Structure IV was supported by infrared[4] spectra which showed the stretching frequencies characteristic of aromatic CH, C=C, Amide I, and Amide II (*cf.* Table I). The spectra showed one band in the region 3246–3448 cm.$^{-1}$, probably due to an overlap of the OH and NH stretching frequencies.

EXPERIMENTAL[5]

A. *General procedure for the reaction of 2-phenyl-5-oxazolone*[6] (I) *with arylmagnesium halides.* To an ethereal solution of the arylmagnesium halide (3 moles) was added a solution of the oxazolone (I) (1 mole) in dry ether. The reaction mixture was refluxed for 2 hr. and left overnight. It was hydrolyzed with a saturated ammonium chloride solution, dried over anhydrous sodium sulfate, and evaporated on a water bath nearly to dryness. The oily residue thus obtained was triturated with petroleum ether (b.p. 40–60°) and allowed to cool. The product was filtered and crystallized from benzene. (*cf.* Table I).

B. *General procedure for the reaction of ω-benzamidoacetophenone derivatives* (III) *with aryl- or alkylmagnesium halides.* To an ethereal solution of the aryl- or alkylmagnesium halide (2 moles) was added a solution of the ω-benzamidoacetophenone derivative (III) (1 mole) in dry benzene. The reaction mixture was refluxed for 2 hr. and left overnight. It was hydrolyzed with a saturated ammonium chloride solution, dried over anhydrous sodium sulfate, and evaporated on a water bath nearly to dryness. The oily residue thus obtained was triturated with petroleum ether (b.p. 40–60°) and allowed to cool. The product was filtered and crystallized from benzene. (*cf.* Table I).

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(4) The infrared spectra were carried out by potassium bromide wafer technique using a Perkin-Elmer Infracord Model 137.

(5) Microanalysis were carried out by Alfred Bernhardt im Max-Planck Institut Mülheim (Ruhr), Germany. The melting points are not corrected.

(6) *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 778.

Potential Anticancer Agents: Some New *O*-Alkyl and *O*-Aryl *N,N'*-Diethylene Phosphorodiamidothionates

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N,N',N''-Triethylenephosphorotriamidothionate (TSPA) or Thio-TEPA, considered a standard anticancer alkylating agent[1] and preferred to its less stable oxygen analog, *N,N',N''*-triethylenephosphorotriamide (TEPA) has been shown to be of value in treating a wide variety of human neoplastic conditions including some solid tumors.[1,2]

In view of this activity we undertook the synthesis of some *O*-alkyl and *O*-aryl *N,N'*-diethylene phosphorodiamidothionates. By substituting an *O*-alkyl or an *O*-aryl group for one of the ethylenimine groups of Thio-TEPA we retained its polyfunctional alkylating properties, anticipating that the new structure would demonstrate improved anticancer activity and reduced toxicity.

The compounds which have been synthesized are now being screened[3] in mice for anticancer activity by the three tumor system, namely, sarcoma-180, adenocarcinoma-755 and leukemia-1210. Some of these compounds have also been tested in the Dunning rat leukemia system. Eleven of the compounds tested in the above systems showed activity in at least one tumor system.

The series of diethylenimine derivatives of monosubstituted *O*-alkyl or *O*-aryl phosphorodichloridothionates prepared in our laboratory are listed in Table I in which some of their physical properties and yields are given and synthetic procedures indicated. Water was used as the reaction medium in the esterification of the phosphorodichloridothionates while in some cases, a water-acetone solution was used. Good yields of relatively pure products were thus obtained. The use of an organic solvent afforded somewhat lower yields and a less pure product due to some polymerization, but cases in which the intermediate phosphorodichloridothionates are sensitive to water, the organic solvent was preferred. When substituted ethylenimines such as 2,2-dimethylethylenimine were used, an organic solvent was also preferred, for it was found that the reaction did not go to completion in water. In general, these compounds are very sensitive to heat and in order to avoid decomposition during distillation, high vacuum and low temperatures have been applied by use of a molecular still. The same synthetic procedures were used in preparing two *O,O'*-dialkyl *N*-ethylene phosphoroamidothionates (I, II) and *N,N'*-diethylenebenzene thiophosphonamide (XVI). No effort was made to obtain maximum yields (Table I).

EXPERIMENTAL

The intermediate *O*-alkyl and *O*-arylphosphorodichloridothionates were prepared by treating thiophosphoryl chloride with the corresponding alkanols or phenols. *O*-Ethyl and *O*-*n*-propyl phosphorodichloridothionates were prepared by modifying the directions given by Pishchimuka[4] in that the reaction mixtures were heated under slight vacuum. The *O*-*n*-butyl and *O*-isoamyl phosphorodichloridothionates were prepared by the procedure given by Manske.[5] A molar excess of the alcohols was heated under reflux with thiophosphoryl chloride in benzene solution.

(1) *Chem. & Eng. News*, special report, Oct. 12, 1959, 53–71.

(2) Ross, R. B., *J. Chem. Ed.*, **36**, No. 8, 368–377 (1959).

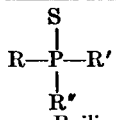
(3) Screening is being carried out by Cancer Chemotherapy National Service Center NIH, Department of Health, Education and Welfare.

(4) P. S. Pishchimuka, *Ber.*, **41**, 3854–3857 (1908); *J. Russ. Phys. Chem. Soc.*, **44**, 1406–1554 (1912).

(5) R. H. F. Manske, R. W. Beattie, and M. Kulka, U. S. Patent **2,575,224**.

TABLE I

O-ALKYL- AND *O*-ARYL-*N*,*N*'-DIETHYLENE PHOSPHORODIAMIDOTHIONATES



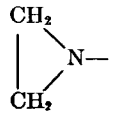
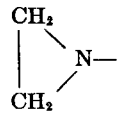
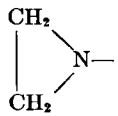
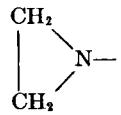
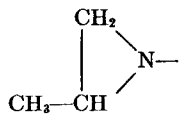
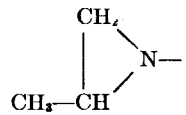
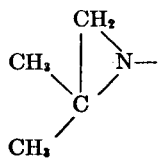
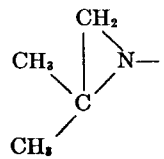
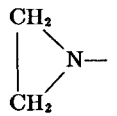
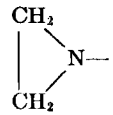
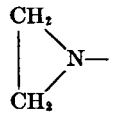
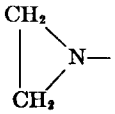
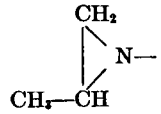
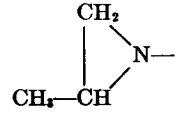
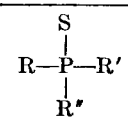
No.	R	R'	R''	Boiling Range/ Mm.[a]	Procedure	Yield, %	$n^{20}D$	d^{20}_4	Nitrogen, % Calcd.	Nitrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
I	CH_3O—	CH_3O—		50°/1.0	A	95.0[b]	1.4963	1.213	8.38	8.47	18.53	18.59
II	C_2H_5O—	C_2H_5O—		55°/1.0	A	89.1[b]	1.4841	1.119	7.17	7.43	15.86	15.83
III	C_2H_5O—			—	A	—	1.5203	1.166	14.55	14.05	16.09	16.12
IV	C_2H_5O—			40°/0.07	A	78.5	1.5000	1.087	12.72	12.16	14.06	13.92
V	C_2H_5O—			63°/0.175	B	58.3	1.4983	1.064	11.28	10.75	12.47	12.64
VI	Cl—CH_2—CH_2—O—			110°/0.03	B	60.0	1.5407	1.292	12.36	12.76	13.67	13.90
VII	*n*-C_3H_7O—			65°/0.05	A	87.1[b]	1.5139	1.135	13.58	13.56	15.02	14.76
VIII	*n*-C_3H_7O—			70°/0.035	A	87.0[b]	1.4981	1.076	11.96	11.57	13.22	13.24

TABLE I (*Continued*)



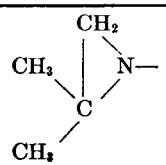
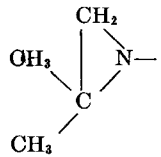
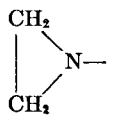
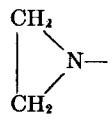
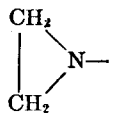
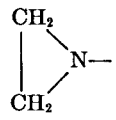
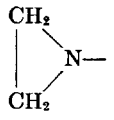
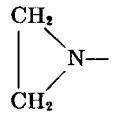
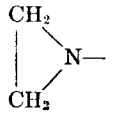
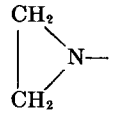
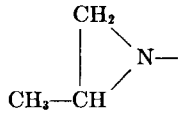
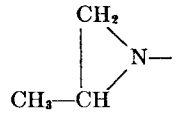
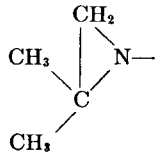
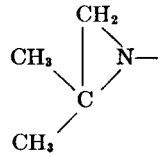
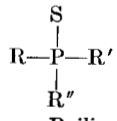
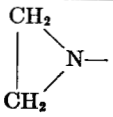
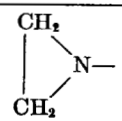
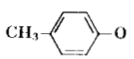
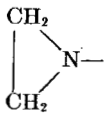
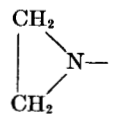
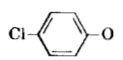
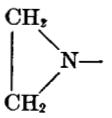
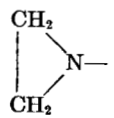
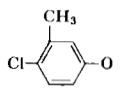
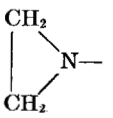
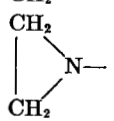
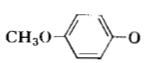
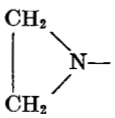
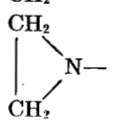
No.	R	R′	R″	Boiling Range/ Mm.[a]	Procedure	Yield, %	n_D^{20}	d_4^{20}	Nitrogen, % Calcd.	Nitrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
IX	*n*-C_3H_7O—			78°/0.050	B	65.0	1.4940	1.042	10.68	10.45	11.81	12.91
X	*n*-C_4H_9O—			83°/0.018	A	75.5	1.5101	1.111	12.72	12.29	14.06	13.56
XI	$(CH_3)_2CH—CH_2—CH_2—O$—			73°/0.045	A	75.7	1.5055	1.086	11.96	11.70	13.20	—
XII	*n*-$C_{10}H_{11}O$—			130°/0.050	D	55.5	1.4940	1.012	9.20	8.86	10.17	10.07
XIII	C_6H_5O—			85°/0.008	A	81.3[b]	1.5801	1.235	11.65	11.79	12.87	12.87
XIV	C_6H_5O—			63°/0.013	A	81.1[b]	1.5560	1.162	10.44	10.46	11.54	11.63
XV	C_6H_5O—			M.p. 64.0°	C	59.5	—	—	9.45	9.52	10.45	10.29

TABLE I (*Continued*)



No.	R	R′	R″	Boiling Range/ Mm.[a]	Procedure	Yield, %	$n^{20}D$	d^{20}_4	Nitrogen, % Calcd.	Nitrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
XVI	C_6H_5—			M.p. 103°	C	86.1	—	—	12.49	12.35	13.81	13.52
XVII				100°/0.020	A	94.6[b]	1.5769	1.213	11.02	10.87	12.18	11.75
XVIII				145°/0.020	B	95.0[b]	1.5857	1.312	10.20	10.85	11.28	11.18
XIX				130°/0.020	B	66.7	1.5819	1.286	9.70	10.41	10.73	10.74
XX				150°/0.023	B	95.9[b]	1.5771	1.249	10.37	10.82	11.46	11.53

[a] Distillation was done in "ASCO-50 Molecular Still." [b] Crude yield (before distillation).

O-(Chloroethyl) phosphorodichloridothionate was prepared from thiophosphoryl chloride and chloroethanol in the presence of triethylamine. The *O*-phenyl and *O*-*p*-cresyl derivatives were prepared according to the procedures given by Autenrieth.[6] A solution of the phenols in aqueous sodium hydroxide was added dropwise to the cold thiophosphoryl chloride. The *p*-chlorophenol, *p*-methoxyphenol, and 4-chloro-3-methylphenol intermediates were prepared by the method according to Tolkmith[7] in which a pyrdine solution of the phenols was added to an excess of thiophosphoryl chloride in benzene. *O,O'*-Dimethyl and *O,O'*-diethyl phosphorochloridothionates were obtained from Victor Chemical Works and Monsanto Chemical Co., respectively, and benzene thiophosphonic dichloride was obtained from Eastman Kodak. All the intermediates were purified by fractional vacuum distillation.

Preparation of O-alkyl and O-aryl N,N'-diethylene phosphorodiamidothionates. Procedure A. A solution of 95.3 g. (0.88 mole) of sodium carbonate and 19.0 g. (0.44 mole) of ethylenimine dissolved in 700 ml. of water was cooled to 5°. To this solution was added dropwise 35.8 g. (0.2 mole) of *O*-ethyl phosphorodichloridothionate under rapid stirring while the temperature was maintained at 5°. After the addition was completed, stirring was continued for 1 hr. at this temperature. The organic layer was separated and dried over anhydrous magnesium sulfate. The water layer was extracted with benzene, the extract dried, and the solvent removed by distillation under vacuum at low temperatures. The dried organic layer and the solvent-free extraction residue were combined and distilled under high vacuum to obtain the purified product, *O*-ethyl *N,N'*-diethylene phosphorodiamidothionate (III).

Procedure B. A solution of 78.2 g. (1.1 moles) of 2,2-dimethylethylenimine and 111.3 g. (1.1 moles) of triethylamine in 2500 ml. of benzene was cooled to between 5° to 10°. A second solution of 96.5 g. (0.5 mole) of *O*-propylphosphorodichloridothionate in 500 ml. of benzene was added dropwise to the first solution under stirring and kept at temperatures between 5°–10°. After the addition was completed, the mixture was stirred for one hour at room temperature. The precipitated triethylamine hydrochloride was removed by filtration under suction and the solvent removed from the filtrate by distilling at 30° under vacuum. The residue was then purified by distilling under high vacuum to give the product, *O*-propyl *N,N'*-bis(2,2-dimethylethylene) phosphorodiamidothionate (IX).

Procedure C. 1. *N,N'*-Diethylene benzenethiophosphonamide (XVI) was prepared as described in procedure B except the product is a crystalline material. On removal of the solvent, a solid separates which was recrystallized twice from toluene, and gave a melting point of 103°.

2. *O*-Phenyl *N,N'*-bis(2,2-dimethylethylene) phosphorodiamidothionate (XV) was distilled in the molecular still and the distillate was recrystallized from toluene–petroleum ether and gave a melting point of 64.0°.

Procedure D. Twenty-three grams (1.0 g.-atom) of sodium was dispersed in 1 l. of dry toluene by stirring and heating to reflux. Then 174.1 g. (1.1 moles) of decyl alcohol was added dropwise. Heating of the mixture was continued until all the sodium had reacted. This mixture was added portionwise at room temperature to a solution of 169.5 g. (1.0 mole) of thiophosphoryl chloride in 2.5 liters of benzene. After the addition was completed, the mixture was heated to reflux for 3 hr. Twenty milliliters of water was added when the mixture had been cooled to room temperature. After being stirred for five minutes, the slurry was filtered and the solution dried over anhydrous magnesium sulfate, and refiltered. The clarified filtrate was then added dropwise to a precooled solution at 5° of 103.5 g. (2.4 moles) of ethylenimine and 242.0 g. (2.4 moles) of triethylamine in 300 ml. of benzene. After the addition was completed, stirring was continued for another 2 hr. at room temperature. Triethylamine hydrochloride was removed by filtration, the filtrate washed with a 5% sodium carbonate solution, dried, and the benzene removed by distillation at 30° under vacuum. The residue was then purified by distillation under high vacuum to give the product, *O*-*n*-decyl *N,N'*-diethylene phosphorodiamidothionate (XII).

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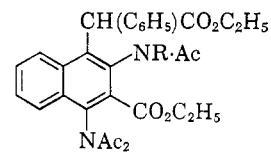
(6) W. Autenrieth and Mayer, *Ber.*, **58**, 840 (1925).
(7) H. Tolkmith, *J. Org. Chem.*, **23**, 1685–1690 (1958).

The Proton Magnetic Resonance Spectrum of Ethyl 1-Diacetylamino-3-acetamido-4-(α-ethoxycarbonylbenzyl)-2-naphthoate

J. E. BANFIELD

Received August 1, 1961

A compound obtained by the reductive acetylation of ethyl 3-amino-4-(α-ethoxycarbonylbenzylidine)-1,4-dihydro-1-imino-2-naphthoate was previously formulated[1] as either ethyl-1-diacetylamino-3-acetamido-4-(α-ethoxycarbonylbenzyl)-2-naphthoate (I. R = H) or ethyl 1,3-di(diacetylamino)-4-(α-ethoxycarbonylbenzyl)-2-naphthoate (I. R = Ac) with a preference, on infrared evidence. for the latter. Proton nuclear magnetic evidence (see Fig. 1), strongly favors the former structure and thus the ν(NH) band in the infrared must be weak or absent[2] for the compound.



I

In Fig. 1, the absorption of the phenyl substituent is seen at $\tau = 2.72$ p.p.m. as a sharp peak of intensity corresponding to five protons, the complex pattern at lower τ values arises from naphthalenic protons. This evidence clearly confirms the tricyclic nature of the precursor, ethyl 3-amino-4-(α - ethoxycarbonylbenzylidine) - 1,4 - dihydro-1-imino-2-naphthoate, as, had cyclization to a naphthalene not occurred, a phenyl peak of intensity corresponding to ten protons could be expected for compound I.

The integral curve (Fig. 1, inset) was consistent with a total of either 30 or 32 protons and thus did not distinguish between I. R = H and I. R = Ac; however the three acetyl peaks at τ = 7.64, 7.58, and 7.40 p.p.m. clearly prove the triacetyl formulation—*e.g.*, I. R = H, as they show absorption peaks of three "*N*-acetyl" CH_3 groups in different environments. This further indicates

(1) J. E. Banfield, *J. Chem. Soc.*, 2098 (1961).
(2) A. G. Cairns-Smith, *J. Chem. Soc.*, 184 (1961).