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Phosphorus–Nitrogen Compounds. 13. Methoxyethyl and Propylamine Derivatives[1,2]

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Both ethanolamine and phosphorylethanolamine occur in high concentrations in malignant tumors[3] which are very active in phosphatide synthesis.[4] Related compounds of type $(RO)_2P(O \text{ or } S)NH(CH_2)_{2-3}OCH_3$, or their hydrolytic products, may serve as inhibitors of biotransformations or utilization of the aforementioned metabolites and/or phosphatidylethanolamine. Selective cytotoxicity of the methoxyethyl or propylamine moieties as a result of preferential chemical and/or enzymatic hydrolysis of the P–N bond may occur since neoplastic cells are reported to be more acidic[5] and contain higher than normal amounts of phosphomonoamidase.[6,7] The compounds, administered in single doses, were inactive when screened against L-1210 lymphoid leukemia.[8] Test animals survived 400 mg/kg doses of the derivatives except in the case of the diethylphosphoramidates II and VIII which were toxic above 12.5 and 100 mg/kg, resp.

Table I

$$(RO)_2\overset{X}{\overset{\|}{P}}NH(CH_2)_nOCH_3$$

No.	R	X	n	Formula	Yield, %	Bp (mm) °C	$n^{20}D$
I	Me	O	3	$C_6H_{16}NO_4P$	98	119–121 (0.30)	1.4398
II	Et	O	3	$C_8H_{20}NO_4P$	97	117–120 (0.25)	1.4361
III	*i*-Pr	O	3	$C_{10}H_{24}NO_4P$	85	108–109 (0.20)	1.4320
IV	Me	S	3	$C_6H_{16}NO_3PS$	97	86–88 (0.10)	1.4836
V	Et	S	3	$C_8H_{20}NO_3PS$	95	109–110 (0.05)	1.4751
VI	Pr	S	3	$C_{10}H_{24}NO_3PS$	89	119–120 (0.20)	1.4724
VII	Me	O	2	$C_5H_{14}NO_4P$	80	88–91 (0.15)	1.4365
VIII	Et	O	2	$C_7H_{18}NO_4P$	98	95–97 (0.10)	1.4330
IX	*i*-Pr	O	2	$C_9H_{22}NO_4P$	94	82–84 (0.05)	1.4287
X	Bu	O	2	$C_{11}H_{26}NO_4P$	93	115–117 (0.05)	1.4374
XI	Me	S	2	$C_5H_{14}NO_3PS$	95	78–80 (0.12)	1.4833
XII	Et	S	2	$C_7H_{18}NO_3PS$	93	75–77 (0.06)	1.4733
XIII	Pr	S	2	$C_9H_{22}NO_3PS$	90	89–92 (0.06)	1.4709

Experimental Section

Ir spectra of all products (Table I), recorded on a Beckman IR-8, were as expected. Refractive indices were measured on a Bausch & Lomb 3L refractometer. All compds were analyzed for C and H; in addition I, II, and VI were analyzed for N.[9] Anal. were within ±0.4% of theor values.

N-Phosphorylation of 2-Methoxyethylamine and 3-Methoxypropylamine. A. Phosphite Methods.—The appropriate phosphite (0.1 mole) in CCl_4 was treated under N_2 with 0.2 mole of amine (III, VII) or 0.1 mole of amine and 0.1 mole of Et_3N (I, II, IX, X) in CCl_4 according to a previously described procedure.[10]

B. Phosphorochloridate Method.—The appropriate phosphorochloridate or phosphorochloridothionate (0.1 mole) was treated with 0.2 mole of amine (V) or 0.1 mole of amine and 0.1 mole of Et_3N (IV, VI, VIII, XI–XIII) in Et_2O according to the method of Michaelis.[11]

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(2) Part 12: L. A. Cates, *J. Med. Chem.*, **14**, 647 (1971).

(3) E. L. Outhouse, *Biochem. J.*, **30**, 197 (1936).

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(5) J. H. Billman, F. Koehler, and R. J. May, *J. Pharm. Sci.*, **58**, 769 (1969).

(6) O. M. Friedman and E. Boger, 139th Meeting of the American Chemical Society, St. Louis, Mo., March 1961, p 26-C.

(7) O. M. Friedman, S. Schichor, and E. Boger, *Proc. Amer. Soc. Cancer Res.*, **3**, 320 (1954).

(8) Testing performed by CCNSC.

(9) Atlantic Microlab, Inc., Atlanta, Ga.

(10) F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 660 (1945).

(11) A. Michaelis and G. Schulze, *Ber.*, **27**, 2572 (1894).

Book Reviews

Annual Review of Pharmacology. Volume 11. Edited by H. W. Elliott, R. Okun, and R. H. Dreisbach. Annual Reviews, Inc., Palo Alto, Calif. 1971. ix + 560 pp. 23 × 16.6 cm. $10.00

The 1971 volume contains 25 reviews, ranging from drug metabolism to Li, from placental drug transfer and teratology to chemotherapy of cancer and parasitic infestations, and from circadian chronopharmacology to marine toxins. There is a preponderance of articles on CNS-active drugs and adrenergic processes; high-lighted by factual and philosophical reminiscences of U. S. von Euler. But other areas (estrogens, drugs affecting the thyroid, antiarrhythmic agents) and a rather historic review of SAR and receptor concepts by Adrien Albert, are also represented. In fact, there is a good deal of looking back far beyond the last biennium, and not so much looking ahead as one might expect.

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Principles of Psychopharmacology. A Textbook for Physicians, Medical Students, and Behavioral Scientists. Edited by W. G. Clark and J. del Giudice, with 69 contributors. Academic Press, New York, N.Y. 1970. xxvi + 814 pp. 24.5 × 17.2 cm. $19.50

The subtitle of this textbook indicates to whom this substantial volume is addressed. Nevertheless, three excellent chemical chapters by J. H. Biel discuss SAR of useful psychopharmacologic agents most adequately even for a chemist. There is a good and comprehensive list of generic and proprietary names (E. Usdin), and an unusually interesting history of psychopharmacologic drugs from Homeric times to the present (A. E. Caldwell) from which one learns that the priestess Pythia pronounced the Delphic oracle while enveloped in a vapor bath of burnt hemp seeds, and not, as previously assumed, of *Datura stramonium*. And who knew that the "lytic cocktail" was first poured by Helen of Troy *after* she returned home from her prolonged extramarital excursion?

The 46 chapters take us through most clinical, sociological, toxicological, and preclinical methodological aspects of psychopharmaca. The biochemical background of these drugs has not fared well in this book, but the volume should do a real service in educating psychiatrists, and in giving physicians and psychopharmacologists ample reading references in their field. There are some errors (isoniazid is spoken of as an MAO inhibitor), but they are mostly of a minor nature.

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