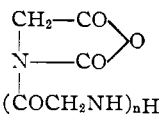
a semi-micro scale, and by partial alkaline hydrolysis.[2] We have now obtained further confirmation of the cyclo-(hexaglycyl) structure by application of the cyclization procedure of Sheehan and Richardson[1] to pentaglycylglycine azide. The latter was prepared from pentaglycylglycine methyl ester[4] which was converted to pentaglycylglycine hydrazide by treatment with hydrazine using a 30% solution of lithium chloride in methanol as solvent. Treatment with nitrous acid and cyclization again yielded cyclo-(hexaglycyl) (23% yield from the hydrazide, 8% over-all from pentaglycylglycine methyl ester). The identity of the materials has been established by comparison of the infrared spectra and of powder and single crystal X-ray photographs of cyclo-(hexaglycyl) with the compound prepared by us from diglycylglycine azide.

The analytical and recrystallization data recorded for cyclo-(hexaglycyl) and the "cyclo-(triglycyl)" of Sheehan and Richardson show certain discrepancies. "Cyclo-(triglycyl)" is described as forming a prismatic hemihydrate on crystallization from water which, if allowed to remain in contact with water, changes to fine needles of an anhydrous form. Cyclo-(hexaglycyl) prepared in these laboratories normally crystallizes from water as a prismatic hemihydrate showing inclined extinction; the formulation of this compound is supported by X-ray unit cell and density measurements. The material appears to be completely stable in contact with its aqueous mother liquor. The other principal forms observed by us are a monohydrate (analysis equivalent to the cyclo-tripeptide hemihydrate), and the anhydrous compound. The monohydrate, obtained by slow crystallization from water at low temperatures, rarely forms crystals of well defined prismatic habit and also appears to be stable in its aqueous mother-liquor. The only metastable modification encountered may be obtained by rapid cooling of hot aqueous solutions and forms fine needles showing parallel extinction. This form is converted to a mixture of the monohydrate and hemihydrate on standing in water at 25°.

The observation that cyclization of diglycylglycine azide yields the cyclic hexapeptide, and that the same material is the major cyclic product formed from N-carboxyglycine anhydride polymerization intermediates such as I, from which the



I, n = 1, 2, 3, etc.

formation of any cyclic peptide (excluding 2,5-diketopiperazine) is theoretically possible, indicates that, for this amino acid, the formation of the 18-membered ring is particularly favored. The other cyclic peptides isolated in lower yields from the N-carboxyglycine anhydride polymerization appear from molecular weight studies to be mixtures of the cyclic penta-, hepta- and possible octa-peptides which are not readily separable. These results indicate that the ease of cyclization of bifunctional peptide derivatives is not a simple function of chain length only, as has been suggested, for example, by Boissonas and Schumann.[5] Such would be the case only if the chains were perfectly flexible and if steric complications were absent. Clearly interaction between the CO and NH groups of the polypeptide chains could result in a very considerable loss of flexibility.

The great stability of cyclo-(hexaglycyl) is shown by its resistance to acid and alkaline hydrolysis, this compound being relatively unaffected by conditions causing a rapid breakdown of 2,5-diketopiperazine. Paper chromatographic studies of partial hydrolysates show the cyclic hexapeptide to be considerably more stable than any of its linear degradation products, glycine and glycylglycine being the only fragments readily observable during partial acid and alkaline hydrolysis.

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Soluble Ester Derivatives of Pentaerythritol Trinitrate

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The use of polynitrate esters as medicinal agents for the treatment of hypertension and as vasodilators has been practiced for many years. Materials such as mannitol hexanitrate, glyceryl trinitrate and pentaerythritol tetranitrate are examples of such compounds. Although these materials have proven to be valuable therapeutic agents, they are characterized by an extremely low degree of solubility in water and other body fluids. The recent availability of the polynitrato alcohol, pentaerythritol trinitrate,[1] has prompted work in this Laboratory toward the synthesis of polynitrate esters containing functional groups which were amenable to water solubilization.

Several monoacid esters of pentaerythritol trinitrate have been prepared by the esterification of this nitrato alcohol with dibasic acid anhydrides. In this manner pentaerythritol trinitrate was esterified with succinic, phthalic, glutaric and β,β-dimethylglutaric anhydrides. The reaction of pentaerythritol trinitrate with methylsuccinic anhydride gave a mixture of the α- and β-methyl hydrogen succinate esters which could not be separated. The monoacid esters thus obtained were then converted to their sodium salts for the purpose of providing water solubility. The pharmacological evaluation of these compounds is in progress and will be reported elsewhere. As a preliminary report, it has been shown that all of the compounds have a very pronounced hypotensive effect when given intravenously to anesthetized dogs.

Experimental[2]

Materials.—Pentaerythritol trinitrate was prepared by the method described by Marans, Elrick and Preckel.[1] Glutaric anhydride was prepared by the reaction of glutaric

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(2) Melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. The microanalyses were performed by H. L. Hunter, G. Maciak and Gloria Beckmann.

TABLE I

MONOACID ESTERS OF PENTAERYTHRITOL TRINITRATE $(O_2NOCH_2)_3—C—CH_2—O—\overset{O}{\overset{\|}{C}}—R$

R	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
o-C_6H_4COOH	35	125.0–125.5	$C_{13}H_{13}N_3O_{13}$	37.24	37.08	3.12	3.08	10.02	9.90
$HOC—CH_2CH_2CH_2—$	85.5	87–88	$C_{10}H_{16}N_3O_{13}$	31.17	31.33	3.92	4.09	10.90	10.83
$HOC—CH_2\overset{CH_3}{\overset{\|}{C}}CH_2—$	27.1	71.5–72.0[a]	$C_{12}H_{19}N_3O_{13}$	34.87	34.96	4.63	4.94	10.17	9.83

[a] Recrystallized from *n*-propyl alcohol.

acid and acetyl chloride.[3] Methylsuccinic acid[4] and β,β-dimethylglutaric acid[5] were dehydrated with acetic anhydride to form methylsuccinic anhydride[6] and β,β-dimethylglutaric anhydride.[7]

General Procedure.—Since all of the esters were prepared in the same general manner, only the preparation of pentaerythritol trinitrate hydrogen succinate is described in detail. The other compounds are described in Table I.

Pentaerythritol Trinitrate Hydrogen Succinate.—A mixture of 25 g. (0.092 mole) of pentaerythritol trinitrate, 16 g. (0.16 mole) of succinic anhydride and 150 ml. of dry acetone was heated under reflux for 8 hours. There were no signs of decomposition of the nitrate ester during this time. After removing the acetone under reduced pressure, the viscous residue was treated with an excess of aqueous sodium bicarbonate solution. The mixture was extracted with diethyl ether and the aqueous phase separated. This aqueous solution, on acidification with concentrated hydrochloric acid, deposited an oily material which quickly crystallized on cooling. The product was removed by vacuum filtration, washed well with cold water and dried to give 28.5 g. (83.5%) of a white crystalline solid, m.p. 91–92°. a sample for analysis was recrystallized from ethanol, m.p. 92–92.5°.

Anal. Calcd. for $C_9H_{13}N_3O_{13}$: C, 29.12; H, 3.53; N, 11.32. Found: C, 29.17; H, 3.62; N, 10.94.

The sodium salt was prepared by dissolving 5 g. (0.013 mole) of the acid ester in a solution of 1.05 g. (0.0125 mole) of sodium bicarbonate in 50 ml. of distilled water. Gentle warming was necessary to effect complete solution. After all of the solid had been dissolved, the water was removed under reduced pressure. The viscous residue was dissolved in 25 ml. of ethanol and diethyl ether added. The white, amorphous solid which precipitated was removed by filtering and dried in a vacuum desiccator. There was obtained 4.4 g. (84.5%) of material which did not have a definite melting point. The sample began to darken at 150° and was completely decomposed at 175°.

Anal. Calcd. for $C_9H_{12}N_3O_{13}Na\cdot{}^1/_2H_2O$: C, 26.87; H, 3.25; N, 10.44; Na, 5.72. Found: C, 26.98; H, 3.21; N, 10.15; Na, 6.01.

Esterification of Pentaerythritol Trinitrate with Methylsuccinic Anhydride.—A mixture of 5.4 g. (0.02 mole) of pentaerythritol trinitrate and 4.5 g. (0.04 mole) of methylsuccinic anhydride in 50 ml. of dry acetone was refluxed for 24 hours. After removing the acetone under reduced pressure, the residue was treated with an excess of aqueous sodium bicarbonate. The aqueous phase was extracted with diethyl ether, separated and then acidified with concentrated hydrochloric acid. An oily material separated which did not crystallize after long standing. It was extracted with diethyl ether, dried over anhydrous magnesium sulfate and the ether evaporated. This gave a viscous residue which, even after repeated attempts, failed to crystallize. It is postulated that the material was a mixture of the α- and β-methyl hydrogen succinate esters, and that this nonhomogenity accounts for its non-crystallinity. This reaction of methylsuccinic anhydride with an alcohol to give a mixture of isomeric products has been described previously.[8]

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A New Method for the Preparation of Diacyl Peroxides[1]

BY DELOS F. DETAR AND LOUIS A. CARPINO

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The usual methods for preparing diacyl peroxides utilize an acid chloride (or in some cases the anhydride) together with an aqueous solution of an alkali metal salt or of an alkaline earth salt of hydrogen peroxide in a variety of modifications.[2,3]

For most peroxides these methods are satisfactory. With acid chlorides that are susceptible to ready hydrolysis or which contain other functions capable of reacting with aqueous peroxidic solutions, the presence of water is detrimental.

A preliminary investigation has shown that the ether-soluble complex of hydrogen peroxide with dicyclohexylamine[4] and the complex of hydrogen peroxide with urea[5] can be used under anhydrous conditions to form benzoyl peroxide in moderate yields.

The new procedure gave a partial success with the acid chloride of *trans*-stilbene-2-carboxylic acid. A crude product containing 51–54% of peroxide was obtained whereas the usual procedures were completely unsuccessful. Up to the present time all attempts to prepare the peroxide of *o*-benzoylbenzoic acid by either the conventional or the new procedures have failed to give a peroxidic product. Some difficulty might have been anticipated since the acid chloride is reported to hydrolyze readily[6] and to react with methanol[7] to give the pseudo ester. On the other hand, ammonolysis of the acid chloride gives the normal amide. Preliminary at-

(1) This work was supported by National Science Foundation Grant NSF G439.

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