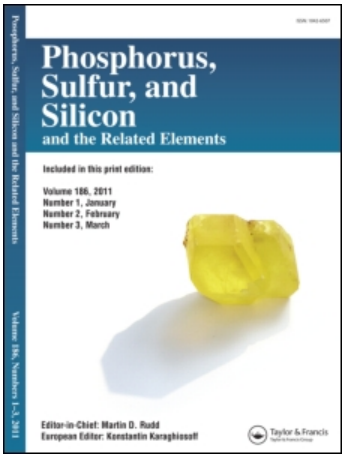

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Isolation, anticholinesterase properties and acute toxicity of the four stereoisomers of the nerve agent soman

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ISOLATION, ANTICHOLINESTERASE PROPERTIES AND ACUTE TOXICITY OF THE FOUR STEREOISOMERS OF THE NERVE AGENT SOMAN

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Abstract The four stereoisomers of pinacolyl methylphosphonofluoridate (soman) were isolated with more than 99% optical purity. The bimolecular rate constants for inhibition of electric eel acetylcholinesterase and the LD_{50}-values (sc, mice) of the stereoisomers were determined.

The synthesis of optically pure C(+)- and C(-)-soman (pinacolyl methylphosphonfluoridate) from the (+)- and (-)-enantiomers of pinacolyl alcohol has enabled us to further resolve these two epimeric mixtures into their respective P(-)- and P(+)-isomers with more than 99% optical purity on a 0.1-2 mg scale. This result was realized by means of (i) complete optical resolution of pinacolyl alcohol, (ii) synthesis of C(+)- and C(-)-soman from the (+)- and (-)-enantiomers of the alcohol, (iii) optimalization of conditions for stereospecific inhibition of α-chymotrypsin with the P(-)-isomers of C(+)- and C(-)-soman, followed by isolation of the C(+)P(+)- and C(-)P(+)-isomers, (iv) isolation of the C(+)P(-)- and C(-)P(-)-isomers after incubation of C(+)- and C(-)-soman, respectively, in rabbit serum, which hydrolyzes stereospecifically the P(+)-isomers. See Table I for a summary of results.

As in the case of the closely related sarin (isopropyl methylphosphonofluoridate), the P(-)-isomers of soman are much stronger inhibitors of AChE than the P(+)-isomers. Against bovine erythrocyte AChE, the ratio of reactivities of the two enantiomers of sarin[1] is $\geq 4.2 \times 10^3$, whereas this ratio for inhibition of electric eel AChE by the P(-)/P(+)-stereoisomers of soman is at least 3.6×10^4.

The maximal reactivation with the bisquaternary mono-oximes HI-6 and HGG-42 of AChE inhibited with "soman" depends on the ratio of the rate of reactivation and the rate of the simultaneously proceeding ageing reaction[2]. Since we have found that AChE inhibited with C(+)P(-)-soman is much more effectively reactivated (maximally to about 45 per cent) than the enzyme inhibited with the C(-)P(-)-isomer (maximally to about 7 per cent), we suggest that this ratio will be less favorable for reactivation in the case of the C(-)P(-)-isomer. If the rates of ageing of the enzymes inhibited with C(+)P(-)- and C(-)P(-)-soman are not much different[3], this would mean a remarkable selectivity of the reactivation reaction with regard to asymmetry in the pinacolyl moiety of soman.

A comparison of the LD_{50}-values (sc, mice) of the four stereoisomers of soman (Table II) shows clearly that the strongly AChE-inhibiting P(-)-isomers are at least 50 times more toxic than the corresponding P(+)-isomers. It should be noted that the dosage of C(+)P(+)-soman which kills 6/6 mice (10 mg/kg) contains only 0.1% of the highly toxic C(+)P(-)-isomer, corresponding with 0.1 LD_{50} of the latter isomer. Therefore, either the LD_{50} of the C(+)P(+)-isomer itself is between 5 and 10 mg/kg or the C(+)P(+)-isomer is partly racemized after administration, e.g. at the site of subcutaneous injection, to the highly potent C(+)P(-)-isomer. A similar reasoning may apply to the LD_{50} of the C(-)P(+)-isomer, which racemizes eventually to the highly toxic C(-)P(-)-isomer. It is also obvious from Table II that C(-)P(-)-soman is more than twice as toxic as C(+)P(-)-soman, in spite of the slightly higher inhibition rates of the C(+)P(-)-isomer (2.8×10^8 and $1.7 \times 10^8 M^{-1} min^{-1}$) compared with the C(-)P(-)-isomer (1.8×10^8 and $2.7 \times 10^7 M^{-1} min^{-1}$) for electric eel and bovine erythrocyte AChE respectively. This result shows clearly that small differences in antichokinesterase activity, measured in vitro, cannot be taken as an indicator for relative acute toxicities. Finally, it is interesting to compare the LD_{50} of C(-)- and C(+)-soman with that of "soman". The close struc-

tural similarity between the toxicologically active C(-)P(-)- and C(+)P(-)-stereoisomers and the nonsifnificant deviation from parallellism in the log dose-probit mortality plots (cf. Table II), suggest that the toxicity of C(+)- and C(-)-soman should be similar and therefore additive. The experimental LD_{50} for "soman" is reasonably in accordance with this assumption, and close to that of C(-)-soman. It should be noted that the fraction of C(-)P(-)-isomer in the LD_{50} of soman (ca. 156/4=39 µg/kg) corresponds approximately with the LD_{50} of the single C(-)P(-)-isomer, whereas this dosage of C(+)P(-)-soman is nonlethal ($LD_{0.1}$=74 µg/kg). Therefore, it is tempting to speculate that mice challenged subcutaneously with 1 LD_{50} of "soman" are killed primarily by the C(-)P(-)-isomer, although the C(+)P(-)-isomer may contribute slightly e.g. by inhibition of aliesterase in the blood.

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TABLE I Summary of results obtained with various isolations from C(-)-soman and C(+)-soman of the four stereoisomers of soman

Isomer of soman	Method of preparation	µMoles of soman incubated	Percentage recovery	Optical purity at phosphorus glc
C(+)P(+)	a	10	20 ± 10 (5)	98.3 ± 0.6 (5)
		60	31	99.8
C(-)P(+)	b	10	20 ± 7 (7)	99.1 ± 0.6 (7)
		56	22	>99.4
C(+)P(-)	c	6	27 ± 7 (6)	99.4 ± 0.5 (7)
		76	22	>99.4
C(-)P(-)	d	6	17 ± 4 (7)	99.2 ± 0.3 (9)
		60	14	99.0

[a]Inhibition of α-chymotrypsin with C(+)-soman. [b]Inhibition of α-chymotrypsin with C(-)-soman. [c]Hydrolysis of C(+)-soman in rat plasma or rabbit serum. [d]Hydrolysis of C(-)-soman in rabbit serum.

TABLE II LD_{50}-values (µg/kg) of the four stereoisomers of soman and of various isomer-mixtures in female (BCBA) F_1-mice, read 24 hours after subcutaneous administration.

Compound	LD_{50} (sc, µg/kg)	Slope (probits/log dose)
C(+)P(-)-soman	99 (94-105) [a]	28.0
C(+)P(+)-soman [b]	($>5x10^3$; $<10^4$)	-
C(+) -soman	214 (205-226)	23.2
C(-)P(-)-soman	38 (36-40)	21.1
C(-)P(+)-soman	($>2x10^3$) [c] ($<2.5x10^3$) [d]	-
C(-) -soman	133 (126-148)	17.7
"Soman"	156 (146-166)	12.1

[a]95% Fiducial limits. [b]Contained 0.1% of the C(+)P(-)-isomer. [c]Contained 0.7% of the C(-)P(-)-isomer. [d]Contained 0.3% of the C(-)P(-)-isomer

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SYNTHESIS AND PROPERTIES OF PHOSPHINOTHRICIN DERIVATIVES

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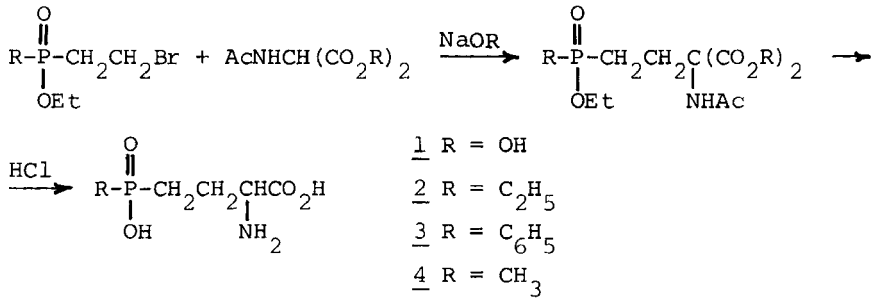
Abstract The synthesis and properties of phosphinothricin derivatives which have different alkyl groups attached to phosphorus or bear a substituent on the nitrogen are described and their biological activities discussed.

INTRODUCTION

It has been known for more than twenty years[1] that the phosphonic (1) and phosphinic acid (2) analogs of glutamic acid possess inhibitory properties towards glutamine synthetase, whereas the phenyl derivative (3) has only slight inhibitory activity. The synthesis of the ethyl (2) and phenyl phosphinic acid (3) analogs of glutamic acid was accomplished by condensation of diethyl acetaminomalonate with the corresponding phosphinates, followed by hydrolysis of the crude reaction mixture[2]:



1 R = OH
2 R = C_2H_5
3 R = C_6H_5
4 R = CH_3

The phosphonic analog was synthesized in the same way[3], starting from 2-bromoethylphosphonate. Phosphinothricin (4) has been isolated from cultures of Streptomyces viridochromogenes[4] and Strepto-