Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.12; H, 7.19; N, 10.00. Found: C, 77.16; H, 7.28; N, 10.05.

Hydrolysis of 7 g. of this compound was effected by heating it in 50 ml. of 6*N* hydrochloric acid on the steam bath for 8 hr. The cooled mixture was filtered, and the solid was recrystallized from methanol-water to give 5.1 g. (90%) of 4-methoxy-α-phenylacetophenone (III. $X = OCH_3$, $Y = H$), m.p. 75–76.5° (lit. m.p. 76°,[5a] and 77–78°).[10]

(*C*) $X = H$, $Y = Cl$. Aminonitrile I ($X = H$)[2] was alkylated on the 0.2-mole scale with *p*-chlorobenzyl chloride essentially by the procedure described in (*A*). The liquid ammonia was evaporated from the reaction product and the residue taken up in ether. After filtering to remove inorganic salts, the ether solution was dried over magnesium sulfate. The solvent was removed to leave 57 g. (100%) of the crude alkylation product as a light yellow oil. A sample of this oil was dissolved in hexane and the solution cooled in a Dry Ice–acetone bath to precipitate a solid, but the pure product was not isolated. The combined oil was dissolved in 105 ml. of concd. hydrochloric acid and the solution refluxed overnight. The mixture was cooled and filtered to give 41.3 g. (90%) of α-(4-chlorophenyl)acetophenone (III. $X = H$, $Y = Cl$), m.p. 133–136° and at 135.5–136° after recrystallization from ethanol (lit. m.p. 133°).[5b,11]

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Some α-Dialkylaminophenylacetonitriles and Corresponding Amino Acids and Aminoamides[1]

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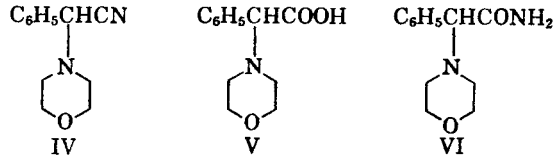
Recently[2] α-dimethylaminophenylacetonitrile (Ia) was prepared from benzaldehyde, dimethylamine, and sodium cyanide through the sodium bisulfite addition compound of the aldehyde, and hydrolyzed to amino acid IIa.

p-XC_6H_4CHCN	p-$XC_6H_4CHCOOH$	p-$XC_6H_4CHCONH_2$
$N(CH_3)_2$	$N(CH_3)_2$	$N(CH_3)_2$
Ia. $X = H$	IIa. $X = H$	IIIa. $X = H$
Ib. $X = Cl$	IIb. $X = Cl$	IIIb. $X = Cl$
Ic. $X = OCH_3$		IIIc. $X = OCH_3$

We have synthesized aminonitriles Ib and Ic, hydrolyzed Ib to amino acid IIb, and converted all three of the aminonitriles Ia–c to the corresponding aminoamides IIIa–c. Also aminonitrile IV was prepared from the appropriate reagents and converted to amino acid V and aminoamide VI. The yields were good to excellent.



IV V VI

In the synthesis of the aminonitriles 25% aqueous dimethylamine was used instead of the anhydrous amine employed earlier.[2] The initial formation of the aldehyde-bisulfite compound seems advantageous especially for solid aldehydes. Even with benzaldehyde the yield of Ia was higher (94%) than that (75%) obtained without the use of the bisulfite.[3]

Whereas ordinary nitriles can be hydrolyzed to the corresponding acids with dilute sulfuric acid, aminonitrile Ia undergoes some reversion to benzaldehyde (27%) even with 50% refluxing sulfuric acid. The conversion of Ia, Ib, and IV to the corresponding amino acids was accomplished by treatment with more concentrated sulfuric acid. However, aminonitrile Ic produced only water-soluble tars; apparently sulfonation and/or cleavage of the ether group occurred. This method appears more convenient than that employed earlier for amino acid IIa, which was obtained from phenylacetic acid through the α-bromo acid bromide.[4]

The intermediate aminoamides were prepared with concentrated sulfuric acid under milder conditions. As these compounds are relatively insoluble, they were readily isolated free from any amino acid that might have been formed. Aminoamide IIIc was obtained in better yield with polyphosphoric acid, which is specific for amide formation.[5]

In Table I are listed some infrared bands. The amino acids IIa, IIb, and V exhibited absorption bands for bonded O—H at 3.5–4.1 μ, and C=O at 6.1–6.3 μ.[6] The aminoamides IIIa–c and VI exhibited characteristic bands for N—H at 3.0–3.1 μ and C=O at 5.9–6.0 μ.[7] However, the aminonitriles Ia–c and IV exhibited only a very weak band or no absorption band for the nitrile group. Ia gave a very faint peak at 4.51 μ[8] which was insufficient for characterization.

Attempts to alkylate amino acid IIa and aminoamide IIIa through their dianions IIa′ and IIIa′ as described for the alkylations of phenylacetic

(1) Supported by the National Institutes of Health Grant CY-4455(C2).

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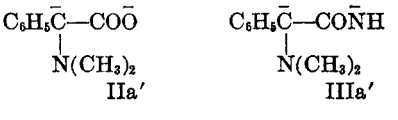
TABLE I

INFRARED BANDS (μ) FOR AMINONITRILES, AMINOACIDS, AND AMINOAMIDES[a]

Ia[b]	Ib[c]	Ic[c]	IV[c]	IIa[c]	IIb[d]	V[d]	IIIa[d]	IIIb[d]	IIIc[c]	VI[d]
3.4–3.6[e]	3.4–3.6[e]	3.4–3.6[e]	3.45–3.55	3.35	3.5–3.8	3.5–3.7	3.0	3.05	3.1	3.1
4.51[f]	12.55	12.35	13.55	3.7–4.1	6.1	6.0	5.9	5.95	6.0	5.9
13.66	13.8	12.8	14.2	6.2–6.35	12.9	13.5	13.0	12.15	12.0	13.0
14.36				13.5	13.9	14.3	13.85–	13.8	13.6	13.85–
				14.0–14.3[e]			14.15[e]			14.15[e]

[a] All spectra were taken on a Perkin-Elmer Infracord. [b] Smear between salt plates. [c] Potassium bromide wafer. [d] Nujol mull. [e] Very broad band which may contain two or three bands. [f] Very weak band.



IIa′ IIIa′

acid[9] and phenylacetamide[10] were unsatisfactory. Addition of the amino acid or aminoamide to two molecular equivalents of potassium amide in liquid ammonia followed by one equivalent of benzyl chloride appeared to produce alkylation product but the pure compound was not isolated. Although most of the amino acid or aminoamide may have been converted to its dianion, sufficient amide ion evidently remained in equilibrium to effect the self-alkylation of the halide, as the purple color associated with this reaction was observed and stilbene was obtained.[11]

Similarly attempts to alkylate the amino acid and aminoamide with *n*-butyl bromide were unsuccessful, and the starting acid and amide were recovered. These results indicate that the α-hydrogens of the amino acid and aminoamide are less active than those of phenylacetic acid and phenylacetamide respectively.

EXPERIMENTAL[12]

α-Dimethylaminophenylacetonitrile (Ia). To a stirred slurry of 416 g. (4.0 mole) of sodium bisulfite in 600 ml. of water was added 424 g. (4.0 mole) of benzaldehyde followed, after 15 min., by 800 g. (4.44 mole) of 25% aqueous dimethylamine.[13] After stirring for 30 min., the mixture was cooled (ice bath) and a solution of 200 g. (4.1 mole) of sodium cyanide in 400 ml. of water was added dropwise. The ice-bath was removed and the stirring continued for 3 hr. The organic layer was separated and combined with three ether extracts of the aqueous layer. The ether solution was dried over anhydrous magnesium sulfate and the solvent removed. The residue was distilled to give 598 g. (94%) of Ia, b.p. 76–78° at 0.8 mm., n_D^{25} 1.5116 reported b.p. 78–79° at 1.1 mm., n_D^{25} 1.5120.[2]

2-(N,N-Dimethylamino)-2-(4-chlorophenyl)acetonitrile (Ib). This aminonitrile was prepared from 0.71 mole each of *p*-chlorobenzaldehyde, sodium bisulfite (in 150 ml. of water), dimethylamine (128 g. of 25% aqueous amine), and sodium cyanide (in 100 ml. of water) essentially as described for Ia above. After the 3-hr. reaction period, the mixture was filtered, the precipitate washed with water and dried *in vacuo*. Recrystallization from absolute ethanol yielded 114 g. (84%) of Ib, m.p. 40–43° and at 43.5–44.5° after two recrystallizations from hexane.

Anal. Calcd. for $C_{10}H_{11}N_2Cl$: C, 61.69; H, 5.70; N, 14.39; Cl, 18.21. Found: C, 61.91; H, 5.54; N, 14.24; Cl, 18.23.

2-(N,N-Dimethylamino)-2-(4-methoxyphenyl)acetonitrile (Ic). This aminonitrile was prepared from 1 mole of anisaldehyde and the appropriate reactants essentially as described above for Ia. There was obtained 105 g. (55%) of Ic, b.p. 107–109° at 0.8 mm., n_D^{25} 1.5210, which crystallized on standing, m.p. 32–35°. After two recrystallizations from hexane, the compound melted at 36.5–38°.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.23; H, 7.14; N, 14.48.

2-Morpholino-2-phenylacetonitrile (IV). This aminonitrile was prepared from one mole each of benzaldehyde, sodium bisulfite, morpholine, and sodium cyanide as indicated above for Ib. After standing overnight, the reaction mixture was worked up to give in two crops from absolute ethanol, 172 g. (85%) of IV, m.p. 68–70°, reported m.p. 68–70°.[3]

2-(N,N-Dimethylamino)-2-(4-chlorophenyl)acetic acid (IIb). This amino acid was prepared by a modification of the earlier procedure for IIa.[2,14] A solution of 39 g. (0.20 mole) of aminonitrile Ib in 40 ml. of concd. sulfuric acid was stirred for 3 hr., and 15 ml. of water was then added to reduce the acid concentration to about 70%. After stirring at 150° for 18 hr., the solution was cooled and poured onto crushed ice. Concentrated ammonium hydroxide was added to *p*H 8. After decolorizing (Norite) and filtering, the solution was acidified with hydrochloric acid to *p*H 6, and cooled. The resulting mixture was filtered, and the filtrate partially evaporated, and the resulting precipitate combined with the solid on the funnel. The product was dissolved in a minimum of hot water, and the solution cooled to give 38 g. (89%) of IIb, m.p. 232–235° and at 232–235° after another recrystallization from water and drying *in vacuo*.

Anal. Calcd. for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 55.83; H, 5.83; N, 6.68; Cl, 16.36.

2-Morpholino-2-phenylacetic acid (V). This amino acid was prepared from 81 g. (0.4 mole) of aminonitrile IV and 80 ml.

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(12) Melting points and boiling points are uncorrected. Analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Spang Microanalytical Laboratory, Ann Arbor, Mich.

(13) This reagent has recently afforded an 88% yield of Ia but the details were not given; H. M. Taylor and C. R. Hauser, *J. Am. Chem. Soc.*, **82**, 1960 (1960).

(14) The melting point of 246–247° for IIa recrystallized from ethanol-water (ref. 2) has now been raised by recrystallization from ethanol-acetone to 260–261°, which agrees with that of IIa prepared in another manner (ref. 4).

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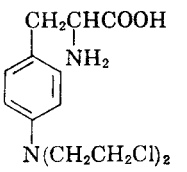
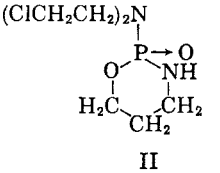
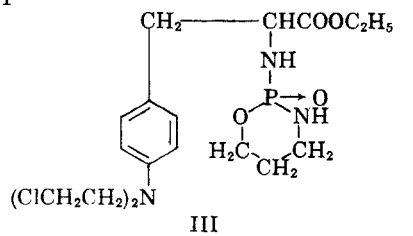
It has been reported that modification of *p*-phenylalanine mustard (I),[2,3] either the L-form[2] or the DL-form,[3] can lead to marked changes in the antitumor properties of the drug. These modifications include acylation of the α-amino group of I as well as the conversion of I to a variety of peptides.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

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, see A. P. Martinez, W. W. Lee, and B. R. Baker, *J. Org. Chem.*, **26**, 4501 (1961). For the fourth paper on phenylalanine mustard, see A. P. Martinez, W. A. Skinner, W. W. Lee, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 860 (1961).

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(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)