Isolation of pure enantiomers of Toxaphene congeners via hydrochlorination and chlorination of Pinene and composition of Soviet Polychloropinene.

Vladimir Nikiforov[1], Alexei Trukhin[1], Fedor Kruchkov[1], Anastasia Kiprianova[1], Sergei Miltsov[1], Roland Kallenborn[2]

[1]St.Petersburg State University, Department of Chemistry, St.Petersburg
[2]NILU, Kjeller

Introduction

Toxaphene is an insecticidal mixture, produced by the controlled photochlorination of camphene[1]. In the USSR similar insecticide – Polychloropinene was produced by chlorination of α-pinene with AIBN (azobisisobutyronitrile) as initiator[2]. Natural camphene occurs in different essential oils in (+)-form as well as (–)-form[3]. Production of artificial camphene starts from natural α-pinene, which is also chiral. All noted types of camphene are used for toxaphene synthesis by different manufacturers. Some congeners in selected samples of technical Toxaphene were shown to have small deviations from racemic distribution[4]. Nevertheless, there is no information about any enantiomerically pure congeners of toxaphene.

The amount of Polychloropinene produced in the USSR is estimated to be 160 thousand tons, which is a significant contribution into the total global production. Unfortunately, there is no traceable sample of Soviet Polychloropinene available. In the present work we report on the preparation of artificial model Polychloropinene mixtures with different content of chlorine in an attempt to find the difference between Toxaphene and Soviet Polychloropinene.

Another goal of our research project is to prepare pure enantiomers of important Toxaphene congeners, to establish their configuration and thus to provide more opportunities to enantiomer-specific environmental analysis of Toxaphene residues.

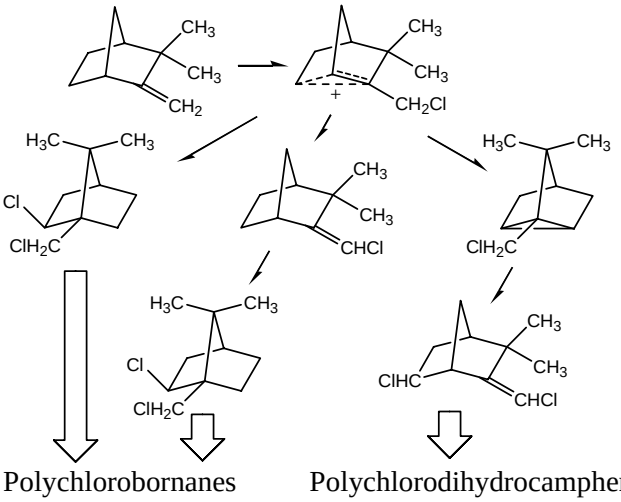
Materials and methods

In the present work we partially modelled the procedure of Polychloropinene production in USSR. The initial reaction was ionic addition of hydrogen chloride to (1S)-α-pinene resulting in a mixture of (1S)-2-endo-chlorobornane and "chlorofenchane" in ca. 10 : 1 ratio. Further exhaustive photochlorination (with a medium-pressure mercury arc lamp) allowed us to prepare complex mixture of chlorinated terpenes with different average content of Cl per molecule – 7-8, 8-9 and 9-10. The mixtures were separated on silica-gel column (i.d. 4.7 cm; height 103 cm; eluent: n-hexane). A number of known hepta- to decachlorobornanes were identified in fractions with help of NMR, GC and GC-MS – but in very unusual ratios. Also several previously unknown congeners were isolated or detected.

Results and discussion

Skeleton rearrangements on the way to Toxaphene and to Polychloropinene

On the addition of Chlorine to Camphene a series of ionic reactions occur. It includes rearrangements of Camphene species to compounds of Bornane and Trycyclene series:



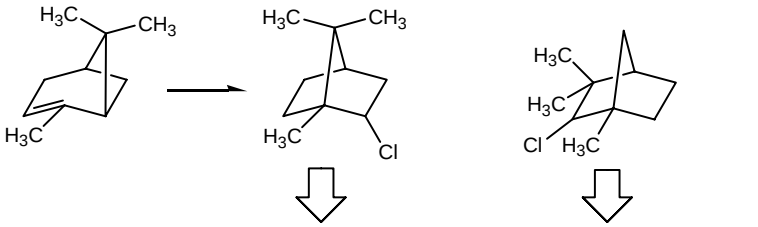
Initially formed non-classic cation has three ways of stabilization

- addition of chloride with formation of the major stable Toxaphene intermediate – 2-exo,10-dichlorobornane
- abstraction of proton from C-10 with formation of cis- and trans-10-chlorocamphenes
- abstraction of proton from C-6 with ring closure leading to 10-chlorotricyclene

10-Chlorocamphene reacts with another molecule of Chlorine and yields 2-exo,10,10-trichlorobornane, which is the second major stable Toxaphene intermediate. 10-Chlorotricyclene reacts with Chlorine with formation of 6,10-dichlorocamphene, which is stable to Chlorine in ionic conditions. On the next step of free-radical chlorination 2-exo,10-dichlorobornane and 2-exo,10,10-trichlorobornane retain their bicyclical structure and form polychlorobornanes, while 6,10-dichlorocamphene also retains its skeleton and forms polychlorodihydrocamphenes. More than 100 polychlorobornanes and polychlorobornenes, obtained by chlorination of camphene are known to date, as well as over 20 polychlorodihydrocamphenes and polychlorocamphenes.

Preparation of Polychloropinene consists of two steps – addition of HCl to pinene and photochlorination of reaction mixture.

Addditon of HCl yields 2-endochlorobornane(Bornyl chloride) and 2-endochlorofenchane (Fenchyl chloride) in 5-10 : 1 ratio. Therefore we expected formation of polychlorobornanes and polychlorofenchanes as main components of Polychloropinene:



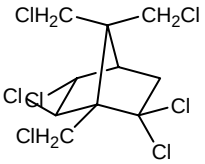
Polychlorobornanes Polychlorofenchanes

Isolation of polychloroterpenes from artificial Polychloropinene mixtures

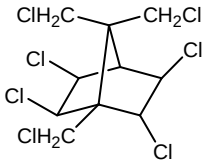
The initial reaction was ionic addition of hydrogen chloride to α-pinene resulting in a mixture of 2-endo-chlorobornane and chlorofenchane. Further exhaustive photochlorination (with a medium-pressure mercury arc lamp) led us to complex mixtures of highly chlorinated terpenes, which were separated on silica-gel column (i.d. 4.7 cm; height 100 - 110 cm; eluent: n-hexane). Three different mixtures were prepared. "7-8" contained mainly hepta and octachlorinated compounds, "8-9"contained octa- and nonachloroterpenes and "9-10" was obtained by exhaustive chlorination and contained nona- and decachloroterpenes.

On GC all mixtures had peak patterns, different fromthose on chromatograms of mixtures of chlorinatted camphene with similar content of chlorine.

From **"7-8"** mixture the two compounds were isolated in pure state – a well-known Toxicant B (2,2,5-endo,6-exo,8,9,10-Heptachlorobornane and previously unknown 2-endo,3-exo,5-exo,6-exo,8,9,10-Heptachlorobornane.



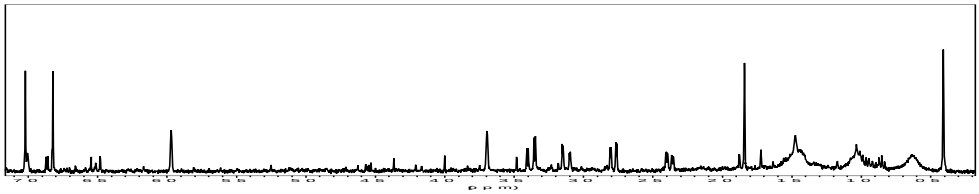
Toxicnat B
2,2,5-endo,6-exo,8,9,10-Heptachlorobornane



2-endo,3-exo,5-exo,6-exo,8,9,10-Heptachlorobornane

Many of the compounds, typical for Toxaphene, like Parlar nos. 26, 38, 39, 58 have not been detected in this mixture at all. None of the typical Toxaphene congeners (except Toxicant B) were major components in fractions. Several other new compounds were identified, but we were unable to purify them to achieve their structure elucidation.

A number of known Toxaphene congeners were detected in a mixture **"8-9"**. Some nonachlorobronanes were major components in several fractions – Parlar nos. 50, 58, 62 and few others. At the same time at least 4 new compounds were identified, but their structures are not finally resolved. One new congener has an interesting NMR spectrum (in C_6D_6, 300MHz):



The following signals are clear: 7.02s, 6.82s, 5.97dd(J=1Hz; 0.5Hz), 3.69d(1.0), 3.37dd(15.5, 3.4), 3.12dd(15.5, 2.1), 2.78dd(12.4, 2.0), 2.38ddd(12.4, 3.4, 1.2). The latter pair of signals, obviously of the same CH_2-group, shows chemical shifts, multiplicity and geminal coupling constant of 12.4 Hz that in combination are typical for CH_2-group in a 5-membered ring. Therefore it could be a methylene bridge in either fenchane or camphene species. The former would be the first case of a polychlorofenchane – but the puzzle is absence of a signal of Me-group. The latter would pose a serious theoretical question – how can a camphene be formed from bornane or fenchane ? If this is the case, then it has to be a camphene with a Cl at the bridgehead – structural feature not known in polychloroterpenes related to Toxaphene.

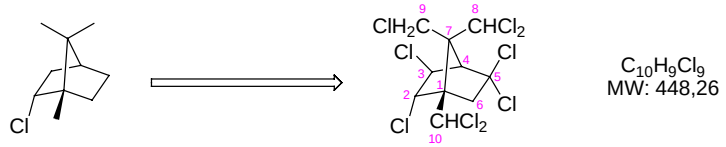
Mixture **"9-10"** contained the same main components as perchlorinated camphene – two nonachlorobornanes – Parlar nos. 50 and 62 and four decachlorobornanes - 2,2,5-exo,5-endo,6-exo,8,9,9,10,10-DCB(DCB1), 2-exo,3,3,5-exo,6-endo,8,9,9,10,10-DCB(DCB2), 2,2,5,5,6-exo,8,9,9,10,10-DCB(DCB3 = Parlar no. 69), 2,2,3-exo,5,5,8,9,9,10,10-DCB(DCB4). DCB2 is a major component of the mixture. This is completely different from what we see in perchlorinated camphene – in this case the DCB2 is the smallest of the mentioned six congeners.

Origin of Polychlorobornanes	Relative content of selected congeners (determined by NMR spectra)					
	Parlar 50	Parlar 62	DCB1	DCB2	DCB3	DCB4
Bornyl Chloride	2.8	2.0	2.0	3.7	1	2.0
Camphene	2.3	4.8	2.4	0.4	1	2.0

Also the ratio of Parlar 50 and Parlar 62 is opposite in the two mixtures.

A new compound was isolated from the mixture **"9-10"** - 2-endo,3-exo,5,5,8,8,9,10,10-Nonachlorobornane. This compound was isolated as single enantiomer.

Structure of (1R)-2-endo,3-exo,5,5-tetrachloro-7-(chloromethyl)-1,7-bis(dichloromethyl) bicyclo[2.2.1]heptane



(1*S*)-2-*endo*-chlorobornane

(1*R*)-2-*endo*,3-*exo*,5,5-tetrachloro-7-(chloromethyl)-1,7-bis(dichloromethyl)bicyclo[2.2.1]heptane
or
(1*R*)-2-*endo*,3-*exo*,5,5,8,8,9,10,10-NCB

Enantiomeric purity of the title compound was confirmed by GC on a chiral phase and established directly with X-ray analysis[5]. NMR spectra confirm the structure.

Position	1	2	3	4	5	6 (exo/endo)		7	8	9 (a/b)		10
δ (^{1}H), ppm	–	dd 5.17	d 5.32	s 3.61	–	bd 3.09	bd 3.73	–	d 6.56	dd 4.28	bd 4.89	bs 6.34
δ (^{13}C), ppm	64.74	65.04	62.41	65.92	84.54	52.09		65.58	73.91	41.60		69.06

It's noteworthy that the 2-endo,3-exo,5,5 substitution pattern in the 6-membered ring of this NCB, as well as 2-endo,3-exo,5-exo,6-exo ring substitution pattern in the HpCB isolated from mixture **"7-8"** are unique and had never been observed in Toxaphene congeners known to date.

Another compound isolated in pure state is a well-known 2,2,5-exo,5-endo,6-exo,8,9,9,10,10-DCB. It formed beautifully looking crystals, but X-ray investigation was unsuccessful. However, its optical rotation was measured and found to be -10°.
Thus we have opened the way to preparation of pure enantiomeres of Toxaphene congeners.

Enantioselectivity in chlorination of terpenes – practice and theory
Production of polychloroterpene insecticides always starts from natural turpentine(always chiral). The first industrial operation is isolation of pinene fraction. Depending on the origin of turpentine it can be levorotatory or dextrorotatory.
The next step in preparation of Toxaphene or Soviet Polychlorocamphene is isomerization of pinene to camphene. It is not documented, whether resulting camphene was optically active. The final industrial step was chlorination of camphene to an average of 8 Cl atoms in a molecule. The process includes a rearrangement of major part of camphene into bornane derivatives. It is known that optical activity of technical Toxaphene is negligible, as well as optical activity of individual congeners isolated from it.
Moreover, numerous laboratory preparations of individual Toxaphene congeners from optically active camphene yielded racemates of individual congeners.
Most likely, for the racemization is due to H-shift in an intermediate non-classical cation (Fig. 1).

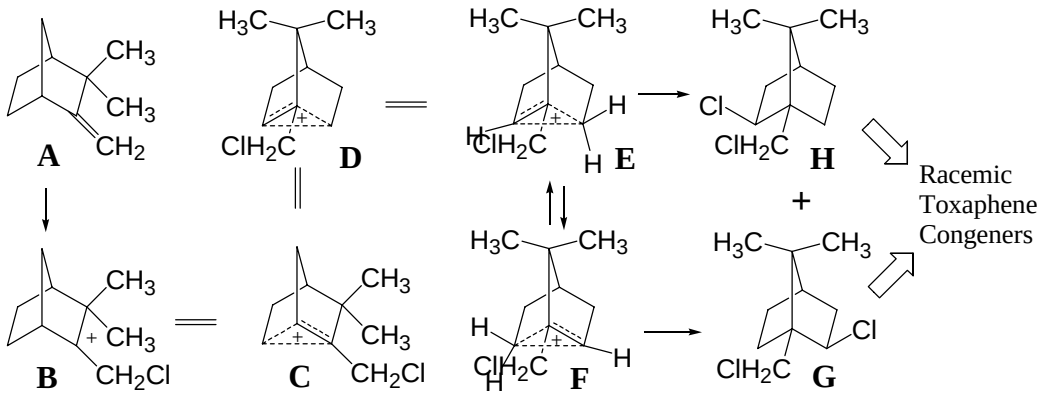


Figure 1. Initial step of ionic chlorination of Camphene

When a single enantiomer of Camphene **A** is taken for the chlorination, it adds Chlorine forming a tertiary cation **B**. Cation **B** is believed to be non-classical, its structure is better presented as **C**, where positive charge is delocalised among 3 carbon atoms. Other presentations of the same structure are **D** and **E**, both retaining enantiomeric purity of starting camphene. Racemization occurs when an endo-Hydrogen in cation **E** shifts to form its enantiomer, cation **F**. This equilibrium is well-known for bornyl cations. Then **E** and **F** add chloride to form a racemic mixture of 2-exo,10-dichlorobornane (**G** and **H**), major precursor to racemic Toxaphene congeners of chlorobornane series.
The Soviet insecticide Polychloropinene was produced in a different way: instead of being converted to camphene and then to dichlorobornane, pinene was hydrochlorinated to yield bornylchloride (2-endo-chlorobornane). Then bornylchloride reacted with Chlorine until an average

of 8 Cl atoms in a molecule is reached. The mechanism of rearrangement of pinene directly to bornane derivative is different (Fig. 2):

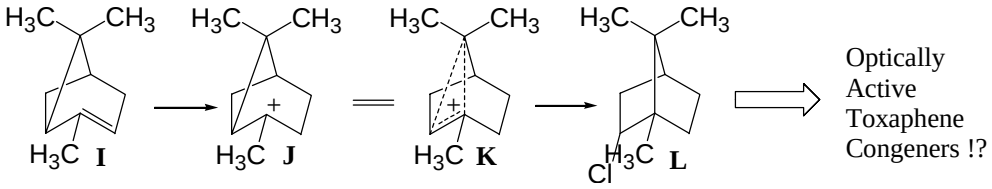


Figure 2. Hydrochlorination of α-Pinene.

When a single enantiomer of α-Pinene **I** is taken for the hydrochlorination, it adds proton forming a tertiary cation **J**. Cation **J** is believed to be non-classical, its structure is better presented as **K**, where positive charge is delocalised among 3 carbon atoms. The cation retains enantiomeric purity of starting pinene. This cation, unlike the one formed from camphene has no ability to hydride shift, therefore it should add chloride with formation of optically active bornylchloride **L**. If further free-radical chlorination proceeds without rearrangements it should lead to optically active chlorobornanes.

Theoretical consideration given above is intentionally simplified. The correct discussion is well beyond the aim of this work. However, it was the scientific ground for our attempt to prepare pure enantiomeres of Polychlorobornanes.

Conclusions

The first findings show that Soviet Polychloropinene must have a composition significantly different from composition of Toxaphene. Major Toxpahene congeners are present in a non-typical ratio and in smaller amounts, while a number of new major congeners of Polychloropinene has been identified. Moreover, Polychloropinene might have contained enantiomerically enriched polychlorobornanes. These two major differencies have to be taken into account when analyzing alterations in congener pattern and enatiomeric ratio in environmental samples.

Acknowledgement

This work was generously supported by Norwegian Research Council, project number 152806/730.

References

1. Saleh M. A. (1991). Rev. Eniron. Contam. Toxicol. 118, 1–85.
2. Nikiforov V. A. (2002). Organohalogen compounds. 59, 315–318.
3. Windholz, M., Budavari, S., Stroumtsos, L. Y. & Fertig, M. N. (1976). The Merck Index: An Encyclopedia of Chemicals and Drugs, 9th ed.; Merck: Rahway, NJ; p. 1734.
4. Buser, H. R. & Müller M. D. (1994). J. Agric. Food Chem. 42, 393–400.
5. Alexei Trukhin, Lars Kr. Hansen, Roland Kallenborn, Anastasia Kiprianova and Vladimir Nikiforov (2004). Acta Crystallographica E, accepted.