Synthesis and Characterization of Toxaphene congeners.

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Summary

Toxaphene is one of the insecticides with the world's highest production volume[1]. Also it is a major organochlorine contaminant in fish and marine mammals in North American and European waters[2]. Analysis of Toxaphen in usual manner is troublesome due to a complexicity of technical product - which is a mixture of about two hundreds hexa- to deca- chloromonoterpenes, mainly chlorinated bornanes and, therefore, use of pure congeners as analitical standards seemed impossible. However, in course of last 20 years, the structures of about 25 major Toxaphene constituents have been elucidated[1,3]. Two persistent congeners were isolated from Beluga whale

(*Delphinapterus leucas*) blubber and identified with a help of NMR and MS. These are 2-exo,3-endo,5-exo,6-endo,8,8,10,10-octachlorobornane and 2-exo,3-endo,5-exo,6-endo,8,8,9,10,10-nonachlorobornane[2]. Now we report isolation and structure elucidation of 5 new congeners. We believe, that availability of most major Toxaphene components as analitical standards can be achieved in a few years.

Experimental

Common way of preparation of Toxaphene congeners includes :

-preliminary chlorination of camphene in darkness
-isolation of 2-exo,10-dichlorobornane (I) from resulted mixture
-further chlorination of I to a desired extent
-separation of a toxaphene-like mixture on silica column
-further purification of enriched fractions on reverse phase LC columns and crystallizations

We changed this procedure slightly - instead of isolation of I, 2-exo,10,10-trichlorobornane (II) was purified and used as toxaphene precursor in further chlorination. We have tried to avoid formation of congners, containing only one chlorine atom at C-10 and to simplify a mixture for separation.

Chlorinated mixture was separated in 20g portions on silica column (2m height, 5cm i.d.) with hexane as eluent at a rate 5-10 ml/min. Fractions of similar composition were combined and evaporated to approximately 5% of initial volume. Several combined fractions yielded crystalline solids on standing (some in few minutes, some in a few weeks). These solids were crystallized several times until a purity 95-99% was achieved.

10 different compounds have been isolated so far.

5 of them are previously reported ones[1,2] :

2-exo,3-endo,5-exo,6-endo,8,8,10,10-octachlorobornane (III)
2-exo,3-endo,5-exo,6-endo,8,8,9,10,10-nonachlorobornane (IV)
2,2,5,5,8,8,9,10,10-nonachlorobornane (V)
2,2,3-exo,5-endo,6-exo8,8,9,10,10-decachlorobornane (VI)
2,2,3-exo,5,5,8,8,9,10,10-decachlorobornane (VII)

The other five have NMR spectra different from those of any previously reported congener. We have identified them as :

2-exo,3-endo,6-endo,8,9,10,10-heptachlorobornane (VIII)
2-exo,3-endo,5-exo,8,9,10,10-heptachlorobornane (IX)
2-endo,3-exo,6-exo,8,9,10,10-heptachlorobornane (X)
2-exo,2(or 3)-endo,3-exo,5,5,8,8,10,10-nonachlorobornane (XI)
2-exo,2(or 3)-endo,3-exo,5-exo,6-endo,8,8(or 9),9,10,10-decachlorobornane (XII)

Structure elucidation

Compounds III-VII were identified by comparison of their NMR spectra with the existing data[1,2].

Compound VIII

^{1}H NMR, $CDCl_3$, 500MHz : 6.65s, 5.16dd(J=10.67Hz, J=3.87Hz), 5.11d(3.85Hz), 4.68ddd(4.5Hz, 4.4Hz, 2.05Hz), 4.62dd(12.23Hz, 2.49Hz), 4.38d(12.23Hz), 4.12d(12.34Hz), 3.68dd(12.23Hz, 2.45Hz), 2.67dddd(14.5Hz, 11Hz, 4.5Hz, 2Hz), 2.63dd(4.3Hz, 4.2Hz), 2.49dd(14.75Hz, 3.91Hz)

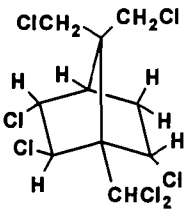
^{1}H NMR, C_6D_6, 500MHz : 6.62s, 5.16d(3.91Hz), 4.54dd(10.93Hz, 3.95Hz), 4.08m, 4.08d(12.32Hz), 4.04dd(12.59Hz, 2.48Hz), 3.52d(12.52Hz), 2.92dd(12.27Hz, 2.48Hz), 2.18dd(14.95Hz, 3.95Hz), 1.95dd(4.61Hz, 4.63Hz), 1.86dddd(15Hz, 11Hz, 4.5Hz, 2Hz)

Spectrum in deuterochloroform is better resolved and we used it for primary assignment. Four signals at 4.62, 4.38, 4.12 and 3.68ppm obviously belongs to four protons at C-8 and C-9. Singlet at 6.65ppm can be only a signal of a single proton at C-10. Thus, the state of methyl groups is cleared.

Assignment of 6 "ring" protons was a little more difficult. First, we supposed, that H-4 is not substituted, because it was never found before. Then one can see, that only two protons at 2.67 and 2.49 have a geminal coupling constant - 14.75Hz. Therefore, there is one CH_2 and three CHCl groups. Signal at 2.63ppm must belong to H-4 proton, while those at 5.16, 5.11 and 4.68 - to protons of CHCl groups. H-4 is doublet of doublets with constants (4.33 and 4.21), corresponding to interaction with 3-exo and 5-exo protons. These two protons must show a small constant of about 2Hz, indeed signals at 4.68 and

2.67 do so. Signal at 4.68 shows also a trans-constant. It means, that 4.68 is a 3-exo proton, adoublet at 5.11 is 2-endo proton. 5-exo proton at 2.67 (one of CH_2 protons, as we found earlier) has only one unidetified cis-constant of 11Hz - it means, that the last proton (5.16dd) is 6-exo.

The spectrum in deuterobenzene and the results of spin-decoupling experiments (irradiation at 2.5, 2.7, 4.7 and 5.17 ppm) are also in accordance with the structure given below.



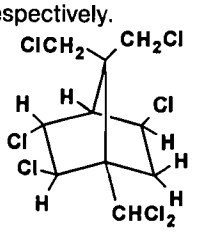
2-exo,3-endo,6-endo,8,9,10,10-heptachlorobornane (VIII)

Compound IX

^1H NMR, $CDCl_3$, 500MHz : 6.48s, 4.84dd(9.52Hz, 4.46Hz), 4.64dd(4.56Hz, 4.58Hz), 4.53d(11.92Hz), 4.43dd(12.05Hz, 2.23Hz), 4.32dd(11.93Hz, 1.97Hz), 4.20d(12.05Hz), 4.07d(4.50Hz), 2.94d(4.72Hz), 2.91dd(15Hz, 4Hz), 2.66dd(15.30Hz, 9.07Hz)

Methyl groups in this compound are similarly occupied. Signals at 4.53, 4.43, 4.32 and 4.20ppm belong to four protons at C-8 and C-9. Singlet at 6.48 is a signal of H-10. There is one methylene group (2.91 and 2.66), proton H-4 (2.94) and three CHCl

groups. Methylene protons, besides gem-coupling, show trans- and cis- coupling respectively. The only other signal with cis-constant (9.52Hz) is at 4.84, which shows no coupling other than with this methylene protons. It means, that methylene group is in 6 position. 2.91 is 6-exo, 2.66 - 6-endo, and 4.84 - 5-endo. 2.94 is, obviously, H-4, and 4.64 and 4.07 - 3-exo and 2-endo, respectively.



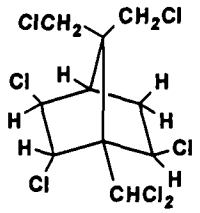
2-exo,3-endo,5-exo,8,9,10,10-heptachlorobornane (IX)

Compound X

^1H NMR, C_6D_6, 500MHz : 6.73s, 5.07d(4.26Hz), 4.66dd(9.30Hz, 4.54Hz), 4.39d(12.04Hz), 4.21dd(12.32Hz, 2.37Hz), 4.01dd(12.08Hz, 2.37Hz), 3.74d(12.34Hz), 3.37d(4.38Hz), 1.99d(5.16Hz), 1.53ddd(15.44Hz, 4.42Hz, 4.37Hz), 1.28dd(15.45Hz, 8.79Hz)

This compound, like compounds VIII and IX, has two CH_2Cl groups (C-8 and C-9; 4.39, 4.21, 4.01 and 3.74ppm), one $CHCl_2$ group (C-10, 6.73ppm), one methylene group (1.53 and 1.28ppm), H-4 proton (1.99ppm) and three CHCl groups. One of methylene protons (1.53) is coupled with two other protons with typical trans-constant (4.37 and

4.42Hz), therefore it is 5-exo. Then 1.28ppm must be a signal of 5-endo proton. Coupling between 5-endo (J=9Hz) and a proton observed at 4.66ppm, allows to identify the latter as 6-endo. Since H-4 is coupled with only one other proton (5exo), proton at C-3 must be 3-endo(5.07ppm). And since 3-endo is a doublet (J=4.26Hz), H-2 is in exo position.



2-endo,3-exo,6-exo,8,9,10,10-heptachlorobornane (X)

Compound XI

^{1}H NMR, $CDCl_3$, 500MHz : 7.19d(0.50Hz), 6.70s, 5.74s, 3.71dd(16.75Hz, 0.84Hz), 3.58d(16.73Hz), 3.11s, 2.00s(3H)

Singlet at 6.70ppm belongs to dichloromethyl group at C-10. 7.19d and 2.00s are the signals of dichloromethyl and methyl groups at C-8 and C-9. There are only four ring protons, two of which belong to methylene group (3.71 and 3.58ppm), relatively broad signal of H-4 is observed at 3.11ppm. Difference NOE experiment, involving irradiation of the signal at 2.00ppm resulted in enhancement of the signal at 3.71ppm. It means, that methyl carbon is C-9, dichloromethyl - C-8, 3.71ppm is a signal of 6-exo proton and

3.58ppm is a signal of 6-endo proton. Since no enhancement of a singlet at 5.74 has been observed, when a doublet at 7.19 was irradiated, signal at 5.74 must belong to 2- or 3-endo proton. ^{13}C NMR without proton-decoupling seems to be the best way to choose the correct structure.

Compound XII

^{1}H NMR, C_6D_6, 500MHz : 7.03d(2.59Hz), 6.24s, 5.27s, 5.13d(4.26Hz), 5.11dd(4.33Hz, 0.81Hz), 4.68d(13.56Hz), 3.94dd(13.55Hz, 2.60Hz), 3.45s

Singlet at 6.24ppm belongs to dichloromethyl group at C-10. 7.03d is the signal of dichloromethyl group at C-8 or C-9; 4.68d and 3.94dd are the signals of chloromethyl group at C-9 or C-8. Broad singlet at 3.45 belongs to H-4 proton. The coupling between signals at 5.13 and 5.11ppm (J=4.3Hz) shows that these two protons are vicinal and in trans position to each other. No trans coupling between one of them and H-4 means that these two protons are 5-endo and 6-exo. The singlet at 5.27 can not be 3-exo (no coupling with H-4), 2-exo position was occupied from the very beginning of the synthetic sequence, therefore it can be 2- or 3-endo. Final structure elucidation requires carbon spectrum without proton decoupling and (or) a series of proton selective decoupling experiments.

Acknowledgements

We would like to thank Dr. Yuri Arkhipov and Dr. Elena Grinenko (St.Petersburg Forestry Academy) and Dr. Ivan Podkorytov (Russian Institute of Synthetic Rubber) for NMR experiments.

References

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