The triene would not form an adduct with maleic anhydride. The photomixture (201 mg.) was quantitatively recovered by chromatography on silica gel after exposure to 62 mg. of maleic anhydride in 4 ml. of benzene for 48 hr. at room temperature.

Extension of the irradiation period led to complex mixtures (v.p.c. analysis). It is noteworthy that cautious exclusion of atmosphere seemed to inhibit the formation of methyl dehydroabietate. When all joints were greased and the solution thoroughly degassed (heated to reflux while flushing with helium), little if any dehydrogenation was observed. A small amount of methyl dehydroabietate was isolated by column chromatography after a prolonged irradiation in which such precautions had not been taken. Infrared comparison with an authentic sample confirmed the identity of this material.

Pyrolysis of the Photomixture.—A solution of 435 mg. of unpurified photomixture (containing totally 15% of A and B) in 22 ml. of diglyme was heated at reflux temperature (160°) under a nitrogen atmosphere for 4 hr. Aliquots (0.50 ml.) were removed periodically by means of a syringe and diluted to 1 ml. with diglyme, and the optical rotation was measured (Table II).

TABLE II

Time, min.	Observed rotation, degree
0	−0.82
15	+0.03
30	+0.08
60	+0.12
120	+0.19
240	+0.22

The final three aliquots were recombined with the solution, and then pentane and cold water were added. The aqueous phase was extracted twice more with pentane. The combined pentane extracts were washed four times with cold water, dried in the usual manner, and finally evaporated to dryness, 381 mg. (94%). The n.m.r. spectrum of the unpurified pyrolysate is shown in Fig. 1C.

The material was chromatographed on alumina to remove the contaminants (mainly A), as in the previous experiment. After separation of the earlier fractions enriched in the impurities (total content, 122 mg.), the column was stripped with 50 ml. of benzene. Evaporation of the benzene eluate furnished 230 mg. (57%) of material of 93% purity (v.p.c. analysis), λ_{max} 265 mμ (ε 7000), $[\alpha]_D$ +30°. With the exception of a few minor differences, the infrared spectrum was superimposable with that of methyl palustrate. The n.m.r. spectrum exhibited the characteristic singlet (τ 4.70) associated with the vinyl hydrogen of methyl palustrate.

Secondary Product A.—From the irradiation of 1.80 g. of methyl palustrate to the steady state there was obtained after two alumina chromatographies 23 mg. of a mixture, which by v.p.c. analysis proved to be 90% A and B. Although the v.p.c. traces indicated 50% A and 40% B, the n.m.r. spectrum showed 70% and 20% to be more nearly correct. This estimate was obtained by comparison of the τ 8.76 methyl signal of B with the τ 8.85 signal of A. The allylic method of B could also be distinguished. The mixture had $[\alpha]_D$ −140°, λ_{sh} 241 mμ (ε 7600), and ν_{max} 1630 and 900 cm.$^{-1}$.

The vinyl region of the n.m.r. spectrum of this mixture had bands at τ 4.30, 5.08, and a complex pattern from 5.25 to 5.50. Three methyl signals were observed at τ 8.85, 8.93, and 9.03. Another sample of A which was uncontaminated with B had essentially the same infrared and n.m.r. spectra; the minor bands attributed to B were absent in the latter.

Secondary Product B.—A mixture of 60% A and B (79 mg.) obtained by judicious combination of various enriched fractions from preceding chromatographies was heated under reflux in 4 ml. of diglyme for 4 hr. The course of the pyrolysis was followed by v.p.c. analysis which demonstrated that A was being converted into B. The pyrolysate was isolated by pentane extraction, then chromatographed on neutral alumina (activity II) with pentane as the eluent.

A series of fractions were collected which contained, for the most part, variable proportions of methyl palustrate and B, from which the physical properties of B could be obtained. The optical rotation was calculated to be about −140°, correcting for the per cent of methyl palustrate. The infrared spectrum had absorption at 893 cm.$^{-1}$. In the vinyl region of the n.m.r. spectrum, there were broad bands at τ 4.33 and 4.50 as well as a rather sharp band τ 5.26. The lower field peaks had approximately the same area as the higher field absorption. A sharp doublet ($J \sim 1$ c.p.s.) was discerned at τ 8.42. Signals from saturated methyl groups were found at τ 8.76, 8.90, 8.98, and 9.00.

Preparation of New Amino Acids and 2,5-Oxazolidinediones

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In the course of preparing some novel peptides by the Leuchs-anhydride route, two new amino acids, DL-2-(*o*-ethoxyphenyl)glycine and 1-aminocyclooctanecarboxylic acid, were prepared by variants of the Strecker synthesis. In addition, 1-aminocyclobutanecarboxylic acid and DL-2-phenylsarcosine were prepared by improved procedures. New 2,5-oxazolidinediones were prepared from these acids as well as from D- and L-2-phenylglycine by direct phosgenation. The preparation and properties of these compounds are described in this paper.

In working with 2,5-oxazolidinediones, we have found that for many of them the admonitions in the literature[1] as to the observance of strict anhydrous conditions in their preparation and to the need of utilizing them within a few hours are not necessary. Air-dried glassware and a commercial source of dioxane were adequate. Storage of the pure compounds at 5° over silica gel resulted in little or no polymerization for extended periods.

The anhydride groupings showed two characteristic absorption peaks at 5.37–5.45 and 5.62–5.77 μ corresponding to carbon–oxygen stretching. If the ring nitrogen was unsubstituted, nitrogen–hydrogen stretching gave peaks at 2.97–3.10 μ.

Experimental

All melting points are corrected. Analyses were run by members of the Microbiological and Physical Chemistry Departments of this laboratory; infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer.

The preparation of D-4-phenyl-2,5-oxazolidinedione is typical for all of the oxazolidinediones.

D-4-Phenyl-2,5-oxazolidinedione.—D-2-Phenylglycine[2] (350 g., 2.32 moles) was suspended in 3 l. of dioxane (Fisher Scientific Co., D-111, certified grade) in a 5-l. four-necked flask fitted with a heating mantle, gas-inlet tube, thermometer, solid carbon dioxide condenser with drying tube, and sealed stirrer. Phosgene was slowly introduced *via* a safety flask until about 460 g. (4.67 moles) was added. The rate of addition was adjusted to maintain the temperature at 50°. When the reaction rate fell off, heating was started to keep the temperature at this level. At the end of 4 hr. from the initial addition of phosgene, solution had occurred. The solid carbon dioxide condenser was replaced with an air condenser, and dry nitrogen was passed through overnight. The dioxane solution was concentrated to an oil on a rotary evaporator. The oil was taken up in ethyl acetate

(1) *Cf.* J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1961, p. 861.

(2) From L. Perrigo Co., Allegan, Mich.

and concentrated until crystallization occurred. The crystals were filtered off, washed with benzene, and dried over silica gel. The mother liquor and washings were concentrated to give further crops. The first crop was 99 g. (24%), m.p. 128–130°, $[\alpha]^{25}D$ −126° (*c* 3.5, ethyl acetate); λ_{max}^{KBr} 3.10, 5.44, and 5.64 μ.

Anal. Calcd. for $C_9H_7NO_3$: C, 61.03; H, 3.98; N, 7.91. Found: C, 61.07; H, 3.82; N, 7.95.

Further crops were obtained for a final yield of 74%. The melting points were in the range 124–129°, and the equivalent weights[3] were in the range 176–180 (177.16 is theory).

Attempts to recrystallize the original crops from ethyl acetate–benzene mixtures resulted in material that melted lower than the starting material but did not differ in elementary analysis, equivalent weight, specific rotation, or infrared spectrum. The melting points obtained were from 109° to 115–118°. Whether this is a polymorphic form has not been established.

Determination of the equivalent weight of a sample of D-4-phenyl-2,5-oxazolidinedione after storage for 3 months at 5° over silica gel showed no significant change in value (178.1 to 177.9). A similar period of storage at room conditions made it insoluble in ethyl acetate, indicating that it was polymerized. Storage over silica gel at room temperature for several days gave no detectable change.

L-4-Phenyl-2,5-oxazolidinedione.—L-2-Phenylglycine[2] was treated in the same manner as the D-isomer to give L-4-phenyl-2,5-oxazolidinedione, m.p. 123–128°.

DL-2-(*o*-Ethoxyphenyl)glycine.—*o*-Ethoxybenzaldehyde (100 g., 0.66 mole) and ammonium carbonate monohydrate (166 g., 1.45 moles) were dissolved in 700 ml. of ethanol and 300 ml. of water and heated to 50° under a reflux condenser. Potassium cyanide (48 g., 0.74 mole) in 400 ml. water was added over 1 hr., and the solution was heated at 60° for 3 hr. The reflux condenser was removed, and the temperature was increased to 90° to distil the ethanol and to decompose the ammonium carbonate. The reaction mixture was cooled, extracted once with ether to remove unreacted aldehyde, and acidified to pH 2. The precipitated hydantoin was filtered off and dried, yielding 87 g. (63%), m.p. 178–182°. This product was pure enough to use in the next step. Reprecipitation gave an analytically pure product, m.p. 183–186°.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.98; H, 5.50; N, 12.72. Found: C, 59.81; H, 5.48; N, 12.94.

The hydantoin (87 g., 0.42 mole) was dissolved in 425 ml. 2.5 *N* potassium hydroxide and refluxed for 2 days. The solution was cooled, acidified to pH 5.5, decolorized, and filtered. Cupric acetate dihydrate (42 g., 0.21 mole) in 300 ml. of hot water was added, and the copper salt crystallized on cooling the mixture in an ice bath. It was filtered off, washed with ethanol, suspended in 300 ml. of water, and treated with hydrogen sulfide. The cupric sulfide was filtered off. The filtrate was decolorized and concentrated to dryness, and the residue was dried. The crude amino acid was dissolved in 200 ml. of warm ethanol and 400 ml. of ether was added. DL-2-(*o*-Ethoxyphenyl)glycine crystallized as the monohydrate, yielding 40 g. (28% over-all yield), m.p. 129–133°.

Anal. Calcd. for $C_{10}H_{13}NO_3 \cdot H_2O$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.99; H, 7.13; N, 6.57.

This amino acid is somewhat unstable; after several months storage under room conditions, a positive pressure was present in the storage container, and a strong odor of ammonia was noted. The infrared spectrum of the sample was unchanged however.

DL-4-*o*-Ethoxyphenyl-2,5-oxazolidinedione.—DL-2-(*o*-Ethoxyphenyl)glycine monohydrate (2.5 g.) was treated with phosgene in 250 ml. of dioxane at 45° for 3.5 hr. The product was crystallized from ethyl acetate, yielding 1.4 g. (54%), m.p. 142–146°. Recrystallized material had m.p. 143–147°; λ_{max}^{KBr} 3.10, 5.44, and 5.77 μ.

Anal. Calcd. for $C_{11}H_{11}NO_4$. C, 59.60; H, 5.00; N, 6.32. Found: C, 59.68; H, 5.03; N, 6.30.

1-Aminocyclobutanecarboxylic Acid.—5,5-Trimethylenehydantoin was prepared by an improved version of the procedure of Ingold, *et al.*[4] Cyclobutane-1,1-dicarboxamide was converted directly to the hydantoin by reaction with sodium hypochlorite.[5] In this conversion, a mildly exothermic aqueous reaction replaces a bromination to the dibromamide and a hydrolysis which can be violent.

Cyclobutane-1,1-dicarboxamide[4] (14.2 g., 0.1 mole) was stirred in 1 l. of 0.5 *N* sodium hypochlorite (commercial bleaching product diluted with water) at 0° until it dissolved. The reaction mixture stood overnight at room conditions. It was then neutralized to pH 5 with concentrated hydrochloric acid and evaporated to dryness *in vacuo*. The residue was extracted with 300 ml. of hot acetone, filtered, and washed with 200 ml. of hot acetone. The acetone solutions were combined and evaporated. Yield of the hydantoin was 13.0 g. (95%), m.p. 221–224° (lit.[4] m.p. 225°).

The hydantoin was hydrolyzed by refluxing with barium hydroxide solution (saturated at room temperature) for 24 hr. The barium ion was removed as barium sulfate and the resulting known 1-aminocyclobutanecarboxylic acid crystallized from aqueous ethanol, m.p. 290–296°. The yield was 76% over-all.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.13; H, 7.88; N, 12.16. Found: C, 52.44; H, 7.84; N, 11.84.

4,4-Trimethylene-2,5-oxazolidinedione.—1-Aminocyclobutanecarboxylic acid (3.0 g.) was treated with phosgene under water reflux in 500 ml. of dioxane at 90° for 1.25 hr. The phosgene flow was stopped and the flask was heated for a similar period at 90°. The product was crystallized from ethyl acetate, yielding 1.4 g. (37%), m.p. 112–114°; λ_{max}^{KBr} 2.97, 5.37, and 5.65 μ.

Anal. Calcd. for $C_6H_7NO_3$: C, 51.00; H, 5.00; N, 9.92. Found: C, 50.84; H, 4.89; N, 9.89.

1-Aminocyclooctanecarboxylic Acid.—By a procedure similar to that given for DL-5-(*o*-ethoxyphenyl)hydantoin, cyclooctanone[6] (50.4 g., 0.40 mole), ammonium carbonate monohydrate (137 g., 1.20 moles), and potassium cyanide (26.8 g., 0.41 mole) were reacted in 400 ml. of 50% ethanol to give 5,5-heptamethylenehydantoin in 78% yield, m.p. 241–242°.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: N, 14.27. Found: 14.47.

The hydantoin (58 g., 0.30 mole) was refluxed in 250 g. of 50% (w./w.) sulfuric acid under nitrogen for 5 days. The solution crystallized upon cooling. Water (400 ml.) was added, and the mixture was warmed and filtered from unreacted hydantoin. The pH of the filtrate was adjusted to 5.5 with solid sodium hydroxide. 1-Aminocyclooctanecarboxylic acid crystallized on cooling, yielding 39 g. (59% over-all yield), m.p. 310–316°.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.19. Found: C, 63.54; H, 9.90; N, 8.08.

4,4-Heptamethylene-2,5-oxazolidinedione.—1-Aminocyclooctanecarboxylic acid (25.0 g.) was treated with phosgene in 1 l. of dioxane at 42° for 2.5 hr. After the phosgene flow was stopped, the solution was heated for 2 hr. at 45–50°. The product was crystallized from ethyl acetate, yielding 19.4 g. (67%), m.p. 109–120°. Recrystallized material had m.p. 115–121°; λ_{max}^{KBr} 3.02, 5.45, and 5.62 μ.

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.95; H, 7.66; N, 7.11; equiv. wt., 197.23. Found: C, 61.33; H, 7.84; N, 6.98; equiv. wt., 197.3.

DL-2-Phenylsarcosine.—Benzaldehyde (106 g., 1 mole), potassium cyanide (65 g., 1 mole), and methylamine (70 g., 1 mole) were dissolved in 300 ml. of 50% ethanol and heated at 60° in a bomb for 5 hr. The reaction mixture was cooled, ethanol was removed *in vacuo*, and 500 ml. of water was added. The solution was acidified to pH 2 with concentrated hydrochloric acid and extracted with ether to remove unreacted aldehyde. The aqueous solution was made strongly basic with solid sodium hydroxide and extracted with ether. The ether extract containing the nitrile was concentrated to an oil, which was dissolved in 1 l. of 6 *N* hydrochloric acid and refluxed for 24 hr. The hydrolysate was cooled, and the hydrochloride salt of DL-2-phenylsarcosine crystallized, yielding 79 g. (39%). The mother liquor was concentrated to 400 ml., and the second crop was filtered off and washed with 100 ml. of ice–water to remove ammonium chloride. The yield was 6.2 g. (3%).

The two crops (85 g., 0.43 mole) were dissolved in 500 ml. of 1.7 *N* sodium hydroxide. The solution was filtered and neutralized with concentrated hydrochloric acid. The free amino acid precipitated and was filtered off and dried, yielding 42 g. (26% over-all yield), subliming at 298–300° (lit. 274°[7] and 270°[8]).

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.72; H, 6.64; N, 8.67.

(3) A. Berger, M. Sela, and E. Katchalski, *Anal. Chem.*, **25**, 1554 (1953); J. S. Fritz and N. M. Lisicki, *ibid.*, **23**, 589 (1951).

(4) C. K. Ingold, S. Sako, and J. F. Thorpe, *J. Chem. Soc.*, 1177 (1922).

(5) I. J. Rinkes, *Rec. trav. chim.*, **46**, 268 (1927).

(6) From Aldrich Chemical Co., Inc., Milwaukee, Wis.

(7) F. Tiemann and R. Piest, *Chem. Ber.*, **14**, 1982 (1881).

(8) F. Knoop, *ibid.*, **52**, 2266 (1919).

DL-3-Methyl-4-phenyl-2,5-oxazolidinedione.—DL-2-Phenylsarcosine (34 g.) was treated with phosgene in 1.5 l. of dioxane for 4 hr. at 40–45°. The product was crystallized from ethyl acetate, yielding 32 g. (81%), m.p. 65–75°. Recrystallized material had m.p. 73–75°, λ_{max}^{KBr} 5.42 and 5.65 μ.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 62.85; H, 4.74; N, 7.33; equiv. wt., 191.19. Found: C, 62.97; H, 4.70; N, 7.35; equiv. wt., 191.3.

N-Hydroxyalkyl-2,4-diamino-*sym*-triazines from Guanamines

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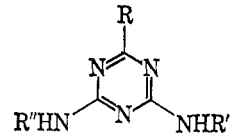
In connection with another investigation, a convenient method was needed for preparation of N-hydroxylalkyl-substituted guanamines[1] in large quantities and in good yield. Although such compounds would in principle be available from the guanamines and alkylene oxides, work in these laboratories showed that these reactants lead to different products. The use of amines and of chlorotriazines,[2] on the other hand, seemed unsuitable because of unavailability of the required chlorotriazines.

Examination of the literature revealed several instances of the so-called transamination or exchange amination of heterocyclic nitrogen compounds. One of the earliest examples of this reaction is recorded in a patent[3] in which melamine is converted to N-alkyl-substituted melamines by heating it with primary or secondary amines in the presence of hydrogen chloride. Similarly, melamine, ammeline, and ammelide have been converted to the corresponding N-aryl-substituted compounds by heating them with arylamine hydrochlorides.[4] Exchange amination was also successfully applied to pyrimidines and purines.[5]

In all of these transaminations amines having no other functional groups were used. The method, however, because of its simplicity and potential adaptability to a larger scale, was admirably suited to our purposes, and in this paper we describe our work which resulted in the introduction of an N-hydroxyalkyl chain into guanamines by use of amino alcohols.

When benzoguanamine hydrochloride was heated at reflux (165–175°) with an excess of ethanolamine a vigorous evolution of ammonia occurred which stopped after about 14 hr. The same result could be obtained when 1 mole of ethanolamine hydrochloride was used for one mole of benzoquanamine and the reaction mixture was heated in an excess of ethanolamine. However, because the guanamine hydrochlorides could be prepared and handled more easily than the amino alcohol hydrochlorides, the former were used nearly exclusively in the later work. Removal of the excess of ethanolamine and pouring the product into water or dilution of the crude product with water gave a good yield of a crystalline compound which analyzed correctly for N,N′-bis(2-hydroxyethyl)benzoguanamine (I) dihydrate. Attempts to obtain crystalline anhydrous I were without success, although various solvents and methods of drying were used. Oily solids or semisolids were obtained which in the presence of water reverted to the crystalline dihydrate. However, crystalline hydrochloride and picrate salts and a dibenzoyl derivative could be prepared.



I, R = Ph; R′ = R″ = CH_2CH_2OH
II, R = Ph; R′ = H; R″ = CH_2CH_2OH
III, R = CH_3; R′ = R″ = CH_2CH_2OH
IV, R = $PhCH_2$; R′ = R″ = CH_2CH_2OH
V, R = $NHCH_2CH_2OH$; R′ = R″ = CH_2CH_2OH
VI, R = $NHCH_2CH_2OH$; R′ = R″ = H
VII, R = Ph; R′ = R″ = $CH_2CH_2CH_2OH$

The hydrogen chloride to guanamine base ratio strongly affected the product composition. At a 1:1 ratio I was obtained in high yield, while at a 1:20 ratio the major product was N-(2-hydroxyethyl)benzoguanamine (II). At still lower ratios the reaction was impractically slow. Compound II was obtained in anhydrous crystalline form and was characterized as the hydrochloride salt. Further reaction of II with ethanolamine hydrochloride in boiling ethanolamine gave I.

After obtaining compounds I and II, it was of interest to determine the scope of the reaction with respect to other amino-*sym*-triazines. Thus, under the conditions used with benzoguanamine, ethanolamine and aceto- and phenylacetoguanamine gave compounds III and IV, respectively, but they were difficult to purify. The reaction of ethanolamine and melamine hydrochloride, however, was more complicated. Although the reaction went smoothly, the product was a water-soluble sirup which resisted all attempts at crystallization. From the analysis of the crude product, however, it did appear that it was mostly N,N′,N″-tris(2-hydroxyethyl)melamine[6] (V), probably contaminated to some degree by mono and bis compounds as well as by melamine itself. Under certain conditions (see Experimental) the crystalline N-(2-hydroxyethyl)melamine (VI) and N,N′,N″-tris(2-hydroxyethyl)melamine hydrochloride could be obtained in low yields from the reaction of melamine and ethanolamine.

The reaction with ethanolamine was extended to 3-amino-1-propanol. Thus, benzoguanamine hydrochloride and this amino alcohol gave under the usual conditions a good yield of N,N′-bis(3-hydroxypropyl)-benzoguanamine (VII). Although compound VII was a sirup which could not be obtained crystalline, it was adequately characterized by preparation of crystalline hydrochloride.

The attempts to extend the reaction of hydroxyalkylation of guanamines to secondary amines were fruitless. Thus, under the conditions used with primary

(1) Guanamine is a trivial name for 6-alkyl or -aryl-2,4-diamino-*sym*-triazine.

(2) J. T. Thurston, *et al.*, *J. Am. Chem. Soc.*, **73**, 2981 (1951), and papers following this.

(3) W. Zerweck and K. Keller, U. S. Patent 2,228,161 (Jan. 7, 1941).

(4) I. Honda, and Y. Oshima, *Yuki Gosei Kagaku Kyokai Shi*, **20**, 756 (1962); *Chem. Abstr.*, **58**, 5687 (1963).

(5) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **82**, 3971 (1960).

(6) N,N′,N″-Tris(2-hydroxyethyl)melamine has been prepared previously; see ref. 2.