of concd. sulfuric acid (diluted after 3 hr. with 35 ml. of water) essentially as described above for IIb. After stirring at 135° for 16 hr., the reaction mixture was worked up to give, in several crops, 75.8 g. (86%) of V, m.p. 207–210° after recrystallization from ethanol and subsequent sublimation *in vacuo*.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.88; H, 6.62; N, 6.20.

2-(N,N-Dimethylamino)-2-phenylacetamide (IIIa). To a 100 ml. of stirred concd. sulfuric acid was added dropwise 80 g. (0.5 mole) of aminonitrile Ia. The resulting hot solution was stirred for 1 hr. (cooling gradually to room temperature) and then poured onto 400 g. of crushed ice. After stirring until solution was achieved, concentrated ammonium hydroxide was added with cooling until precipitation ceased. The solid was collected, washed with water, and dried at 80° *in vacuo*. The crude product (75 g.) was recrystallized from 1500 ml. of benzene (filtered hot) to give in several crops, 69.5 g. (78%) of IIIa, m.p. 152–154°.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.25; H, 8.03; N, 15.60.

2-(N,N-Dimethylamino)-2-(4-chlorophenyl)acetamide (IIIb). This aminoamide was prepared from aminonitrile Ib (added in small portions) essentially as described above for aminoamide IIIa. The product was obtained in 80% yield melting at 124–125.5° and at 128–129° after further recrystallization from benzene.

Anal. Calcd. for $C_{10}H_{13}N_2ClO$: C, 56.47; H, 6.16; N, 13.17; Cl, 16.67. Found: C, 56.34; H, 6.34; N, 12.98; Cl, 16.61.

2-(N,N-Dimethylamino)-2-(4-methoxyphenyl)acetamide (IIIc). Although only water-soluble tars were obtained when aminonitrile Ic was added to concentrated sulfuric acid without cooling, the aminoamide IIc was obtained in low yield when 38 g. (0.20 mole) of Ic was added slowly to 40 ml. of sulfuric acid at 25°. The solution was kept at this temperature for 3 hr., poured onto crushed ice and 44% of starting material Ic was recovered by ether extraction. After neutralization to *p*H 8 with concentrated ammonium hydroxide, filtration and recrystallization from benzene, 6.7 g. (16%) of IIIc, m.p. 164–167° was obtained. A small sample, sublimed *in vacuo*, melted at 166–167°.

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.75; N, 13.45. Found: C, 63.54; H, 7.59; N, 13.48.

A higher yield of aminoamide IIIc was obtained by heating a solution of 19 g. (0.1 mole) of Ic in 180 g. of polyphosphoric acid on the steam bath for 1.25 hr., and then pouring it onto crushed ice. The resulting mixture was heated until solution was achieved. After cooling, sodium carbonate was added until precipitation ceased. The solid was collected on a funnel, dried, and recrystallized by dissolving in chloroform and adding hexane to give, in two crops, 13 g. (60%) of IIIc, m.p. 164–166°. The melting point was not depressed on admixture with a sample of IIIc, prepared as described above.

2-Morpholino-2-phenylacetamide (VI). To 40 ml. of concd. sulfuric acid was added with stirring 40 g. (0.198 mole) of aminonitrile IV. The mixture was heated on the steam bath for a few seconds to achieve complete solution, and then poured onto crushed ice. Concentrated ammonium hydroxide was added to *p*H 8. After cooling, the solid was collected, washed with water, dried, and recrystallized from benzene give 33.3 g. (77%) of VI, m.p. 153–156.5° and at 155–156.5° after further recrystallization from benzene.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found:[15] C, 65.19; H, 7.17; N, 12.59.

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(15) Determined on a sample, m.p. 153–154°, obtained in a preliminary experiment by W. C. Chambers in this laboratory.

Potential Anticancer Agents. LXIV.[1] Alkylating Agents Related to Phenylalanine Mustard. V. A Cyclic Phosphorodiamidate Related to Cytoxan

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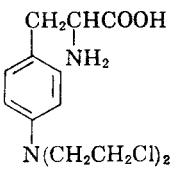
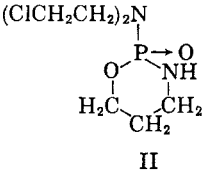
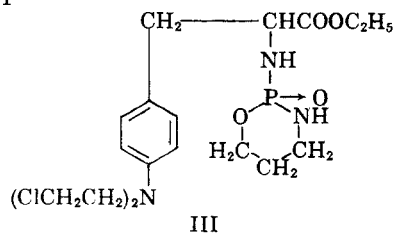
It has been reported that modification of *p*-phenylalanine mustard (I),[2,3] either the L-form[2] or the DL-form,[3] can lead to marked changes in the antitumor properties of the drug. These modifications include acylation of the α-amino group of I as well as the conversion of I to a variety of peptides. Another clinically important alkylating agent, cytoxan, (II),[4] was designed as an active



I



II



III

transport form of the nitrogen mustard moiety, with that alkylating group to be liberated selectively at the tumor site by the increased amounts of phosphamidase enzymes reported in tumor tissue.[5] A cyclic phosphorodiamidate of I (or of an

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(2) F. Bergel and J. A. Stock, *J. Chem. Soc.*, 3658 (1960).

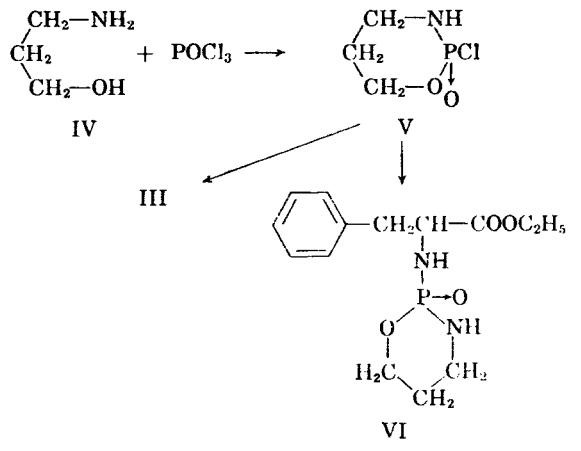
(3) See L. F. Larionov, *Cancer Research*, **21**, 99 (1961), for a review of this work with pertinent references.

(4) For a summary of data and references relating to Compound II, see Cancer Chemotherapy Reports, **1959**, No. 3, p. 21 (a publication of the Cancer Chemotherapy National Service Center).

(5) (a) See E. Boger and O. M. Friedman, *J. Am. Chem. Soc.*, **80**, 2583 (1958) for leading references. (b) O. M. Friedman and R. Chatterji, *J. Am. Chem. Soc.*, **81**, 3750 (1959)

ester of I[6]) might afford a compound that would be relatively less toxic to normal cells and have a better chemotherapeutic index than *p*-phenylalanine mustard (I), inasmuch as I should be released more selectively at the tumor site. The preparation of such a cyclic phosphorodiamidate, compound III, is the subject of this paper.

The reaction of 3-amino-1-propanol (IV) with phosphoryl chloride in dichloromethane containing triethylamine as an acid acceptor yielded the crude



phosphoramidochloridate (V). Short-path vacuum distillation afforded an analytical sample of V in only 5–10% yield. However, material of nearly equal purity was obtained in 48% yield by several treatments of the crude product with benzene to remove small amounts of contaminating salts.

In order to work out experimental conditions for the preparation of III, synthesis of the cyclic phosphorodiamidate (VI) of ethyl DL-phenylalanate was first explored. The use of crude V in methylene chloride containing triethylamine gave the crystalline phosphorodiamidate (VI) in 28% yield. When the procedure was applied to the ethyl ester hydrochloride of I using crude V, only 11% of the mustard phosphorodiamidate (III) could be isolated. The use of purified V, however, yielded 54% of III, isolated as a crystalline solid that was chromatographically homogeneous and analytically pure.

Biological evaluation of compound III is in progress.

EXPERIMENTAL[7]

2-Chloro-tetrahydro-2H-1,3,2-oxazaphosphorine P-oxide (V). A stirred solution of 2.8 g. (37 mmoles) of 3-amino-1-propanol (IV), 6.6 g. (74 mmoles) of triethylamine (dried over sodium hydroxide), and 50 ml. of dry dichloromethane, maintained at 5–10°, was treated dropwise with a solution of 5.1 g. (34 mmoles) of phosphoryl chloride in 25 ml. of dry dichloromethane. The mixture was stirred for 16 hr. at room temperature with exclusion of moisture, then was filtered to remove the precipitated triethylamine hydrochloride. The filtrate was evaporated *in vacuo* (bath 40°) and the residual sirup treated with 20 ml. of dry dichloromethane. The mixture was filtered and the filtrate evaporated *in vacuo*, affording 4.5 g. (89%) of a sirup which slowly crystallized on standing. Further purification was effected by stirring the crude product with two 20-ml. portions of dry benzene, the solution from each benzene treatment being filtered and the filtrate evaporated *in vacuo*. The purified product (2.4 g., 48%) crystallized on standing in a desiccator overnight. Near-identity of the infrared spectrum of this material with that of the analytical sample (see below) indicated the presence of only a few percent of unremoved amine salts. The product was very sensitive to atmospheric moisture and could not be recrystallized conveniently.

The analytical sample was prepared from the crude product in 5% yield by short-path distillation in a sublimation apparatus at 85–90° (0.015 mm.). A large distillation residue remained. The distillate slowly crystallized on the cold finger, yielding the analytically pure solid, m.p. 80–83°; $\lambda_{max(\mu)}^{Nujol}$ 3.09, 6.75 (NH), 7.85 (P=O), 9.14, 9.62 (P—O—C), 10.04 (P—N).

Anal. Calcd. for $C_3H_7ClNO_2P$: C, 23.2; H, 4.53; Cl, 22.8; N, 9.01. Found: C, 23.3; H, 5.18; Cl, 22.7; N, 8.92.

Ethyl 3-{p-[bis(2-chloroethyl)amino]phenyl}-N-(tetrahydro-2H-1,3,2-oxazaphosphorin-2-yl)-DL-alanate P-oxide (III). A suspension of 5.45 g. (14.8 mmoles) of ethyl 3-{*p*-[bis-(2-chloroethyl)amino]phenyl}-DL-alanate hydrochloride (m.p. 161–163°, prepared from I in 81% yield as described[8] for the L-isomer) in 48 ml. of dry dichloromethane was treated with 4.20 ml. (30 mmoles) of triethylamine (dried over sodium hydroxide) in order to prepare a solution of the ester. To the resulting mixture, stirred at room temperature, was added rapidly a solution of 2.40 g. (15.4 mmoles) of the purified chloride (V) in 24 ml. of dry dichloromethane. The solution was stirred for 16 hr. at room temperature with the exclusion of moisture, then was diluted with 40 ml. of dichloromethane and extracted in succession with water (two 20-ml. portions). 1*M* hydrochloric acid (40 ml.), water (20 ml.), saturated aqueous sodium bicarbonate (40 ml.), and water (two 20-ml. portions). The dichloromethane solution was dried over magnesium sulfate, stirred with Norit and filtered. The filtrate was evaporated *in vacuo*, affording 4.6 g. of a pale yellow sirup which, on rubbing under a layer of ether, formed a solid, m.p. 91–93°. The solid was dissolved in benzene and the solution was filtered. The filtrate evaporated *in vacuo* yielded, after treatment of the residual sirup with ether, 3.6 g. (54%) of solid, m.p. 95–97° whose chromatographic behavior and infrared spectrum were identical to those of the analytical sample. From another experiment an analytical sample was obtained by recrystallization from ethyl acetate-heptane and had a m.p. of 100–102°; $\lambda_{max(\mu)}^{Nujol}$ 3.0, 3.17, 6.59 (NH), 5.75 (ester C=O), 8.12, 8.24, 8.49 (P=O, C—O—C), 10.31 (P—N), 12.0, 12.39 (*p*-disubstituted benzene). The compound, detected by ultraviolet examination, was homogeneous on descending paper chromatography in benzene-methanol-water (2:6:1) with R_f 0.42 on Schleicher and Schuell acetylated paper (No. 2495) and R_f 0.83 on Whatman No. 1 paper.

Anal. Calcd. for $C_{18}H_{28}Cl_2N_3O_4P$: C, 47.8; H, 6.24; Cl, 15.7; N, 9.30. Found: C, 48.0; H, 5.91; Cl, 15.8; N, 9.13.

Ethyl 3-phenyl-N-(tetrahydro-2H-1,3,2-oxazaphosphorin-2-yl)-DL-alanate P-oxide (VI) was prepared from ethyl 3-phenyl-DL-alanate hydrochloride and crude monochloride (V) using the procedure for the synthesis of III (see above), giving a 28% yield of solid, m.p. 131–134°. Recrystallization from benzene afforded the analytical sample, m.p. 136.0–136.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.09, 3.19 (NH), 5.70 (ester C=O), 8.05, 8.29 (P=O), 9.25, 9.52, 9.70 (P—O, C—O—C), 10.29 (P—N), 13.05, 13.32, and 14.0 (monosubstituted benzene).

Anal. Calcd. for $C_{14}H_{21}O_4N_2P$: C, 53.8; H, 6.75; N, 8.97. Found: C, 53.9; H, 6.47; N, 8.93.

(6) Compound I and its simple esters have been reported to have very similar antitumor activity.[2]

(7) Boiling points and melting points are uncorrected. The latter were obtained with the Fisher-Johns apparatus.

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A Convenient Preparation of Arylmaleic Anhydrides

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Arylmaleic anhydrides are often desirable as components in Diels-Alder reactions, both for synthetic purposes and as a convenient means of studying the influence of aryl substituents of varying electronic requirements on the rate of formation and stereochemistry of the adducts.[1-3] A particular point of interest is the finding[4] that phenylmaleic anhydride can serve as diene as well as dienophile.

Studies of this sort have been limited only by the difficulty of preparation of some members of this class, especially those containing alkoxy substituents. The practical methods of synthesis appear to be the following:

(a) Dehydrogenation of arylsuccinic anhydrides by bromine[5] or *N*-bromosuccinimide.[6] This is probably the method of choice for the phenyl[6] and *p*-nitrophenyl[1b] compounds, but cannot be used on aryl rings containing activating substituents because of ring bromination.[7] The Experimental section describes an attempt to dehydrogenate 3,4-methylenedioxyphenylsuccinic anhydride by bromine and *N*-bromosuccinimide, both of which apparently brominated the aromatic ring, since the halogen could not be removed from the product by boiling with lutidine.

(b) The Meerwein addition of diazonium salts to maleic acid and its derivatives.[8] This reaction is applicable to a variety of aryl substituents, but gives only low to moderate yields.

(c) Addition of hydrogen cyanide to the formyl derivative of an ethyl arylacetate, followed by hydrolysis and dehydration, gives arylmaleic anhydrides in 15–30% over-all yields.[2,3,9] Attempts to apply this method, in the present study, to the formyl and oxalyl derivatives of 3,4-dimethoxyphenylacetonitrile were unsuccessful.

Other methods, such as the Reformatsky reaction on ethyl phenylglyoxylate and the condensation of ethyl glyoxylate with ethyl arylacetates have been used in specific cases,[10] but do not appear to be of general utility.

As arylsuccinic acids are easily available in high yield by the addition of cyanide to the condensation products of aromatic aldehydes with cyanoacetic acid and its derivatives,[11] the dehydrogenation of these compounds with reagents other than positive halogen seemed worth pursuing. The well known ability of selenium dioxide to introduce a double bond in conjugation with 1,4-diketones[12] prompted an investigation of its application to the present problem.

It has been found that selenium dioxide in boiling acetic anhydride rapidly dehydrogenates arylsuccinic acids in high yield. The use of acetic anhydride as solvent makes it possible to use the free succinic acids as starting materials. Phenyl (IIa), *p*-methoxyphenyl- (IIb), and 3,4-methylenedioxyphenylmaleic anhydrides (IIc) were prepared in this way in yields of 86, 80, and 66%, respectively, from readily available acids (I). The first two anhydrides had properties in agreement with those described in the literature, while the third was identified by hydrogenation to the known succinic anhydride. 3,4-Methylenedioxyphenylmaleic anhydride (IIc) readily added butadiene to form the adduct III.

(1) (a) L. E. Miller and D. J. Mann, *J. Am. Chem. Soc.*, **72**, 1484 (1950); (b) L. E. Miller and C. J. Strickler, *J. Am. Chem. Soc.*, **76**, 698 (1954); (c) K. Alder, F. Brochhagen, C. Kaiser, and W. Roth, *Ann.*, **593**, 1 (1955); (d) M. Mousseron, P. Winternitz, and G. Rouzier, *Compt. rend.*, **238**, 1661 (1954); (e) C. S. Rondestvedt, Jr., and A. H. Filbey, *J. Org. Chem.*, **19**, 548 (1954); (f) W. R. Vaughan and K. S. Anderson, *J. Org. Chem.*, **21**, 673 (1956).

(2) A. J. Lauck, Ph.D. thesis, Univ. of Illinois, 1956; *Diss. Abs.*, **17**, 240 (1957).

(3) H. Ruus, Ph.D. thesis, Univ. of Illinois, 1956; *Diss. Abs.*, **17**, 1223 (1957).

(4) L. E. Miller and D. J. Mann, *J. Am. Chem. Soc.*, **73**, 45 (1951).

(5) H. Alexander, *Ann.*, **258**, 67 (1890).

(6) L. E. Miller, H. B. Staley, and D. J. Mann, *J. Am. Chem. Soc.*, **71**, 374 (1949).

(7) C. J. Strickler, Ph.D. Thesis, Univ. of Illinois, 1952; E. D. Bergmann, R. Pappo, and D. Ginsburg, *J. Chem. Soc.*, 1369 (1950).

(8) (a) H. Meerwein, E. Buchner, and K. van Emster, *J. prakt. Chem.*, **152**, 237 (1939); (b) L. Denivelle and D. Razavi, *Compt. rend.*, **237**, 570 (1953); (c) E. C. Taylor, Jr., and E. J. Strojny, *J. Am. Chem. Soc.*, **76**, 1872 (1954); (d) C. S. Rondestvedt, Jr., and O. Vogl, *J. Am. Chem. Soc.*, **77**, 2313 (1955); (e) C. S. Rondestvedt, Jr., M. J. Kalm, and O. Vogl, *J. Am. Chem. Soc.*, **78**, 6115 (1956); (f) E. Simonitsch, H. Frei, and H. Schmid, *Monatsh. Chem.*, **88**, 541 (1957).

(9) D. W. Hein, *J. Am. Chem. Soc.*, **77**, 2797 (1955).

(10) C. S. Rondestvedt, Jr., and A. H. Filbey, *J. Org. Chem.*, **19**, 119 (1954).

(11) (a) A. Higson and J. F. Thorpe, *J. Chem. Soc.*, **89**, 1455 (1906); (b) A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121**, 1699 (1922); (c) W. Baker and A. Lapworth, *J. Chem. Soc.*, **127**, 560 (1925); (d) J. Bredt and J. Kallen, *Ann.*, **293**, 338 (1896); (e) R. H. Siddiqui and Salah-ud-din, *J. Ind. Chem. Soc.*, **18**, 635 (1941).

(12) S. Austin, A. C. C. Newman, and H. L. Riley, *J. Chem. Soc.*, **136**, 391 (1933); K. F. Armstrong and R. Robinson, *J. Chem. Soc.*, **137**, 1650 (1934); C. S. Barnes and D. H. R. Barton, *J. Chem. Soc.*, 1419 (1953); J. C. Banerji, D. H. R. Barton, and R. C. Cookson, *J. Chem. Soc.*, 5041 (1957).