

## Dialkylaminoalkyl Diphenylphosphine Oxides\*

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Dialkylaminoalkyl diphenylphosphinates and related phosphonate esters were first synthesized by Smith and Burger<sup>1</sup> for comparison with traditional ester-type anticholinergics,  $\text{Ar}_2\text{CHCO}_2(\text{CH}_2)_n\text{NR}_2$ . Biological screening of  $\beta$ -dimethylaminoethyl diphenylphosphinate and its methiodide salt revealed pronounced anticholinergic and cholinesterase inhibitory activity, as well as a certain degree of analgetic and diuretic activity. Examination of molecular models of these esters showed that the larger phosphinate ester centre permits a considerable amount of play of the dialkylaminoalkyl chain, which is absent in the molecules of the potent analgetic-anticholinergic agents of the methadone and morphinan groups. Since rigidity around the quaternary carbon atom is a distinguishing feature associated with potent analgetic behaviour, it was deemed possible that an increase of steric crowding at the phosphorus atom might enhance both anticholinergic and analgetic properties also. Such steric crowding is achieved to a considerable extent in dialkylaminoethyl and dialkylaminomethyl diphenylphosphine oxides, even though a little flexibility is still retained in the models of these compounds. Unfortunately, we were unable to synthesize homologues with at least one *o*-tolyl group whose models attain a high degree of rigidity. Difficulties in obtaining *o*-substituted aromatic phosphine oxides have been observed by Burger and Dawson.<sup>2,3</sup>

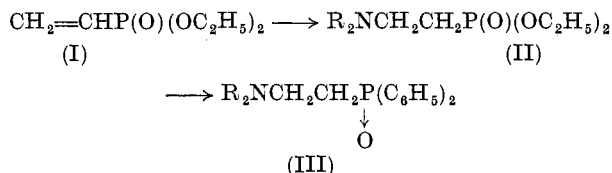
The dialkylaminoethyl and dialkylaminomethyl diphenylphosphine oxides described in this article were tested for analgetic properties by the Eddy method, but—surprisingly—failed completely to lower the pain threshold in mice even in high doses.

\* This research was supported in part by grants from the Virginia-Carolina Chemical Corporation and the Institute for Neurological Diseases and Blindness, National Institutes of Health, B-1445.

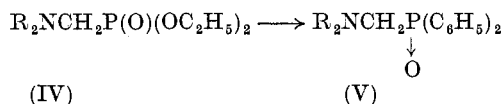
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Oral administration of diphenylmorpholinomethyl- and diphenylpyrrolidinomethylphosphine oxides (500 mg/kg) moderately reduced pernicious preening activity in mice. The morpholino-derivative caused central nervous system depression at doses beginning at 250 mg/kg, the pyrrolidino-derivative at 500 mg/kg.\*

The syntheses of the two series of phosphine oxides proceeded by the following sequences. Diethyl vinylphosphonate (I)<sup>4</sup> was added to the appropriate amine to yield diethyl 2-dialkylaminoethylphosphonates (II).<sup>5</sup> These esters were reacted with phenyllithium; the resulting dialkylaminoethyl diphenylphosphine oxides (III) were converted to water-soluble salts for biological tests.



The lower homologues were prepared from diethyl dialkylaminomethylphosphonates (IV), obtained in turn by the Fields reaction<sup>6</sup> using diethyl hydrogen phosphonate, formaldehyde and the appropriate secondary amine. The esters (IV) were distilled, and without further purification allowed to react with phenyllithium. The dialkylaminomethyl diphenylphosphine oxides (V) were formed in yields of 50–70 per cent.






### Experimental

*Preparation of diethyl 2-dialkylaminoethylphosphonates.* To diethyl vinylphosphonate (16.4 g, 0.1 mole) was added 0.1 mole of the appropriate secondary amine. The mixture usually became quite hot and cooling was often necessary. It was allowed to

\* We are obliged to Dr James W. Wilson of Smith Kline and French Laboratories for these tests.







stand overnight and distilled the next day. The yields, refractive indexes, and  $n_D^{20}$  calculated and observed, are shown in Table I. The index of refraction measured at 25° was converted to that at 20° by use of the correction factor of 0.0004 per degree  $n_D^{20}$  and comparing this experimental value with that derived from bond constants.

Table I. Physical properties of diethyl 2-dialkylaminoethylphosphonate  
( $R_2NCH_2CH_2P(O)(OC_2H_5)_2$ )

$R_2N$	b.p., °C/mm	$n_D^{25}$	$n_D^{20}$ Calcd.	$n_D^{20}$ Obs.
$(CH_3)_2N$	100/1.0	1.4329	299	300
	120/2	1.4509	343	341
	120/2	1.4529	364	363
	137/1	1.4590	367	367





*2-Dialkylaminoethyl diphenylphosphine oxides.* Diethyl 2-dialkylaminoethylphosphonate (10 g) was added to a solution of phenyllithium (0.3 mole) in ether (300 ml). The reaction mixture was refluxed for 3 h and then hydrolysed by pouring on ice. The mixture was acidified with hydrochloric acid and extracted three times with ether. The ether extract was discarded, the aqueous portion was made basic with potassium hydroxide and extracted three times with benzene. The benzene extracts were combined and dried over anhydrous potassium carbonate, and the benzene was removed on a rotating evaporator. The crude phosphine oxides were tan-coloured solids which were recrystallized from methylcyclohexane to colourless needles. Melting points and analyses are recorded in Table II. The infrared spectra closely resembled those of methyl and ethyl diphenylphosphine oxide. The hydrochlorides were formed in isopropyl ether, and recrystallized from isopropyl alcohol-isopropyl ether combinations. Their properties are described in Table II.

Table II. 2-Dialkylaminoethyl diphenylphosphine oxides  
 $R_2NCH_2CH_2P(O)(C_6H_5)_2$ 

R <sub>2</sub> N	m.p., °C (corr.)	Analysis, %			
		Calcd.		Found	
		C	H	C	H
(CH <sub>3</sub> ) <sub>2</sub> N	111.5–112.5	70.31	7.38	70.19	7.53
	83–85	72.22	7.41	71.66	7.53
 · H <sub>2</sub> SO <sub>4</sub>	206–208	54.40	6.90	54.47	6.11
	111	72.81	7.71	72.79	8.00
 · HCl	248–250 (d.)	65.23	7.20	65.38	7.35
	120–122	68.55	7.03	68.90	7.24
 · HCl	220 (d.)	61.45	6.59	61.34	6.89

*Diethyl dialkylaminomethylphosphonates.* For the preparation of these compounds, a procedure adapted from that of Fields<sup>6</sup> was used. To a stirred equimolar mixture of diethyl hydrogen phosphonate and the respective amine was added formaldehyde






 Table III. Physical properties of diethyl dialkylaminomethylphosphonates  
 $R_2NCH_2P(O)(OC_2H_5)_2$ 

R <sub>2</sub> N	b.p., °C/mm	<i>n</i> <sub>D</sub> <sup>25</sup>
(CH <sub>3</sub> ) <sub>2</sub> N	83–85/0.5	1.4281
	110/0.1	1.4471
	128–131/0.1	1.4541
CH <sub>3</sub> N 	110/0.5	1.4595
	124/1.0	1.4549

(1 mole). After the exothermic reaction had subsided, the mixture was cooled, poured into water (100 ml) and extracted with benzene, and the benzene solution was evaporated in a rotating evaporator. The residual oils were distilled; although the infrared spectra still showed hydroxyl peaks, the materials were sufficiently pure for use in the subsequent reaction. Physical characteristics are shown in Table III.

*Dialkylaminomethyl diphenylphosphine oxides.* To a stirred solution of phenyllithium (0.3 mole) was added, under nitrogen and over a period of 15 min, the diethyl dialkylaminomethylphosphonate (10 g, 0.05 mole). The mixture was decomposed by pouring into ice water, and the basic material isolated in the usual manner. The free bases solidified on cooling and were recrystallized from methylcyclohexane. Hydrobromide salts were prepared in dry ether solution and recrystallized from isopropyl alcohol-isopropyl ether. Data on the bases and their salts are listed in Table IV.

Table IV. Dialkylaminomethyl diphenylphosphine oxides  
 $R_2NCH_2P(O)(C_6H_5)_2$

R <sub>2</sub> N	m.p., °C (corr.)	Analysis, %			
		Calcd.		Found	
		C	H	C	H
(CH <sub>3</sub> ) <sub>2</sub> N	189–190	69.48	7.00	69.28	7.39
(CH <sub>3</sub> ) <sub>2</sub> N·HBr	237–238 (d.)	52.95	5.63	52.69	5.65
 N	154–156	71.56	7.07	71.83	7.21
 N·HBr	240 (d.)	55.75	5.78	55.88	5.80
 N·HBr	245–247	56.86	6.10	56.44	6.32
CH <sub>3</sub> N  N	165–166	68.77	7.37	68.94	7.72
 N	163–165	67.59	6.69	67.80	7.01

*Summary.* Several dialkylaminoethyl and dialkylaminomethyl diphenylphosphine oxides have been synthesized and subjected to limited pharmacological screening.

*(Received 1 March, 1961)*

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