SYNTHESIS OF ORGANOPHOSPHORUS DERIVATIVES OF LUPININE AND SOLASODINE AND INVESTIGATION OF THEIR CHOLINERGIC ACTIVITIES

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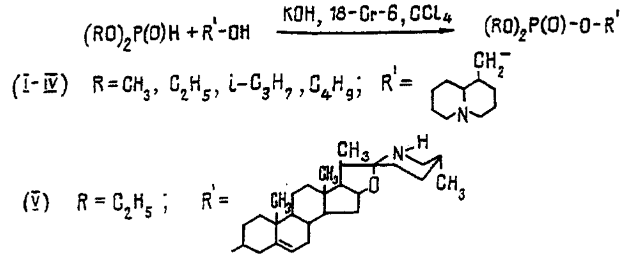
The synthesis of lupinine O-(dialkyl phosphate)s and of solasodine O-(diethyl phosphate) has been achieved under the conditions of phase-transfer catalysis and their antienzyme activities have been studied.

It is known that organophosphorus cholinesterase inhibitors derived from diesters of phosphorus acid containing a nitrogen atom in their structure exhibit a high anticholinesterase activity [1, 2]. Particular interest is presented by compounds with large hydrophobic groupings, which are capable of showing selective activity in relation to butyrylcholinesterase [2-4].

In view of this, it appeared of interest to synthesize and study the anticholinesterase activities of organophosphorus compounds with a phosphate structure containing lupinine and solasodine residues as ester radicals. The synthesis of lupinine O-(dialkyl phosphate)s (I-IV) and of solasodine O-(diethyl phosphate) (V) has been achieved in benzene under the conditions of phase-transfer catalysis in the presence of catalytic amounts of dibenzo-18-crown-6.



The corresponding methiodides were obtained by the action of methyl iodide on (I-IV).

The yields, physicochemical constants, and details of the IR and NMR (^1H and ^{31}P) spectra of the compounds synthesized are given in Tables 1 and 2.

A study of the antienzyme activities of compounds (I-V) showed that all the substances synthesized possessed a moderate reversible inhibiting activity in relation to the enzymes cytochrome P-450 and BuCE of horse blood serum, and weak activity in relation to the ACEs of human blood erythrocytes ($p\overline{K}_1$ 3.53-4.08) and of aphids ($p\overline{K}_1$ 3.27-3.42), and they irreversibly suppressed the enzyme glutathione S-transferase. The nature of the alkyl radical showed no great influence on the antienzyme activity.

The greatest inhibiting activity on the enzyme cytochrome P-450 was possessed by phosphate (III) (pI_{50} 5.0). Phosphates (III) and (IV) proved to be highly selective inhibitors of aphid BuCE ($p\overline{K}_1$ 5.64 and 5.70, respectively).

Methiodide of Lupinine O-(Dimethyl Phosphate) (I). Dropwise, 3.2 g (0.029 mole) of dimethyl phosphite in 8.3 g (0.054 mole) of carbon tetrachloride was added to a mixture of 4.56 g (0.027 mole) of lupinine, 2.24 g (0.04 mole) of KOH, 8.31 g (0.054 mole) of carbon tetrachloride, and a catalytic amount (5-10 mg) of dibenzo-18-crown-6 in 30 ml of absolute benzene. The solution was stirred at room temperature for 8-9 h. The precipitate was filtered off, and the solvent was evaporated in a rotary evaporator. The residual liquid

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TABLE 1. Yields, Physicochemical Constants, and Characteristic Frequencies in the IR Spectra of the Methiodides of Lupinine O-(Dialkyl phosphate)s (I-IV) and of Solasodine O-(Diethyl phosphate) (V)

Compound	R	Yield, %	mp, °C	$[\alpha]^{20}$, deg, (1.0	ν, cm^{-1}	
					P=O	P–O–C
I	CH_3	77.3	115–116	–48	1240	1050
II	C_2H_5	79.8	137–138	–33	1250	1050
III	i-C_3H_7	81,6	130–131	–28	1230	1040
IV	C_4H_9	75,4	148–149	–42	1250	1050
V	C_2H_5	54,2	192–193	–53	1230	1020

TABLE 2. Parameters of the NMR (^1H, ^{31}P) Spectra of the Methiodides of Lupinine O-(Dialkyl phosphate)s (I-IV) and of Solasodine O-(Diethyl phosphate) (V)

Compound	Chemical shift, δ, ppm					SSCC, J, Hz
	CH_3–C	–CH_2–O	CH_2–O	CH_3N^+	^{31}P	J_{HH}
I	1.3 t	4,12 m	3,8–4,0 m	3,54 s	–1,2	7.0
II	1,1 t	4,10 m	3,8–4.05 m	3,50 s	–2,8	7,0
III	1.3 d	4,6 m	3,9–4.05 m	3,48 s	–4,0	6.0
IV	0,90d	3.75 m	3,7–4,05 m	3,48 s	–1,0	6,5
V	1.22t	3.94 m	—	—	–2.0	7.0

product was dissolved in acetone, and 4.26 g (0.03 mole) of methyl iodide was added. After 5 h, the crystalline product was filtered off. Compounds (II-IV) were synthesized by the same method.

Solasodine O-(Diethyl Phosphate) (V). Dropwise, 1.93 g (0.014 mole) of diethyl phosphite in 3.70 g (0.024 mole) of carbon tetrachloride was added to a mixture of 5.17 g (0.012 mole) of solasodine, 1.00 g (0.018 mole) of KOH, 3.70 g (0.024) mole of carbon tetrachloride, and 5-10 mg of dibenzo-18-crown-6 in 40 ml of absolute benzene. The reaction mixture was heated at 65-70°C for 36 h. The precipitate was filtered off, and the solvent was distilled off. The residue was recrystallized from benzene, giving 3.5 g (54%) of compound (V).

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