8.84; N, 3.96. Found: C, 78.15; H, 8.76; N, 4.23}, and N-(−)-menthyloxycarbonyl-(−)-α-(1-naphthyl)ethylamine {mp 119°; $[\alpha]_D$ −43.1° (*c* 1.18, EtOH). Found: C, 78.28; H, 8.67; N, 4.17}.

Registry No.—(−)-Methyl chloroformate, 14602-86-9; (−)-menthyloxycarbonol-(−)-α-phenylmethylcarbinol, 17397-39-6; (−)-menthyloxycarbonyl-L-(−)-3-phenylacetic acid methyl ester, 17397-40-9; racemic (−)-menthyloxycarbonyl-DL-phenylalanine methyl ester, 17397-47-6; (−)-menthyloxycarbonyl-L-phenylalanine methyl ester, 17397-41-0; (−)-menthyloxycarbonyl-D-phenylalanine methyl ester, 17397-42-1; N-(−)-menthyloxycarbonyl-(−)-α-phenylethylamine, 17397-43-2; N-(−)-menthyloxycarbonyl-(+)-α-phenylethylamine, 17397-44-3; N-(−)menthyloxycarbonyl-(+)-α-(1-naphthyl)ethylamine, 17397-45-4; N-(−)-menthyloxycarbonyl-(−)-α-(1-naphthyl)ethylamine, 17397-46-5; α-phenylmethylcarbinol, 98-85-1; α-phenylethylcarbinol, 93-54-9; α-phenylpropylcarbinol, 614-14-2; α-phenylbutylcarbinol, 583-03-9; α-(*p*-tolyl)-propylcarbinol, 6282-37-7; α-phenylcyclohexylcarbinol, 945-49-3; tactic acid methyl ester, 17392-83-5; α-hydroxyisovaleric acid methyl ester, 17417-00-4; α-hydroxyisoenproic acid methyl ester, 17392-84-6; 3-phenylacetic acid methyl ester, 17417-01-5; alanine methyl ester, 10065-72-2; valine methyl ester, 4070-48-8; leucine methyl ester, 2666-93-5; phenylalanine methyl ester, 2577-90-4.

Acknowledgments.—This investigation was supported by National Aeronautics and Space Administration Grant NsG 81.

Cyclization of N-Oxalyl-α-amino Acid Derivatives[1]

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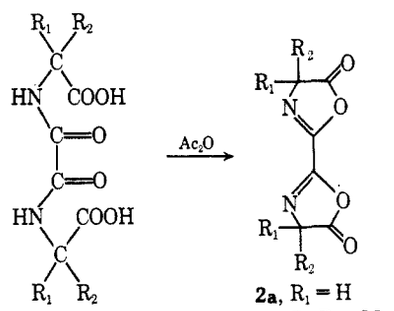
We have reported synthesis of the cyclic L-proline-N-oxalic anhydride[2] by treatment of L-proline in an inert solvent with excess oxalyl chloride. Under the same or milder conditions, glycine, DL-valine, or L-leucine gave tarry products from which no anhydride could be isolated. After removal of excess oxalyl chloride and even after treatment with boiling water, however, the crude reaction products sometimes gave a positive hydroxamic acid test, suggesting the presence of some anhydride or other acylating species.

One possibility considered for reaction of oxalyl chloride with an α-amino acid possessing a primary amino group was N-acylation followed by an alternative cyclization to an azlactone [5(4H)-oxazolone; 2-oxazolin-5-one]. The known tendency of azlactones to polymerize under mild conditions[3] would account for the intractable tars found whenever azlactone formation was possible (*i.e.*, when NH was still present in the N-acylamino acid). In this paper we report an investigation of N-oxalyl derivatives of α-aminoisobutyric acid containing the NH requisite for azlactone formation but lacking the α-H atom requisite for polymerization *via* acylation on the 4 position of any azlactone formed.

No examples of 2-oxazolin-5-ones containing a carboxy, carbalkoxy, or carboxamide group attached to the 2 position could be found in the literature, although a large number of N-oxalyl derivatives of α-amino acids have been prepared, in particular the N,N′-oxalylbis(α-amino acids).[4] Cleaver and Pratt prepared a large number of N,N′-diacylbis(α-amino acids) and successfully dehydrated them to 5-oxazolones in hot acetic anhydride.[5] If α-H atoms were present, degradation occurred, presumably *via* the Dakin–West reaction,[6] unless cyclization conditions were carefully controlled. Even with careful control, however,[5] the N,N′-oxalylbis(α-amino acids) (**1a**) failed to dehydrate to the corresponding diazlactones (**2a**).



1a, $R_1 = H$
b, $R_1, R_2 = Me$

2a, $R_1 = H$
b, $R_1, R_2 = Me$

We have now been able to carry out such a cyclization on N,N′-oxalylbis(α-aminoisobutyric acid) (**1b**) in hot acetic anhydride to obtain a small yield of 2,2′-bis(4,4-dimethyl-5-oxazolone) (**2b**). The structure of **2b** was indicated by elemental analysis and infrared (ir) spectrum and confirmed by the nuclear magnetic resonance (nmr) spectrum, which showed only a strong singlet (CH_3) at τ 8.54; no indication of NH or OH was present in either the ir or nmr spectrum. Compound **2b** is unusually stable for a "saturated-type" azlactone[3] without aromatic substitution, in contrast to 4,4-dimethyl-5-oxazolone itself, for example.[7] In addition to the 10% yield of azlactone, a 32% yield was obtained of a compound presumed by analysis and behavior to be a mixed anhydride of 1 mol each of the starting material and acetic acid. Mild hydrolysis of either compound regenerated **1b**.

A compound of perhaps greater interest was N-oxalyl-α-aminoisobutyric acid (**3**), since cyclization could lead either to the anhydride **4** (as in the proline case) or to 4,4-dimethyl-5-oxazolone-2-carboxylic acid (**5**). Acylation of α-aminoisobutyric acid ethyl ester by ethoxalyl chloride went smoothly, but difficulties

(1) Journal Paper No. J-5856 of the Iowa Agriculture and Home Economics Experiment Station, Ames, Iowa, Project No. 1384. Abstracted from the M.S. thesis of J. Medina-Castro, Iowa State University, Ames, Iowa, 1963. J. Medina-Castro's address: Departamento de Química Orgánica, Facultad de Química, Bioquímica y Farmacia, Universidad de Chile, Santiago, Chile.

(2) W. R. Hearn and R. E. Worthington, *J. Org. Chem.*, **32**, 4072 (1967).

(3) H. E. Carter, *Org. Reactions*, **3**, 198 (1946).

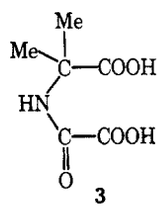
(4) J. T. Bornwater, *Rec. Trav. Chim.*, **31**, 105 (1912). For other references, see W. R. Hearn and R. A. Hendry, *J. Amer. Chem. Soc.*, **79**, 5212 (1957).

(5) C. S. Cleaver and B. C. Pratt, *ibid.*, **77**, 1544 (1955).

(6) H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 745 (1928).

(7) M. T. Leplawy, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, **11**, 39 (1960).

were encountered in isolating **3** after saponification of the diethyl ester. The barium salt gave reasonably good elemental analyses but the free acid was extremely hygroscopic and cyclization experiments were inconclusive.



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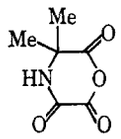

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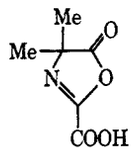

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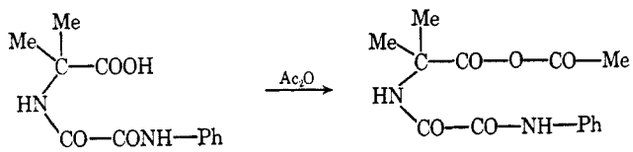
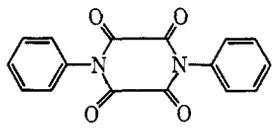
A third compound studied was the N-oxanilyl derivative (**6**) of α-aminoisobutyric acid. Cyclization of **6** would lead to 4,4-dimethyl-5-oxazolone-2-carboxanilide. Physical properties of this product were expected to be similar to those of 2-phenyl-4,4-dimethyl-5-oxazolone, easily prepared by treatment of N-benzoyl-α-aminoisobutyric acid with acetic anhydride.[8] Attempts to cyclize **6** by heating for long periods in the presence of acetic anhydride at 115–117° gave only insignificant amounts of crystalline product. With heating for shorter periods on a steam bath, a satisfactory yield of a crystalline product was obtained; however, elemental analysis indicated that this compound was the open-chain mixed anhydride **7** of starting material and acetic acid.



6 **7**

Failure to isolate azlactones from cyclization experiments with N-oxalyl and N-oxanilyl derivatives probably indicates poor choice of conditions rather than lack of formation of the substituted 5-oxazolone-2-carboxylic acid and 5-oxazolone-2-carboxanilide. The following series of reactions may be considered:[9] (1) acylamino acid + $(CH_3CO)_2O \leftrightarrows$ azlactone + $2CH_3COOH$; (2) azlactone + $CH_3COOH \leftrightarrows$ mixed anhydride; (3) mixed anhydride + $CH_3COOH \leftrightarrows$ acylamino acid + $(CH_3CO)_2O$. Azlactone formed in reaction 1 would encounter sufficient acetic acid to drive reaction 2 toward the mixed anhydride; excess acetic anhydride would drive reaction 3 to the left, also toward the mixed anhydride. With the N-oxanilylamino acid, only the mixed anhydride was isolated. With the N,N′-oxalylbis(amino acid), a small amount of azlactone was isolated but always in the presence of a large amount of mixed anhydride; the ratio of the two products obtained after different reaction times appeared to demonstrate that azlactone was an initial product.

In the preparation of **6** two interesting side reactions were encountered. Reaction of oxanilyl chloride with α-aminoisobutyric acid ethyl ester gave a crystalline compound which turned out to be 1,4-diphenyl-2,3,5,6-tetraoxopiperazine (**8**). This compound was first prepared in 1890 by Abenius[10] by chromic acid oxidation of the 2,5-dioxo compound. Warren and Briggs[11] obtained a compound of formula $(C_8H_5NO_2)_x$ by action of thionyl chloride on oxanilic acid; they believed their product to be oxanil **9**. Buckley and Henbest[12] reviewed the work of Warren and Briggs and concluded that the reported oxanil was actually **8**. The diphenyltetraoxopiperazine has apparently not been reported since; we find that it can be obtained in 65% yield by reaction of oxanilyl chloride with 2 mol of triethylamine in benzene. To avoid this side reaction when acylating with oxanilyl chloride, we dissolved the amino acid ethyl ester hydrochloride in ethyl acetate rather than the less polar benzene solvent and ran the reaction without added base.



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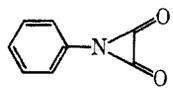

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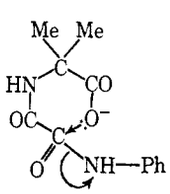
The second unexpected side reaction occurred in our first attempt to obtain **6** by saponification of N-oxanilylisobutyric acid ethyl ester. When the ester was suspended in 1 *N* sodium hydroxide and stirred at room temperature for 3 hr, the compound was cleaved to aniline and an extremely hygroscopic acidic compound. The acid product was assumed to be **3**; the surprising lability of the anilide to such mild hydrolytic conditions was explained by assuming that the carboxylate anion resulting from saponification of the ester participated in a "neighboring-group attack" on the carboxanilide carbon. Elimination of aniline would give a cyclic anhydride intermediate which would rapidly be hydrolyzed in 1 *N* base. Saponification of the ester group without cleavage of the anilide bond was effected by using milder alkali and shorter reaction times.



Experimental Section[13]

Starting Materials.—α-Aminoisobutyric acid was purchased from Nutritional Biochemicals Corp. and oxalyl chloride from Eastman Kodak Co.; both were used without further purification. Ethoxalyl chloride was prepared[14] from potassium ethyl oxalate and thionyl chloride and distilled at 134–135°. Oxanilyl chloride was prepared[15] from aniline hydrochloride and oxalyl chloride in benzene; the crude product obtained on evaporation of the solvent was used without further purification, mp 78–80°

(8) H. W. Thompson, R. R. Brattain, H. H. Randall, and R. S. Rasmussen in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, pp 382–414.

(9) R. E. Steiger, *Helv. Chim. Acta*, **17**, 563 (1934).

(10) P. W. Abenius, *J. Prakt. Chem.*, **41**, 80 (1890).

(11) V. H. Warren and R. A. Briggs, *Ber.*, **64**, 26 (1931).

(12) D. Buckley and H. B. Henbest, *J. Chem. Soc.*, 1888 (1956).

(13) Melting points were determined on a Kofler hot stage or a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., except for N by micro Kjeldahl, performed in our own laboratory. Ir spectra were obtained on potassium bromide pelletized samples with a Model 21 Perkin-Elmer spectrophotometer. The nmr spectrum was obtained with a Varian Model A-60 spectrometer operated at 60 Mc; tetramethylsilane was used as an internal standard for calibration; and the sample was dissolved in pyridine.

(14) P. L. Southwick and L. L. Seivard, *J. Amer. Chem. Soc.*, **71**, 2532 (1949).

(15) I. G. Farbenindustrie, A. G., German Patent 463,140 (July 5, 1928); *Chem. Abstr.*, **22**, 4130 (1928).

(lit.[15] mp 82°). Benzene was dried over sodium; other solvents were dried over anhydrous sodium carbonate before use.

α-Aminoisobutyric Acid Ethyl Ester Hydrochloride.—α-Aminoisobutyric acid (50 g) was suspended in 400 ml of absolute ethanol; dry HCl was bubbled through the stirred suspension until all material went into solution (*ca.* 2 hr). The solution was refluxed for 4 hr with exclusion of moisture. Concentration of the solution to about 150 ml, addition of 150 ml of ether, and chilling in an ice bath yielded crystals which were collected and washed twice with cold ether. The filtrate was concentrated and the process was repeated to yield a second crop. Recrystallization of combined crops gave 54.5 g (67%) of product, mp 156°.

Anal. Calcd for $C_6H_{14}ClNO_2$: N, 8.38; neut equiv, 167.6. Found: N (micro Kjeldahl), 8.25; neut equiv, 168.2.

N,N′-Oxalylbis(α-aminoisobutyric acid) Diethyl Ester.—To a suspension of 8.4 g (0.05 mol) of α-aminoisobutyric acid ethyl ester hydrochloride in 50 ml of benzene was added 2.14 ml (0.025 mol) of oxalyl chloride. The mixture was refluxed for 3 hr with exclusion of moisture; by that time evolution of HCl had ceased and all starting material was in solution. Allowing the solution to cool to room temperature gave 10.5 g (66.5%) of crystalline product, mp 109–110°.

Anal. Calcd for $C_{14}H_{24}N_2O_6$: N, 8.87. Found: N (micro Kjeldahl), 8.25.

N,N′-Oxalylbis(α-aminoisobutyric acid) (1b).—The above diester (8.0 g) was suspended in a mixture of 200 ml of aqueous 0.5 *N* sodium hydroxide and 100 ml of 95% ethanol. The suspension was stirred for 1 hr at room temperature (24°). A small amount of unreacted material was removed by filtration, and the alkaline filtrate was neutralized with 6 *N* hydrochloric acid to pH 2. After chilling in an ice bath the precipitate was collected by filtration: yield, 5.8 g (83.5%); mp 284°, after sublimation at 239°.

Anal. Calcd for $C_{10}H_{16}N_2O_6$: C, 46.14; H, 6.2; N, 10.77. Found: C, 45.95; H, 6.5; N, 10.72.

Cyclization of 1b.—A sample of 9.0 g (0.034 mol) of **1b** was added as a fine powder to 60 ml (0.64 mol) of acetic anhydride and the mixture was heated for 40 min on a steam bath with exclusion of moisture. A small amount of undissolved material was removed by rapid suction filtration. Excess acetic anhydride was distilled off at reduced pressure (22–25° at 2–3 mm) until white crystals began to separate. The distillation was stopped and the flask was allowed to cool in ice. The product collected by suction filtration at this point proved to be 2,2′-bis(4,4-dimethyl-5-oxazolone) (**2b**): yield after recrystallization from benzene, 0.82 g (10.6%); mp 191–192°.

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.60; H, 5.40; N, 12.50. Found: C, 53.34; H, 5.47; N, 12.17.

Major ir peaks occur at 1830, 1628, 1464, 1190, 1148, 1008, 960, and 895 cm^{-1}. This spectrum is very similar to that published for the analogous single-ring compound 4,4-dimethyl-5-oxazolone; the latter compound was too unstable to isolate but its ir spectrum was obtained in a carbon tetrachloride solution after reaction between N-formyl-α-aminoisobutyric acid and thionyl chloride in the presence of triethylamine.[7] The nmr spectrum of **2b** shows a strong single proton peak at τ 8.54 as its only feature, with no indication of N–H or O–H protons farther downfield.

A second crystalline product was obtained by covering the acetic anhydride filtrate of **2b** with *n*-pentane and allowing the solution to stand in a freezer. Repeating this process twice gave a total of 4.12 g (32%) of product corresponding to a mixed anhydride formed from 1 mol of **1b** and 1 mol of acetic acid.

Anal. Calcd for $C_{12}H_{18}N_2O_7$: C, 46.70; H, 6.01; N, 9.27. Found: C, 46.45; H, 6.30; N, 9.76.

N-Ethoxalyl-α-aminoisobutyric Acid Ethyl Ester.—α-Aminoisobutyric acid ethyl ester hydrochloride (17.0 g, 0.10 mol) was suspended in 60 ml of ethyl acetate, and ethoxalyl chloride (23.3 g, 0.17 mol) was added. The mixture was refluxed for 3 hr with exclusion of moisture. Unreacted material was removed by suction filtration, and excess ethyl acetate was removed in a rotary evaporator, leaving a syrupy residue. Distillation of the syrupy material at reduced pressure gave 21.8 g (92%) of the desired ester, bp 106–108° (0.45–0.5 mm).

Anal. Calcd for $C_{10}H_{17}NO_5$: N, 6.06; sapon equiv, 115.6. Found: N, (micro Kjeldahl), 5.6; sapon equiv, 113.0.

N-Oxalyl-α-aminoisobutyric Acid (3). Method A.—N-Ethoxalyl-α-aminoisobutyric acid ethyl ester (21.8 g) was suspended in 200 ml of 1 *N* sodium hydroxide and stirred for 1 hr at 30°. The solution was kept at 5° for 2 hr and then acidified by addition of enough Dowex-50 resin (50–100 mesh) in the hydrogen form to bring the pH to 1. After 30 min of stirring, the resin was removed by filtration and the filtrate was lyophilized. The yield of very hygroscopic yellowish solid was 7.3 g (44%).

Anal. Calcd for $C_6H_9NO_5$: N, 7.99; neut equiv, 87.6. Found: N (micro Kjeldahl), 7.44; neut equiv, 99.0.

Method B.—The ethoxalyl ester (14.1 g) was saponified with 280 ml of 0.5 *N* barium hydroxide by stirring at room temperature. The barium salt of **3** was precipitated by addition of 80 ml of 95% ethanol, warming, and allowing the mixture to cool slowly. A yield of 19.3 g (87.5%) of very fine crystals was obtained.

Anal. Calcd for $C_6H_7BaNO_5 \cdot 3H_2O$: C, 18.82; H, 3.92; N, 3.67. Found: C, 18.70; H, 3.54; N, 3.84.

Solubility of the barium salt in water was 7.5 g/100 ml at 19.5°. A sample of 12.0 g (0.038 mol) of the salt was treated with the equivalent amount of 2 *N* sulfuric acid (38.7 ml) added slowly from a buret with continuous stirring. Barium sulfate was removed by centrifugation, and the supernate was concentrated in a rotary evaporator under reduced pressure (bath temperature, 50°) to a syrupy residue. As treatments with acetone and ether failed to solidify the syrup, it was dried under high vacuum over phosphorus pentoxide at 50°. The dried syrup covered with *n*-pentane gave white crystals on standing overnight in the freezer: yield, 5.9 g (65%); mp 114–115° (sealed capillary). Analytical results were not satisfactory for **3**; the product was extremely hygroscopic and may have been contaminated by products of further hydrolysis (oxalic acid and α-aminoisobutyric acid).

Attempted Cyclization of 3.—An exhaustively dried sample (4.25 g, 0.024 mol) of **3** prepared by method A was refluxed for 50 min on a steam bath with 40 ml (0.42 mol) of acetic anhydride. Excess acetic anhydride was removed by distillation [24° (1.5 mm)], and the remaining syrupy material was left in the freezer for 48 hr. No crystals were obtained until the syrup was warmed with *n*-pentane and returned to the freezer for another 12 hr. The crystalline product was collected by suction filtration, yielding 1.23 g (32% for either the anhydride **4** or the oxazolone **5**), mp 63–64° (sealed capillary). Elemental analyses were unsatisfactory for any reasonable product and showed a large amount of incombustible residue; the particular sample of **3** used had not actually been analyzed and could have been contaminated with sodium salt if the Dowex-50 treatment had been incomplete. Although no conclusions could be drawn from this attempted cyclization because of the impure product, the presence of bands at 1825 and 1740 cm^{-1} in the ir spectrum suggested that some of the product was in the form of a linear or cyclic anhydride.

N-Oxanilyl-α-aminoisobutyric Acid Ethyl Ester. Method A.—α-Aminoisobutyric acid ethyl ester hydrochloride (7.5 g, 0.045 mol) was added to a solution of 9.2 g (0.05 mol) of oxanilyl chloride dissolved in 60 ml of benzene. While the temperature of the mixture was kept below 5° with an ice bath, a solution of 16 ml (0.11 mol) of triethylamine was added with stirring and with exclusion of moisture over a period of 25 min, during which time the solution turned deep yellow. Stirring was continued for 2 hr and then the reaction mixture was chilled in a refrigerator for 8 hr. Filtration with suction removed 14 g of benzene-insoluble material. The filtrate was taken to dryness in a rotary evaporator, leaving a syrupy residue with a penetrating odor. The residue was dissolved in a minimum of 95% ethanol, and the solution was chilled in a freezer, giving slightly yellowish crystals of the desired product: yield, 2.1 g (17%); mp 101°.

Anal. Calcd for $C_{14}H_{18}N_2O_4$: N, 10.08. Found: N (micro Kjeldahl), 10.10.

The 14 g of benzene-insoluble solid was extracted with water at 50° to remove triethylamine hydrochloride and dried, giving 3.0 g (21%) of a compound identified as the tetraoxopiperazine by-product, **8**. After recrystallization from nitromethane, the compound sublimed at 330° (lit.[11] 335–340°).

Anal. Calcd for $C_{16}N_{10}N_2O_4$: N, 9.52. Found: N (micro Kjeldahl), 9.41.

As a reference compound, **8** was also prepared in 65% yield by treating oxanilyl chloride with triethylamine alone in benzene. Ir spectra of the two samples were identical, with peaks corresponding to those reported for **8**.[11]

Method B.—The oxanilyl ester was prepared in higher yield in ethyl acetate as solvent. α-Aminoisobutyric acid ethyl ester hydrochloride (4.19 g, 0.025 mol) was added to 4.6 g (0.025

mol) of oxanilyl chloride dissolved in 50 ml of ethyl acetate. After refluxing for 4 hr under dry conditions, the reaction mixture was cooled and 2 g of solid was removed by suction filtration. The filtrate was evaporated to a syrup, the syrup was stirred with 95% ethanol, and the ethanolic solution was chilled in a freezer to give crystals of the desired product. A second crop was collected by concentrating the ethanolic filtrate, giving a total of 3.73 g (53%). Ir spectra of the products from methods A and B were identical.

Anal. Calcd: N, 10.08. Found: N (micro Kjeldahl), 10.33.

N-Oxanilyl-α-aminoisobutyric Acid (6).—The finely powdered ester (5.25 g, 0.018 mol) was suspended in 500 ml of 0.5 *N* sodium hydroxide solution plus 100 ml of 95% ethanol. After the mixture had been stirred for 1 hr at room temperature (28°), a small amount of unreacted material was removed by suction filtration. The filtrate was acidified to pH 2 with concentrated hydrochloric acid, the mixture being cooled in an ice bath. The precipitate was collected by filtration, washed with cold acidified water, and dried at 100°: yield, after recrystallization from 95% ethanol, 3.44 g (73%); mp 203–204°.

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 56.45; H, 5.60; N, 11.18. Found: C, 56.97; H, 5.61; N, 11.31.

Attempted Cyclization of 6.—A sample of 2.0 g of **6** was added to 15 ml of acetic anhydride and the mixture was heated on a steam bath for 45 min. Excess acetic anhydride was distilled off at 24° (1.8 mm), and the syrupy residue remaining in the distillation flask was chilled in a freezer. The crystals which separated were obtained by suction filtration. Two crops were combined and recrystallized from benzene plus *n*-pentane, yielding 0.83 g (36%) of product which analyzed for the mixed anhydride **7**, mp 103–104°.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.60; H, 5.52; N, 9.57. Found: C, 57.63; H, 5.57; N, 9.23.

Registry No.—α-Aminoisobutyric acid ethyl ester hydrochloride, 17288-15-2; **1b** diethyl ester, 17288-16-3; **1b**, 17288-17-4; mixed anhydride from **1b** and acetic acid, 17288-18-5; **2b**, 17288-19-6; **3** diethyl ester, 17288-20-9; **3**, 17288-21-0; barium salt of **3**, 17288-22-1; **6** ethyl ester, 17288-23-2; **6**, 17288-24-3; **7**, 17288-25-4.

Synthesis of Fat-Soluble Analogs of Pyridoxal 5′-Phosphate[1]

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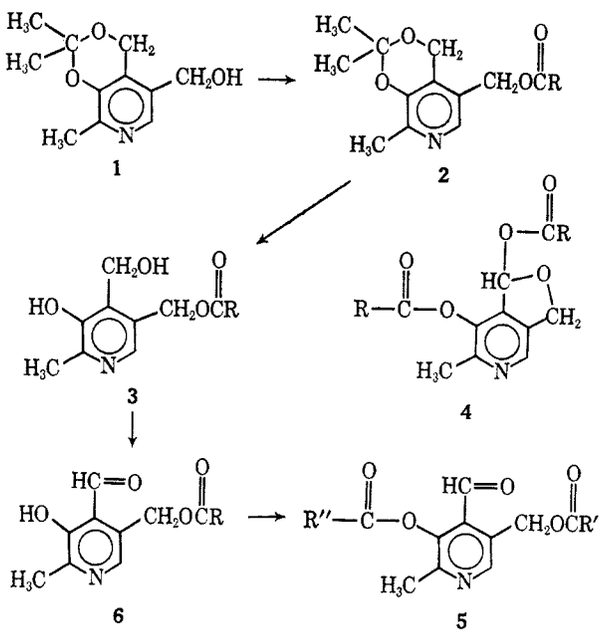
Received April 29, 1968

The coenzymatic form of vitamin B_6 is pyridoxal 5′-phosphate. Very few analogs of this compound in which the phosphate ester has been replaced by another acidic group[2] and none in which it has been replaced with a carboxylic acid have been reported. Our interest in the biological properties of such compounds prompted us to synthesize the compounds pyridoxal 5′-palmitate and pyridoxal 5′-benzoate (**6a** and **6b**). Furthermore, we converted these esters into 3,5′ diesters. Such diesters of pyridoxal have not been previously synthesized. The pyridoxal 5′ esters were prepared using methods reported for the synthesis of analogous compounds[3] (see Scheme I).

SCHEME I



a, R = $(CH_2)_{14}CH_3$
b, R = C_6H_5
c, R′ = $(CH_2)_{14}CH_3$; R″ = CH_3
d, R′ = C_6H_5; R″ = CH_3
e, R′ = R″ = $(CH_2)_{14}CH_3$

When pyridoxal 5′ esters (**6a** and **6b**) were treated with acetic anhydride or palmitoyl chloride in pyridine, the corresponding pyridoxal 3,5′ diesters (**5c**, **5d**, and **5e**) were obtained. The diesters are of special interest in view of the recent work of Prosser, Sheppard, and Libby[4] who claimed to have synthesized pyridoxal 3,5′-diacetate by treating pyridoxal hydrochloride in pyridine–chloroform mixture with acetic anhydride. Korytnyk, *et al.*,[5,6] have conclusively established the structure of the compounds obtained when pyridoxal is treated with acetic anhydride or palmitoyl chloride as pyridoxal 3,4′ diesters (1,3-dihydro-1,7-diacyloxy-6-methylfuro[3,4-*c*]pyridine) (**4**), thus questioning the previously reported synthesis of pyridoxal 3,5′-dipalmitate.[7] However, Prosser, *et al.*,[4] to explain the nuclear magnetic resonance (nmr) spectrum of the compound which they had obtained (aldehydic proton signal and lack of acetal proton signal), attributed its pyridoxal 3,5′ diester structure to possible isomerization during the isolation procedure. It has been shown in the literature that, since pyridoxal exists predominantly in the cyclic hemiacetal form,[8] attempts to esterify[5,6] or etherify[9,10] it directly will result in the formation of the corresponding cyclic 4′ ester or acetal derivative. Nevertheless, the possibility existed that a rearrangement took place in the course of drying and neutralization, resulting in the formation of the free aldehyde form.

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