onstrated that amino acid coupling can have a marked effect upon the growth-regulating properties of a compound. Such properties are also modified by combination with inexpensive protein hydrolyzates prepared from animal and vegetable sources.[9]

A previous report on the synthesis of 28 amino acid derivatives of 2,4-D appeared in 1952;[10] this note extends the 2,4-D series to 48 amino acid derivatives. The 20 new derivatives were prepared to elucidate further the mode of action and specificity of aryloxyalkylcarboxylic acids as plant growth regulators, as well as to investigate further the use of amino acids as bioactive formulating agents. Many of the compounds from the various series have been submitted to various cooperating agencies for evaluation as plant growth regulators, herbicides, fungicides, anticancer agents, insect repellents, and nematocides. One report[2] on herbicidal evaluation describes *N*-(2,4-dichlorophenoxyacetyl)-D-asparagine as effective in killing pigweed, mustard, and broadleaf weeds without effect on corn and gladiolus in postemergence sprays at $^1/_2$ to 1 pound per acre application rates. Details on the specific biological properties of these compounds will be reported elsewhere.

EXPERIMENTAL

The compounds listed in Table I were prepared by Schotten-Baumann techniques in accordance with descriptions outlined in previous publications. No special directives are necessary here in view of earlier descriptions and the absence of any particular preparative difficulties.

Some of the D-amino acids used in this work were obtained through the courtesy of the late Dr. Jesse P. Greenstein of the National Institutes of Health, Bethesda, Md.; others, and the 2,4-D used, were purchased from commercial sources and utilized without further purification. The 2,4-D was converted to its acyl chloride by the method of Freed[11] and also described by us.[10]

In general the yields of reaction products were fairly high but appreciably losses were taken in the purification processes because it was essential that traces of free acid be removed from the derivatives and that optical purity be obtained. The optical values received were essentially equal and opposite for the D- and L-isomeric compounds. The special variations used in the purification techniques are indicated in the footnotes of Table I.

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The Structure of the Addition Product from Hydrogen Cyanide and a 2-Vinyldihydro-1,3-oxazine

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A recent article[1] described the preparation of several 2-alkenyl-4,6,6-trimethyldihydro-1,3-oxazines from unsaturated nitriles and 2-methyl-2,4-pentanediol and the reaction of one of these dihydro-1,3-oxazines with hydrogen cyanide. The heterocyclic bases were prepared according to the general method first described by Tillmanns and Ritter[2] who condensed a series of nitriles with 2-methyl-2,4-pentanediol in cold 92% sulfuric acid.

Treatment of I with hydrogen cyanide in glacial acetic acid yielded an addition product which could possess structure II or III as a result of either 1,4- or 3,4- addition, respectively. On the basis of the infrared spectrum of the adduct, II was concluded to represent the true structure. This reaction has now been re-examined and III is claimed to be the correct structure of the adduct. This claim is based upon an alternate synthesis of III, alkaline hydrolysis of the addition product, and a revised interpretation of the infrared spectrum in the light of recent studies.[3]

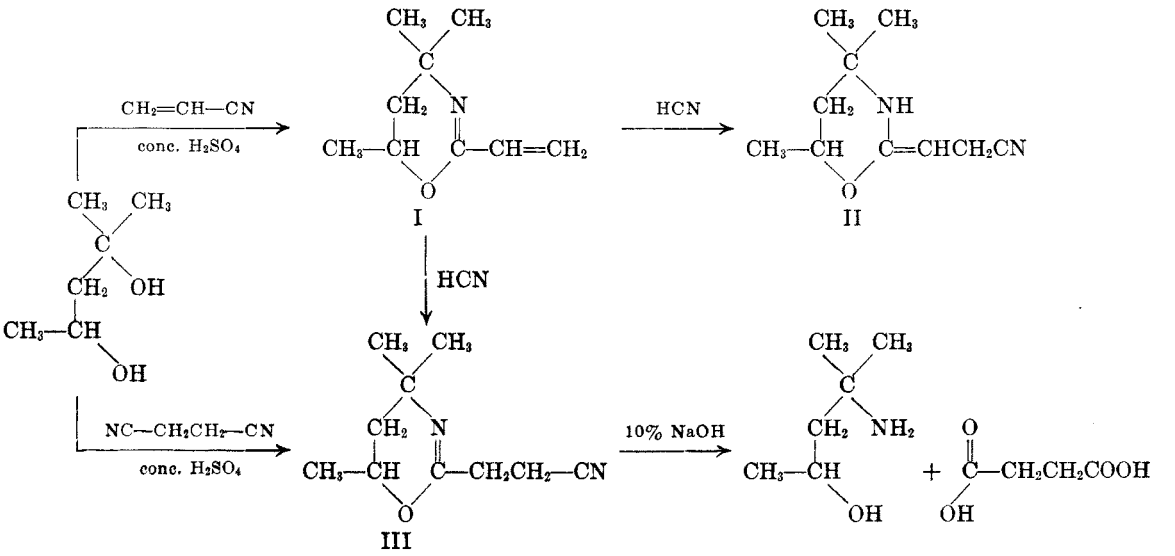
The alternate method of synthesis of the addition compound was accomplished by treating 2-methyl-2,4-pentanediol with succinonitrile in cold concentrated sulfuric acid. Comparison of this product with that obtained by treating I with hydrogen cyanide according to the method of Lynn[1] showed that both compounds were identical in every respect. This method of obtaining III is one which is currently under investigation in our laboratory for the preparation of a wide variety of *N*-heterocycles of the type, IV. It has been found possible, however, to limit the reaction of the dinitriles to only one of the nitrile groups, thus enabling the facile preparation of III. Other *N*-heterocycles such as 1-pyrrolines, 2-thiazolines, and dihydropyridines have already been reported.[4] Extension

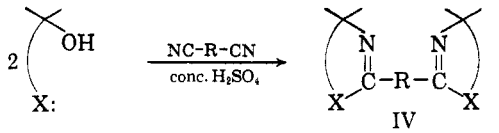
(1) J. W. Lynn, *J. Org. Chem.*, **24**, 711 (1959).

(2) E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).

(3) A. I. Meyers, *J. Org. Chem.*, **24**, 1233 (1959).

(4) A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1918 (1958).





X = S, O, N; R = alkylene, arylene

of this ring closure reaction to dihydro-1,3-thiazines, dihydro-1,3-oxazines, and benzothiazines will be reported in the near future.

Additional proof in support of III was obtained by refluxing the hydrogen cyanide addition compound with 10% aqueous sodium hydroxide[5] for 24 hr. and isolating 4-methyl-4-amino-2-pentanol and succinic acid in quantitative yield. This mode of hydrolysis strongly supports the presence of the C=N link rather than the exocyclic C=C link in the molecule.

With regard to the infrared spectrum of the hydrogen cyanide addition compound, examination of the 6μ region reveals a single intense band at 6.00μ which had originally been assigned[1] to the stretching frequency of the C=C link. This intense band (not at all typical of the cyclic unconjugated C=C link) has recently been the subject of a study[3] on the spectral position of the C=N link in nitrogen heterocycles. It has been found, as a result of this study, that unconjugated 1-pyrrolines, 2-thiazolines, and more recently dihydro-1,3-thiazines[6] containing a 2-alkyl substituent exhibit a sharp intense band in the 6.00–6.10μ region. Two additional dihydro-1,3-oxazines containing a 2-alkyl substituent were prepared and their absorption in the 6μ region were compared (Table I). The moderately strong band in the 6.88–6.92μ region is due to —CH_2— deformation frequencies.[7] Examination of the 3μ region showed a weak band at 3.00μ which did not reappear when the oxazines were dried in benzene over potassium hydroxide pellets. Thus, it was concluded that a trace of water was responsible for the absorption in the 3μ region and not the presence of the N—H link. Furthermore, the structure of the 2-methyldihydro-1,3-oxazine, whose spectrum was used as a comparison, is well known.[5]

TABLE I

ABSORPTION OF 2-ALKYL-4,6,6-TRIMETHYLDIHYDRO-1,3-OXAZINES IN THE 6μ REGION

2-Alkyl Substituent	Absorption in 6μ Region (%T)
$-CH_3$	6.00 (4.0); 6.90 (39.4)
$-CH_2CH_3$	6.01 (4.0); 6.88 (42.6)
$-CH_2CH_2CN$	6.00 (3.5); 6.92 (27.0)

An additional study on the infrared spectra of *N*-heterocycles containing the C=N link is presently in progress and a communication in this respect is forthcoming.

EXPERIMENTAL[8,9]

The infrared spectra were performed in a Perkin-Elmer Model 21 recording spectrophotometer employing a sodium chloride prism. The samples were studied in a 5–6% carbon tetrachloride solution utilizing a cell with 0.48 mm. spacing.

2-(2-Cyanoethyl)-4,6,6-trimethyldihydro-1,3-oxazine (III). (a). Prepared by the addition of hydrogen cyanide in glacial acetic acid to 2-vinyl-4,6,6-trimethyldihydro-1,3-oxazine according to the method of Lynn.[1]

(b). To 40 g. (0.50 mol.) of succinonitrile in 100 ml. of concentrated sulfuric acid previously cooled to 3° in an ice bath was added with stirring 39.6 g. (0.25 mol.) of 2-methyl-2,4-pentanediol during a 3-hr. period. The temperature during the addition was maintained between 7–10°. The orange mixture was stirred for an additional hour at 3–5° and then poured over 300 g. of chipped ice. The aqueous

(5) M. E. Smith and H. Adkins, *J. Am. Chem. Soc.*, 60, 407 (1938).

(6) A. I. Meyers, unpublished observation.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1958, p. 20.

(8) All melting points and boiling points are uncorrected.

(9) Microanalyses were performed by Dr. Alfred Bernhardt, Mulheim (Ruhr), West Germany.

acid solution was extracted with three 75-ml. portions of chloroform and then cautiously neutralized by the addition of a sufficient amount of 35% sodium hydroxide solution. The red oil that appeared was taken up in ethyl ether and the alkaline solution further extracted with three 75-ml. portions of ether. The ethereal extracts were combined and dried over potassium carbonate. After the ether was removed at atmospheric pressure, the residual oil was distilled *in vacuo*. There was obtained 17.8 g. (40%) of a colorless oil b.p. 104–106°/3.5 mm., n_D^{30} = 1.4544 (lit.[1] b.p. 87°/1.3 mm.; n_D^{30} = 1.4542). Picrate (from ethanol) m.p. 282° dec.

Alkaline hydrolysis of III. Ten g. (0.055 mol.) of III were added to 100 ml. of 10% aqueous sodium hydroxide and refluxed for 24 hr. The colorless oil which was present was taken up in ether and the remaining aqueous layer was saturated with sodium chloride and extracted twice with an equal volume of ether. The ether extracts were combined and dried over anhydrous sodium carbonate. After removal of the ether, distillation of the residue yielded 6.3 g. of 4-amino-4-methyl-2-pentanol, b.p. 71–72°/12 mm., n_D^{20} = 1.4345 (lit.[5] b.p. 74–75°/15 mm., n_D^{20} = 1.4335).

Acidification of the alkaline aqueous solution yielded succinic acid, m.p. 272–274° dec. Admixture with an authentic sample of succinic acid showed no depression in the melting point.

2,4,4,6-Tetramethyldihydro-1,3-oxazine. This compound was prepared according to the method of Tillmanns and Ritter.[2] B.p. 58°/25 mm., n_D^{25} = 1.4355.

2-Ethyl-4,6,6-trimethyldihydro-1,3-oxazine. Prepared in the same manner as the 2-methyl derivative. B.p. 67°/20 mm., n_D^{25} = 1.4385.

Anal. Calcd. for $C_9H_{17}ON$: C, 69.67; H, 10.96. Found: C, 69.62; H, 10.91.

Acknowledgment. The author wishes to express his gratitude to the Research Corporation and the National Institutes of Health (DGMS-6248) for funds granted to support a study of which the present work is a part. Thanks are due to Mr. R. T. O'Connor and his staff at the Southern Regional Research Laboratory, United States Department of Agriculture, for determining the infrared spectra.

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Synthesis of 5-Alkyl-2-iminohexahydro-*s*-triazine-1-carbonitriles and 3,3′-Ethylenebis-(6-iminohexahydro-*s*-triazine-1-carbonitrile)

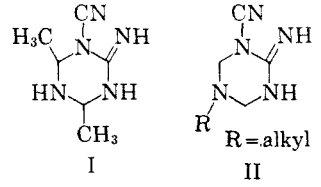
EDWARD H. SHEERS

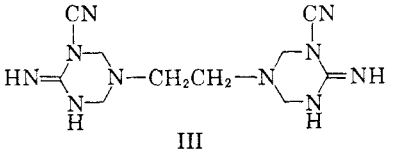
Received August 5, 1959

The condensation of primary alkylamines with one mol. of urea or thiourea and 2 mol. of formaldehyde to give 5-alkylhexahydro-*s*-triazinones and 5-alkylhexahydro-*s*-triazinethiones[1] suggested that cyanoguanidine might react in a similar fashion to form a cyclic derivative.

Pohl[2] showed that cyanoguanidine condenses with acetaldehyde-ammonia to give 2-imino-4,6-dimethylhexahydro-*s*-triazine-1-carbonitrile (I). This reaction has not been reported with any aldehyde-ammonia above C_2. This, together with the fact that the higher aliphatic aldehydes are not readily available, somewhat limits the scope of Pohl's reaction.

Cyanoguanidine reacted readily with one mol. of alkylamine and 2 mol. of formaldehyde to give high yields of 5-alkyl-2-iminohexahydro-*s*-triazine-1-carbonitriles (II), a new series of colorless, solid hexahydro-*s*-triazine derivatives. With 0.5 mol. of ethylenediamine and 1 mol. of formaldehyde cyanoguanidine yielded the expected 3,3′-ethylenebis(6-iminohexahydro-*s*-triazine-1-carbonitrile) (III). This condensation appears to be quite general in nature.





EXPERIMENTAL

The cyanoguanidine used was American Cyanamid Company's commercial grade (purity 99%+). All other compounds used were Eastman White Label grade. All melting points are uncorrected.

Typical procedure for 5-alkyl-2-iminohexahydro-s-triazine-1-carbonitriles: 5-Butyl-2-iminohexahydro-s-triazine-1-carbonitrile. To 400 ml. water, there were added 43 g. cyanoguanidine, 37 g. *n*-butylamine, and 81 ml. formalin while stirring vigorously. The temperature rose to 54°. Stirring was continued for 1 hr. after the addition was complete. A colorless oil deposited which crystallized on standing overnight. This product was collected by filtration and recrystallized from 95% ethanol. The yield was 80% of theory and consisted of colorless platelets having a melting point of 149–150°.

Anal. Calcd. for $C_8H_{15}N$: C, 53.01; H, 8.34; N, 38.64. Found: C, 52.89; H, 8.45; N, 38.80.

3,3′-Ethylenebis(6-iminohexahydro-s-triazine-1-carbonitrile). To a solution of 43 g. cyanoguanidine in 200 ml. water, there were added 20 g. ethylenediamine and 81 ml. formalin while stirring vigorously. The temperature rose to 72°. The hot, clear solution was stirred, and white crystals of the product, m.p. 225–226°, deposited within 1 hr. in 75% yield.

Anal. Calcd. for $C_{10}H_{16}N_8$: C, 48.37; H, 6.50; N, 45.13. Found: C, 48.54; H, 6.47; N, 45.11.

(1) Burke, W. J., *J. Am. Chem. Soc.*, **69**, 2136 (1947); U. S. Patent **2,304,624** (1942); *cf.* also Paquin, A. M., *Angew. Chem.*, **A60**, 267 (1948).

(2) Pohl, F., *J. prakt. Chem.*, **77**, 538–539 (1908).