Synthesis of Tetramic Acids

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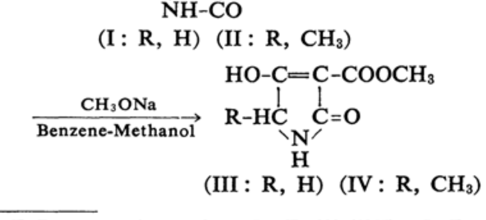
Recent interest has been shown in the study of acids concerning tetramic acid nucleus which was found to be a metabolic product obtained by micro-organisms[1].

There is only one report concerning the synthesis of tetramic acid in the case of α-acetyltetramic acids[2] which was prepared from α-amino acid esters and diketene. It was shown there that α-acetyltetramic acid is not a desirable intermediate for the preparation of tetramic acid itself because α-acetyl derivatives are resistant to alkaline hydrolysis.

In the present study, the synthesis of some tetramic acids was tried and the ultraviolet spectra of tetramic acid derivatives were measured.

In the first place, ethyl ethoxycarbonylacetaminoacetate (I) was prepared from ethyl α-aminoacetate and ethoxycarbonylacetyl chloride in the hope that the activation of the methylene group by the adjacent carboxyl group would facilitate the cyclisation to yield tetramic acid.



(I: R, H) (II: R, CH_3)

(III: R, H) (IV: R, CH_3)

When the acetate I was refluxed in benzene-metanol solution in the presence of the sodium methoxide, α-methoxycarbonyltetramic acid (III) was obtained in a 80% yield by the self-ester condensation. The formation of methyl ester may be attributed to the ester exchange between the ester and solvent methanol.

When ethyl α-aminopropionate was treated with ethoxycarbonylacetyl chloride in a cold alkaline solution, ethyl α-(ethoxycarbonylacetamino)propionate (II) was obtained as an oil. The treatment of the crude oily product with sodium methoxide in benzene-methanol gave α-methoxycarbonyl-γ-methyltetramic acid (IV).

Tetramic acid (V) was prepared from III by hydrolysis with aqueous barium hydroxide, followed by neutralisation. Similarly hydrolysis of IV gave γ-methyltetramic acid (VI). Tetramic acid and γ-methyltetramic acid liberated carbon dioxide from sodium hydrogen carbonate and gave a red color with ferric chloride.

The light-absorption properties of tetramic acid derivatives resemble that of tetronic acids and the spectrum of α-methoxycarbonyl-γ-methyl tetramic acid in aqueous solution exhibits pH dependence.

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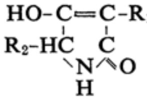
[1] T. Rosett et al., *Biochem. J.*, **67**, 390 (1957); C. E. Stickings, ibid., **74**, 232 (1959); C. E. Stickings and R. J. Townsent, ibid., **74**, 36 (1960).

[2] R. N. Racey, *J. Chem. Soc.*, **1954**, 850.

TABLE I. ULTRAVIOLET LIGHT ABSORPTION



Compound		Short wavelength		Long wavelength	
R_1	R_2	λ_{max}, mμ	ε_{max}	λ_{max}, mμ	ε_{max}
H	H (in water)	239	5.69×10^3	320	6.99×10^3
H	H (in 0.1 N NaOH)	240	6.57×10^3	312	8.00×10^3
$COOCH_3$	H (in water)	228	1.23×10^4	262	1.05×10^4
$COOCH_3$	CH_3 (in water)	228	1.31×10^4	263	1.04×10^4
$COCH_3$	H*	239	9.55×10^3	277	1.35×10^4
$COCH_3$	CH_3*	240	9.25×10^3	280	1.09×10^4
$COCH_3$	C_6H_5 (in 0.001 N NaOH)	242	1.04×10^4	282	1.35×10^4
$COCH_3$	$COOC_2H_5$** (in EtOH)	241	1.50×10^4	281	1.20×10^4

* Lacey (1954)

** The details of this compound will be published in the near future.

The absorption maximum of tetramic acid displays two bands at 239 mμ and 320 mμ, and the introduction of an α-alkoxycarbonyl group displaces the maximum to shorter wavelength. The introduction of α-acetyl group has little influence on the peak at 239 mμ, but the group causes a shift of the absorption maximum at 320 mμ to shorter wavelength.

Although the introduction of the γ-alkyl or aryl group has little influence on the absorption maximum and its intensity of the two bands, yet the presence of an γ-alkoxycarbonyl group shows an increase in intensity of the peak at 240 mμ.

In position and intensity of the absorption maximum α-methoxycarbonyl-γ-methyltetramic acid exhibits the two characteristic bands at 228 mμ and 263 mμ in aqueous solution at different pH value as follows.

TABLE II. THE pH VALUE EFFECT ON THE LIGHT ABSORPTION OF α-METHOXYCARBONYL-γ-METHYLTETRAMIC ACID IN WATER

pH	Short wavelength		Long wavelength	
	λ_{max}, mμ	ε_{max}	λ_{max}, mμ	ε_{max}
	228	1.31×10^4	263	1.05×10^4
11	229	2.63×10^4	263	2.14×10^4
3	230	2.08×10^4	257.5	1.34×10^4

Experimental

Ethyl Ethoxycarbonylacetaminoacetate (I):— Ethoxycarbonylacetyl chloride (22.5 g.) was added during 2 hr. to a mixture of ethyl α-aminoacetate hydrochloride (21 g.) and 50% potassium carbonate (100 ml.) at 0°C, and the mixutre set aside overnight, then extracted with chloroform. The chloroform-extracts were washed with cold water, dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue crystallized, m. p. 60~61°C, 27 g. (84%). Chromatography of this product on alumina afforded a pure crystalline substance, m. p. 64~65°C, on elution with benzene.

Found: C, 50.03; H, 7.21; N, 6.59. Calcd. for $C_9H_{15}O_5N$: C, 49.76; H, 6.96; N, 6.45%.

α-Methoxycarbonyltetramic Acid (III).—Ethyl ethoxycarbonylacetaminoacetate (21 g.) in benzene (100 ml.) was refluxed with agitation with a solution of sodium methoxide (from 2.3 g. of sodium and 40 ml. of methanol) for 3.5 hr. and set aside overnight. Water was added and the solvent layer extracted with water (2×60 ml.). The aqueous extracts were carefully acidified with concentrated sulfuric acid and then precipitated a crystalline product. This material was dissolved with aqueous sodium hydrogen carbonate, acidification of the solution with sulfuric acid precipitated α-methoxycarbonyltetramic acid. The white micro-crystals were washed with cold water, m. p. above 360°C (decomp.).

Found: C, 45.80; H, 4.46; N, 8.64. Calcd. for $C_6H_7O_4N$: C, 45.86; H, 4.49; N, 8.92%.

α-Methoxycarbonyl-γ-methyltetramic Acid (IV).—Ethoxycarbonylacetyl chloride (22.5 g.) was added during 2 hr. to a mixture of ethyl α-aminopropionate hydrochloride (23 g.) and 50% potassium carbonate (100 ml.) at 0°C, and the mixture set aside overnight, then extracted thoroughly with chloroform. The chloroform extracts were washed with cold water, dried on anhydrous sodium sulfate and the solvent evaporated at reduced pressure. The product was a pale yellow oil (28 g. 80%).

In order to remove traces of water from this product, it was dissolved in benzene, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 27.7 g. of the oil product which was used directly in the next step.

The above crude product (23 g.) in benzene (100 ml.) was refluxed with agitation with a solution of sodium methoxide (from 2.4 g. of sodium and 30 ml. of methanol) for 3 hr. and set aside overnight.

Water was added and the benzene layer was extracted with water.

The combined extracts were carefully neutralized with concentrated sulfuric acid and extracted thoroughly with chloroform. The organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to yield 15 g. of crude acidic product.

Recrystallization from ethyl acetate (or, better, methanol) yielded 13.5 g. (61%), m. p. 135～136°C.

Found: C, 49.64; H, 5.28; N, 8.11. Calcd. for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.18%.

Tetramic Acid (V).—α-Methoxycarbonyltetramic acid (1.5 g.) and 0.2 N barium hydroxide (50 ml.) were boiled under reflux for 3 hr., after cooling carefully concentrated hydrochloric acid was added to the mixture and then carbon dioxide was evolved.

The mixture was filtered and evaporated to a small volume at reduced pressure. After standing overnight tetramic acid separated as microcrystals from the solution. The product was washed with cold water, m. p. above 360°C. Yield, 0.65 g. (66%).

Found: C, 48.39; H, 5.15; N, 13.97. Calcd. for $C_4H_5O_2N$: C, 48.48; H, 5.09; N, 14.14%.

γ-Methyltetramic Acid (VI). — α-Methoxycarbonyl-γ-methyltetramic acid (1.7 g.) and 0.2 N barium hydroxide (50 ml.) were boiled under reflux for 2.5 hr. After cooling the mixture carefully neutralized with concentrated hydrochloric acid and then carbon dioxide evolution was observed. The solution was filtered, was concentrated in vacuo and microcrystals were obtained. Yield, about 0.67 g. (60%).

Found: N, 12.34: Calcd. for $C_5H_7O_2N$: N, 12.38%.

α-Acetyl-γ-phenyltetramic Acid. — Prepared by the use of Lacey's procedure from phenylglycine ester: m. p. 126°C.

Found: C, 66.36; H, 5.20; N, 6.38. Calcd. for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.10; N, 6.45%.

2,4-dinitrophenylhydrazone, m. p. 246°C.

Found: C, 54.66; H, 4.06; N, 17.24. Calcd. for $C_{18}H_{15}O_6N_5$: C, 54.41; H, 3.81; N, 17.63%.

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