Phosphorus–Nitrogen Compounds XV: *N*-1-Adamantylphosphoramidic Dichloride and Dimethyl and Diphenyl *N*-1-Adamantylphosphoramidate

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Abstract □ *N*-1-Adamantylphosphoramidic dichloride and the dimethyl and diphenyl esters of the corresponding acid were synthesized and evaluated for biological activity. The dimethyl ester delayed the onset of tremorine-induced tremors and reduced locomotor activity, while the diphenyl derivative slightly antagonized perphenazine-induced catatonic reactions. None of the agents displayed activity against lymphoid leukemia.

Keyphrases □ *N*-1-Adamantylphosphoramidic dichloride—synthesis, pharmacological screening as antiparkinsonism and anticancer agents □ *N*-1-Adamantylphosphoramidate, dimethyl and diphenyl—synthesis, pharmacological screening as antiparkinsonism and anticancer agents □ Amantadine derivatives—synthesis of *N*-1-adamantylphosphoramidic dichloride and dimethyl and diphenyl *N*-1-adamantylphosphoramidate as potential antiparkinsonism and anticancer agents □ Antiparkinsonism agents, potential—synthesis of amantadine derivatives, screening □ Anticancer agents, potential—synthesis of amantadine derivatives, screening

Among the many derivatives containing the adamantyl moiety, the most extensively studied is amantadine (1-adamantanamine, I). Early investigations of this agent mainly involved its antiviral properties, whereas several recent studies were concerned with antiparkinsonism activity. The beneficial effects in Parkinson's disease have been related to release of dopamine from neuronal storage sites (1, 2) rather than through anticholinergic mechanisms (1, 3), which is the basis for the action of agents commonly employed in treating this disease state.

Since good cholinolytic activity in three phosphoramidates, especially in those containing the diphenylphosphate grouping, was found previously (4), the two esters reported here were considered as potential antiparkinsonism agents. Amantadine, in addition to having therapeutic action *per se*, contributes the highly lipophilic adamantyl moiety to ensure ready distribution of the compounds to the CNS. A recent study (5) employed this grouping in the design of an analog of procyclidine hydrochloride. The effect of introducing an adamantyl fragment in prospective therapeutic agents has been the subject of many other inquiries (6); no investigation, however, has been reported on the consequence of phosphorylation of the 1-amino derivative of adamantane[1].

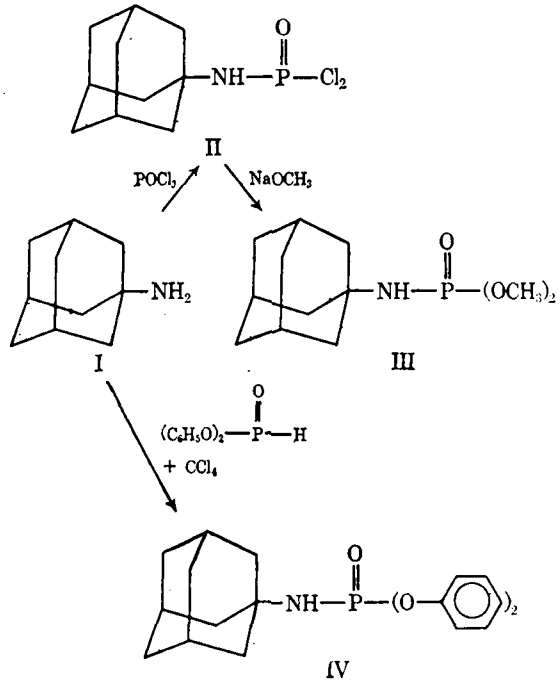
DISCUSSION

The desired adamantylphosphoramides (III and IV) were prepared by reacting sodium methoxide with *N*-1-adamantylphosphoramidic dichloride (II) and diphenylphosphonate with I and carbon tetrachloride (Scheme I). Compound II was synthesized using the phosphorus oxychloride–amine method (7). Information pertinent to these compounds, including spectral data, is presented in Table I.

Compounds III and IV were screened for antiparkinsonism activity by two methods. The onset of tremorine-induced tremors in mice, occurring within 10 min., was prolonged to 25 min. in the case of III at a dose of 250 mg./kg. No prolongation was noted with III at 125 mg./kg. or with IV at 250 mg./kg. Derivative III (250 mg./kg.) also doubled the period required for tremor induction produced by oxotremorine. Perphenazine-induced catatonic reactions were antagonized to the extent of 8% (III) and 25% (IV). These tests, summarized in Table II, indicate a potential activity of a weak nature for the esters in Parkinson's disease. Locomotor activity in mice was also shown to be reduced 25% by III. During gross observation studies, III caused ataxia and hindlimb paralysis and IV produced sedation and hypnosis in mice (250 mg./kg.). None of three new adamantylphosphoramides gave a beneficial response when tested against L-1210 lymphoid leukemia[2].

EXPERIMENTAL

***N*-1-Adamantylphosphoramidic Dichloride (II)**—This compound was prepared using the method of Michaelis (7) whereby a solution of freshly distilled phosphorus oxychloride (20.0 g., 0.13 mole) in anhydrous ether (20 ml.) was placed in a flask fitted with a thermometer, drying tube, and dropping funnel. Amantadine (20.0 g., 0.13 mole) and triethylamine (14.6 g., 0.14 mole) in anhydrous ether (150 ml.) were added dropwise with magnetic stirring



Scheme I

[1] During the time of this writing, the diphenyl ester was reported in Abstract 49, Division of Medicinal Chemistry, 165th ACS National Meeting, Dallas, Tex., Apr. 1973, by Warner, Mirth, Day, Turesky, and Soloway.

[2] The rationale for anticancer properties in these compounds and a description of active related agent(s) will be presented in a future paper.

Table I—*N*-1-Adamantylphosphoramidic Dichloride and Dimethyl and Diphenyl *N*-1-Adamantylphosphoramidate

Compound	Melting Point[a]	Yield, %	Formula	Analysis[b], % Calc.	Analysis[b], % Found	Spectral Data: IR[c] Maximum, μ	Spectral Data: NMR[d] δ, p.p.m.	Spectral Data: NMR[d] (Number of Protons)
II	129–131.5°	71.7	$C_{10}H_{16}Cl_2NOP$	C 44.80 H 6.02 N 5.22	44.49 6.01 5.08	3.15 (N—H) 8.04 (P—O)	1.95 1.68	(9) (6)
III	69–71°	64.2	$C_{12}H_{22}NO_3P$	C 55.16 H 8.49 N 5.36	55.04 8.58 5.25	3.15 (N—H) 8.30 (P—O) 9.79 (P—O—C)	3.70[e] 2.00 1.75 1.63	(6) (3) (6) (6)
IV	123.5–125°	68.9	$C_{22}H_{26}NO_3P$	C 68.92 H 6.83 N 3.65	68.74 6.96 3.62	3.15 (N—H) 6.35 (C—H) 8.15 (P—O) 9.70 (P—O—C)	7.25 1.90 1.60	(10) (9) (6)

[a] Taken on a Fisher-Johns apparatus and are corrected. [b] Performed by Atlantic Microlab, Inc. [c] Obtained on a Beckman IR-8 spectrophotometer using a Nujol mull. [d] Obtained on a Varian T-60 spectrometer using deuterated chloroform as the solvent and tetramethylsilane as the reference. [e] Doublet, J = 12 Hz.

Table II—Pharmacological Activities of the Amantadine Derivatives

Compound	Dose, mg./kg. i.p.	Onset of Tremors, min.	Perphenazine Reaction Score (Drug Effect, %) Test[a]	Perphenazine Reaction Score (Drug Effect, %) Control	Anticancer Screening[b] (L-1210 Lymphoid Leukemia in BDF_1 Mice) mg./kg.	Anticancer Screening[b] (L-1210 Lymphoid Leukemia in BDF_1 Mice) % T/C
II	–	–	—	–	400[c]	–
					200	93
III	125[d]	11	—	—	400	95
	250[d]	25	0.92 (8)	0.00 (100)	—	—
	250[e]	11	—	—	—	–
IV	250[d]	10	0.75 (25)	0.00 (100)	400	87
Tremorine	–	10	—	—	—	—
Oxotremorine	—	5	–	—	–	–
Atropine	—	–	0.92 (8)	0.00 (100)	—	—
Perphenazine	—	—	—	1.00 (0)	—	—
Vehicle[f]	—	—	–	0.00 (100)	–	–

[a] Perphenazine (5 mg./kg.) 15 min. pretreatment. [b] Performed by the screening contractors of the National Cancer Institute. Only highest, nontoxic dose is indicated. [c] No survivors out of six. [d] Compound followed with tremorine (0.6 mg./kg.) in 30 min. [e] Compounds followed with oxotremorine (0.5 mg./kg.) in 15 min. [f] Sodium carboxymethylcellulose, 1%.

over 1 hr. at 5–10°, during which time a white precipitate formed. After remaining overnight at room temperature, the reaction mixture was filtered and the filtrate was spin-evaporated to yield 25.0 g. of crystalline material. Recrystallization from ether gave the pure product.

Dimethyl *N*-1-Adamantylphosphoramidate (III)—To a stirred solution of II in 25 ml. of methanol was added a sodium methoxide solution prepared by reacting 1.15 g. of sodium metal with 30 ml. of absolute methanol. The temperature of the reaction mixture rose 30° and a white precipitate formed. After cooling and filtering, water was added to the filtrate and, when kept overnight, yielded 3.3 g. of III.

Diphenyl *N*-1-Adamantylphosphoramidate (IV)—According to the procedure of Atherton *et al.* (8), I (9.0 g., 0.06 mole) and triethylamine (6.0 g., 0.06 mole) in 80 ml. of carbon tetrachloride were placed in a flask fitted in the same manner as described for II. Diphenylphosphonate (11.7 g., 0.5 mole) in 15 ml. of carbon tetrachloride was added dropwise to this solution over 30 min. with a temperature rise of 35° and formation of a dense, white precipitate. After remaining overnight, the reaction mixture was filtered and the filtrate was spin-evaporated to yield a granular substance which gave 13.2 g. of pure IV when recrystallized from dilute ethanol.

Male Swiss albino mice (18–25 g.) in groups of four were used in the pharmacological screening. Compounds III and IV were suspended in 1% sodium carboxymethylcellulose and tested for antagonism of tremorine- (9) and oxotremorine- (10) induced tremors and perphenazine-produced catatonia (11). Atropine (2 mg./kg.) prevented tremorine-caused tremors for over 1 hr., except in the case of one animal which had tremor induction in 25 min. In addition, III reduced locomotor activity[3] by 25% at a dose of 250 mg./kg.

[3] Actophotometer, model ME-5200.

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