 1 - *Carbomethoxy* - 3 - oxo - 5 - *methylcyclohexane* (**15**)

Compound **9** (750 mg; 2.06 mmole) desolved in 20 ml AcOH was refluxed with an excess of Zn dust for 1.5 hr. After cooling the acid was neutralized with a sat $NaHCO_3$aq and the

mixture was continuously extracted with chloroform. Evaporation yielded a yellow oil, that was chromatographed through a silicagel column (eluens 4:1 n-hexane/EtOAc). Two pure fractions were obtained: 100 mg of *cis*-**15** as a colourless oil (R_f 0.33) and 216 mg of *trans*-**15** as a yellow oil R_f 0.20 yield: 90%. (**15**) *Cis*: IR: ν(COOMe): 1735 cm^{-1} (s); ν(CO): 1720 cm^{-1} (s); Mass spectrum: M^+ 170 (42%); *m/e* 111 (100%): $M^+ - COOMe$. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.72 (m, H1a); δ 2.45 (m, H2a); δ 2.55 (m, H2e); δ 2.00 (m, H4a); δ2.39 (m, H4e); δ 1.88 (m, H5a); δ 1.48 (m, H6a); δ 2.15 (m, H6e); δ 1.08 (d, CH_3); δ 3.71 (s, $COOCH_3$). (15) *Trans*: IR: ν(COOMe): 1735 cm^{-1}(s); ν(CO): 1715 cm^{-1} (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.08 (m, H1); δ 2.63 (m, H2), δ 2.39 (m, H'2); δ 2.47 (m, H4); δ 2.02 (m, H'4), δ 2.16 (m, H5); δ 2.13 (m, H6); δ 1.72 (m, H'6); δ 1.00 (d, CH_3); δ 3.69 (s, $COOCH_3$).

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