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1,2-Cyclic Monoacyl-rac-Glycerothio-phosphates of Cantharidin Analogues

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Abstract: A series of 1,2-cyclic monoacyl-rac-glycerothiophosphates of cantharidin and its analogues were synthesized in a one-pot procedure in overall yields of 44~55.5% by means of hexaethylphosphorus triamide as phosphorylating reagent.

Keywords: Synthesis, cantharidin and its analogues, cyclic glycerothiophosphate.

Mylabris, the dried body of the Chinese blister beetle, has been used as Chinese medicine for over 2000 years. Its active constituent, cantharidin, has antitumor activities and causes leukocytosis[1]. The synthesis of cyclic glycerophospholipid containing cantharidin analogues has so far not been reported in literature. The conjugates of this type are not only new prodrugs of cantharidin antitumor agents but also may generate two cytotoxic groups against different target sites inside a neoplastic cell[2]. Such types of compounds may be of interest in chemistry, biochemistry and pharmacology. This paper deals with the synthesis of 1,2-cyclic monoacyl-rac-glycerothiophosphates of cantharidin analogs as new models of phospholipids.

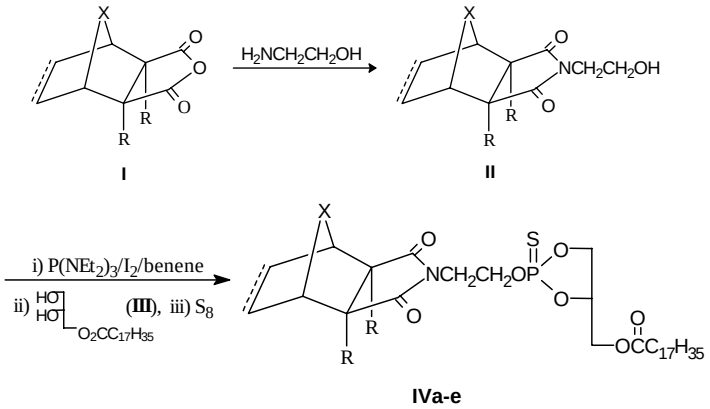
Table 1. Experimental Results of Compounds **IVa-e**

Compd. **	R	X	----	Rf*	Yield/%
IVa	H	O	single bond	0.585	29.3
IVa'	H	O	single bond	0.425	23.0
IVb	H	CH_2	double bond	0.615	24.8
IVb'	H	CH_2	double bond	0.315	19.2
IVc	H	O	double bond	0.738	25.5
IVc'	H	O	double bond	0.538	19.9
IVd	H	CH_2	single bond	0.662	28.7
IVd'	H	CH_2	single bond	0.508	23.1
IVe	CH_3	O	single bond	0.493	31.2
IVe'	CH_3	O	single bond	0.338	24.3

* solvent petroleum ether:ethyl acetate=3:2

** IVa-e and IVa'-e' are a pair of diatereoisomers

Scheme 1



IVa-e

The condensation of aminoethanol with cantharidin or its analogues **I** gave N-hydroxyethyl derivatives **II**. Then 1-monoacyl glycerol **III** reacted with N-hydroxyethyl compound of cantharidin or its analogs **II**, using hexaethyl-phosphorous triamine as phosphorylating reagent. As a result, cyclic thiophosphotriesters **IV** were obtained according to the following general procedure[3,4].

General procedure: A mixture of iodine (0.1 mmol) and hexaethylphosphorus triamide (2.1 mmol) in anhydrous benzene was stirred at 60~70°C for about 15 min until the reaction mixture became clear. powdery **II** (2 mmol) was added and the reaction mixture was continuously stirred at 60~70°C for about 1 hr. Then **III** (2 mmol) was added , and the mixture was heated at 60~70°C for 5 hr. The resultant cyclic phosphite was transformed to thiophosphate **IV** by adding sulfur (2.1 mmol) and keeping the reaction mixture at 60~70°C for 30 min. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel column eluted with petroleum ether-ethyl acetate (3:2) to afford oily products in pure form.

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References and Notes

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4. IR, ^1H , ^{31}P NMR and elemental analytical data of compounds IV have been deposited in the editorial office of CCL.

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