methanol–NH_4OH crystallized from methanol in rods, m.p. 181–182°.

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.27; H, 8.48.

(b) *From* IIIb. A mixture of 10 ml. of 48% HBr and 1.3 g. of IIIb hydrobromide was refluxed vigorously for 20 min. The solid gradually changed to a fluid, dark oil. The mixture was ice cooled, and the aqueous layer was decanted. The residue was dried *in vacuo* then dissolved in 4 ml. of acetone. The solution was again evaporated to dryness *in vacuo*. The residue crystallized from 4 ml. of acetone in a yield of 1.0 g. (after cooling at −5°). It melted at 165–168° and was identical with the (±)-IIIa hydrobromide described above.

(−)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide. This levorotatory IIIa was prepared from (−)-Ia as described above for the conversion of (±)-Ia to (±)-IIIa. It melted at 284–287° and had $[\alpha]_D^{20}$ −84.1° (*c*, 1.12, 95% ethanol).

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.82; H, 7.02.

The *base* (prepared from the hydrobromide with aqueous methanolic NH_4OH) crystallized from aqueous methanol or absolute methanol in needles, m.p. 159–159.5°, $[\alpha]_D^{20}$ −122° (*c* 0.74, 95% ethanol).

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 81.94; H, 8.44.

(+)-2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide. As described in the conversion of (±)-Ia to (±)-IIIa above, (+)-Ia yielded (+)-IIIa hydrobromide, m.p. 284–287°, $[\alpha]_D^{20}$ +84.4° (*c* 1.47, 95% ethanol).

Anal. Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.65; H, 7.15.

The *base* crystallized from methanol in needles, m.p. 159–160°, $[\alpha]_D^{20}$ +120° (*c*, 0.60, 95% ethanol).

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.35; H, 8.41.

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BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE JOHNS HOPKINS UNIVERSITY, UNIVERSITY OF SANTA CLARA AND SAN JOSE STATE COLLEGE]

2,2′,2″-Tripyrrylmethenes[1,2]

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The potassium permanganate oxidation of 2,2′,2″-tripyrrylmethanes yields the corresponding methenes in varying yields. Di-2-(3,5-dimethyl-4-carbethoxy)pyrryl ketone was isolated as a by-product from the oxidation of 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane. 2,2′,2″-(3,3′,3″,5,5′,5″-Hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethene forms an inclusion compound with isooctane. Spectral properties of the methenes and prodigiosin are compared and differences noted.

2,2′,2″-Tripyrrylmethenes constitute a relatively unexplored class of organic compounds. Further interest in such compounds stems from Wrede and Rothhaas[4] suggestion that prodigiosin is 2,2′,2″-(4-*n*-amyl-4′-methoxy-5-methyl)tripyrrylmethene. Fischer and Gangl[5] reported the synthesis of two 2,2′,2″-tripyrrylmethenes by oxidation of the corresponding tripyrrylmethanes with lead dioxide in acetic acid. The tripyrrylmethanes can be synthesized by several procedures.[6–8] More recently, Treibs and Hintermeier[9] described the preparation of five other 2,2′,2″-tripyrrylmethenes through the condensation of an α,α′-dipyrryl ketone, or an α-carbo-t-butoxypyrrole, and an α-free pyrrole promoted with phosphorous oxychloride in chloroform. An attempt on our part to oxidize 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane to the methene by the procedure of Fischer and Gangl gave only a low yield of the methene, as attested by a microscopic examination of the reaction product. Hydrogen peroxide in aqueous acetic acid and oxygen in benzene gave a slight color change to the reaction mixture, indicative of only a small degree of oxidation. Since Corwin and Brunings[10] found that 2,2′-(3,3′,5,5′-tetramethyl-4,4′-dicarbethoxy)dipyrrylmethane can be oxidized to the corresponding dipyrrylmethene in a good yield with potassium permanganate, we were led to try the conversion of 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane to the tripyrrylmethene by this method. We have tried the oxidation at

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different conditions (Table I, Experimental) and have found that the tripyrrylmethene is easily obtained by this procedure in a yield up to 68%. The nature of the oxidation product was established through analysis and platinum catalyzed hydrogenation to the starting methane.[11] When the oxidation of the tripyrrylmethane was conducted with an excess of potassium permanganate and an extended reaction time was employed, the yield of the tripyrrylmethene was lowered noticeably and di-2-(3,4-dimethyl-4-carbethoxy)pyrryl ketone was isolated from the reaction mixture. This is as would be expected if the initially formed tripyrrylmethene were subsequently oxidized. By means of the permanganate oxidation of the appropriate tripyrrylmethanes we have also succeeded in synthesizing 2,2′,2″ - (4,4′,4″ - tricarbethoxy - 5,5′,5″-trimethyl)tripyrrylmethene (46%), 2,2′,2″-(3,4′,-4″,5 - tetracarbethoxy - 3′,3″,4,5′,5″ - pentamethyl)-tripyrrylmethene (36%) and 2,2′,2″-(3,4′,4″,5-tetracarbethoxy - 4,5′,5″ - trimethyl)tripyrrylmethene(11%).

2,2′,2″ - (3,3′,3″,5,5′,5″ - Hexamethyl - 4,4′,4″-tricarbethoxy)tripyrrylmethene was found to form an inclusion compound with isooctane containing 2.358 moles of the methene per mole of isooctane when an attempt was made to crystallize the methene from the latter. Crystallization of the inclusion compound from ethyl alcohol yielded the methene.

The ultraviolet-visible absorption characteristics for isopropyl alcohol solutions of the tripyrrylmethenes and the absorption maxima in the visible portion of the spectrum for acidified isopropyl alcohol solutions are recorded in Table II (Experimental). The band occurring in the visible region of the spectrum of 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethene is remarkable in comparison with the same band of the other tripyrrylmethenes, in that it is broader and the contour suggests three bands close together. The closest approach to this is in the spectrum of 2,2′,2″-(3,3′,3″,-5,5′,5″ - hexamethyl - 4,4′,4″ - tricarbethoxy)tripyrrylmethene, which bears a faint resemblance. The change in the spectrum of 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethene upon acidification in contrast with the change in the spectra of the other compounds under the same circumstances is equally noteworthy. Hubbard and Rimington[12] considered that the spectrum of 2,2′,2″(3-bromo - 3′,3″,4,5′,5″ - pentamethyl - 4′,4″ - 5 - tricarbethoxy)tripyrrylmethene[5] lends support to the Wrede and Rothhaas formula for prodigiosin. On the other hand, Treibs and Hintermeir[9] have stated that the absorption curves, not included in their report, and properties of the tripyrrylmethenes prepared by them do not give any support to the Wrede and Rothhaas proposal for prodigiosin. We have compared the spectrum of prodigiosin (ϵ_{max} 4.3 × 10^4 at 466 mμ)[13] and prodigiosin perchlorate (ϵ_{max} 11.5 × 10^4 at 540 mμ)[13] in isopropyl alcohol with those of the tripyrrylmethenes described in the present paper and similarly have not found evidence favoring the Wrede formula. Two weak bands shown by prodigiosin at 280 and 336 mμ are missing in the spectra of the tripyrrylmethenes. Models show that in the tripyrrylmethenes methyl or carbethoxy substituents in the 3 positions of the rings should offer greater hindrance to the three rings approaching coplarity than in a molecule free of these substituents. From this standpoint 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″ - trimethyl)tripyrrylmethene should be more like prodigiosin than any of the others. However, this is not exactly the case. Furthermore, the shift in the visible band upon acidification of this methene is less like that for prodigiosin than any of the others, although the intensity of the bands are comparable. A comparison of the infrared spectra (KBr) of the tripyrrylmethenes with that of prodigiosin reveals that a strong band in the spectrum of the latter occuring at 6.16 μ, which is appropriate to a C=N stretching[13] is not found in the spectra of the tripyrrylmethenes. Instead, these compounds show only a weak band at around 6.13 μ, or the band is not apparent.

EXPERIMENTAL[14]

2,2′,2″-Tripyrrylmethanes. The tripyrrylmethanes were synthesized by the method of Feist[6] and purified by crystallization from 95% ethyl alcohol, or a mixture of 95% ethyl alcohol and water. In this fashion 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethane, m.p. 239.5–240.0° (dec.) (lit.[15] 246°), was obtained from 2-formyl-4-carbethoxy-5-methylpyrrole and 2-methyl-3-carbethoxypyrrole; 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane, m.p. 199° (dec.) (lit.[16] 194°), from 2-formyl-3,5-dimethyl-4-carbethoxypyrrole and 2,4-dimethyl-3-carbethoxypyrrole; 2,2′,2″-(3,4′,4″,5-tetracarbethoxy-3′,3″,4,5′,5″-pentamethyl)tripyrrylmethane, m.p. 190–192° (dec.) (lit.[7] 194°), from 2-formyl-3,5-dicarbethoxy-4-methylpyrrole and 2,4-dimethyl-3-carbethoxypyrrole. A new tripyrrylmethane, described here, was synthesized by the same procedure.

The reaction of 0.54 g. of 2-formyl-3,5-dicarbethoxy-4-methylpyrrole with 0.685 g. of 2-methyl-3-carbethoxypyrrole yielded 0.495 g. (20%) of 2,2′,2″-(3,4′,4″,5-tetracarbethoxy-4,5′,5″-trimethyl)tripyrrylmethane, a lightt an, almost white, solid, m.p. 197.5–198.0° (dec.).

(11) Treibs and Hintermeir[9] describe the reduction of 2,-2′,3″-(2″,4″,5,5′-tetramethyl-4,4′5″-tricarbethoxy)tripyrrylmethene to the methane with zinc dust and acetic acid. Using this same procedure they report that 2,2′,2″-(3,3′,3″,-5,5′,5″-hexamethyl-4,4′,4″- tricarbethoxy)tripyrrylmethene yields a product (analysis not given), m.p. 265–267°.

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Anal. Calcd. for $C_{28}H_{35}O_8N_3$: C, 62.09; H, 6.51; N, 7.76. Found: C, 61.95; H, 6.65; N, 7.83.

2,2′,2″-(3,3′,3″,5,5′,5″-Hexamethyl-4,4′,4″-tricarbethoxy)-tripyrrylmethene. The following procedure for one experiment is illustrative of that used in the different experiments for the synthesis of this compound, as well as for the syntheses of the other tripyrrylmethenes described later. Detailed variations are given at the appropriate points.

A 0.775 g. sample of 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethane was dissolved in 30 ml. of acetone with heating. The acetone was previously purified by refluxing with potassium permanganate and then distilling. The solution of the tripyrrylmethane was cooled to room temperature and stirred, while 5.65 ml. of a solution of potassium permanganate containing 0.1611 g. of the salt was added within a short time. Stirring was continued until a total of 10 min. had elapsed from the initial addition of the permanganate. The manganese dioxide that had precipitated was filtered off on a sintered glass filter and washed with a little acetone. The red filtrate and washing were combined and evaporated leaving a mixture of a red solid, showing some green sheen, and water. The water was removed by filtration and the residue was crystallized from 95% ethyl alcohol. The resulting tripyrrylmethene, an orange solid melting at 202.0–210.2° (dec.) weighed 0.3189 g. Most of this product melted with decomposition at 207.1–210.2°. An additional 0.1149 g. (combined yield 56%) of the tripyrrylmethene, m.p. 209.0–214.0° (dec.) was obtained from the mother liquor. A recrystallized sample of the methene placed on the heating block at 195–196°, melted with decomposition at 210.7–211.6°.

Anal. Calcd. for $C_{28}H_{35}O_6N_3$: C, 65.99; H, 6.92; N, 8.25. Found: C, 65.93; H, 7.00; N, 8.23.

A mixture of 0.517 g. of the methene in 40 ml. of 95% ethyl alcohol and 0.2732 g. of platinum oxide was shaken under hydrogen at 25.5° and 759 mm. until the uptake of hydrogen appeared to have ceased. During this period the solution changed from an initial red color to a light yellow. The hydrogenated product, a white solid, was recrystallized from alcohol and melted with decomposition at 193–194°. The infrared absorption spectra of the reduction product and authentic tripyrrylmethane were identical.

Anal. Calcd. for $C_{28}H_{37}O_6N_3$: C, 65.73; H, 7.29; N, 8.21. Found: C, 66.14; H, 6.96; N, 8.12.

TABLE I

PERMANGANATE OXIDATION OF 2,2′,2″-(3,3′,3″,5,5′,5″-HEXAMETHYL-4,4′,4″-TRICARBETHOXY)-TRIPYRRYLMETHANE[a]

Expt. No.	Methane (g.)	Eqs. $KMnO_4$[b] / Eq. Methane	Reaction[c] Time (Min.)	Methene %	Methene M.p. (dec.)
1	0.47	0.83	10	31	—[d]
2	0.775	1.009	10	56	—[e]
3	6.16	1.047	—	68	214.0–215.0°
4	0.94	1.65	45	18	206.9–208.0°

[a] Acetone was used as a solvent for all experiments except No. 4 where dioxane was employed. [b] Calculated for: 3Tripyrrylmethane + $2MnO_4^-$ = 3Tripyrrylmethene + $2MnO_2$ + $2OH^-$ + $2H_2O$. [c] Disappearance of the permanganate color was completed before the time shown, but stirring of the mixture was continued until the stated period had elapsed. [d] Collected in two fractions: 0.1115 g., m.p. 202.0–208.1°, and 0.0354 g., m.p. 202.0–205.0° (bulk). [e] Collected in two fractions, see preceding detailed experimental description.

Several oxidations were performed at different conditions and these are summarized in the following table. The previously described oxidation is included for the purpose of comparison.

Di-2-(3,5-dimethyl-4-carbethoxy)pyrryl ketone, weighing 0.140 g., was isolated as a dull orange colored solid from the alcohol mother liquors of the tripyrrylmethene from Experiment 4. After one recrystallization from ethyl alcohol the melting point was 223.1–228.4°. The recrystallized product was still orange in color, but when crushed it gave a white solid The color was apparently due to adsorbed methene. A mixture melting point with authentic di-(2,4-dimethyl-3-carbethoxy)pyrryl ketone,[17] m.p. 225.4–228.4°, gave no depression and the infrared spectra of the two were found to be the same.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.19; H, 6.74; N, 7.38.

2,2′,2″-(3,3′,3″,5,5′,5″-Hexamethyl-4,4′,4″-tricarbethoxy)-tripyrrylmethene—isooctane inclusion product. A sample of the methene, m.p. 210.1–211.0° (dec.) was recrystallized from isooctane. The orange crystals that formed melted and resolidified in the range 101.0–122.3° and as the temperature was raised remelted at 200.0–203.0° (dec.). In another experiment the first transition was completed for the most part at 108.6–110.1° with droplets remaining at 119.0°. The final melting occurred at 200.0–203.7° (dec.). In a third experiment, the first change occurred at 109.0–121.0°. The ultraviolet-visible absorption spectrum of the inclusion product in isopropyl alcohol is the same as that of the methene when one calculates the molecular extinction coefficients for the different wave lengths for the inclusion product on the basis of the methene content determined by analysis.

Anal. Calcd. for $(C_{28}H_{35}O_6N_3)_{2.35}(C_8H_{18})$: C, 67.57; H, 7.70; N, 7.53. Found: C, 67.57; H, 7.59; N, 7.30.

Upon recrystallization from 95% ethyl alcohol the methene, m.p. 206.5–208.0° (dec.) was recovered. A mixture melting point with authentic 2,2′,2″-(3,3′,3″,5,5′,5″-hexamethyl-4,4′,4″-tricarbethoxy)tripyrrylmethene showed no depression.

2,2′,2″-(4,4′,4″-Tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethene. A solution of 1.3953 g. of 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethane in 100 ml. of acetone was treated with 9.77 ml. of an aqueous solution containing 0.3134 g. of potassium permanganate in a manner similar to that used in the preceding tripyrrylmethene synthesis. After recrystallization from 95% ethyl alcohol, 0.6351 g. (46%) of red crystalline 2,2′,2″-(4,4′,4″-tricarbethoxy-5,5′,5″-trimethyl)tripyrrylmethene, m.p. 227.5–229.0° (dec.) was obtained. Using a slower heating rate a recrystallized sample was found to melt with decomposition at 221.9–223.3°.

Anal. Calcd. for $C_{25}H_{29}O_6N_3$: C, 64.22; H, 6.25; N, 8.99. Found: C, 64.24; H, 6.24; N, 8.76.

2,2′,2″-(3,4′,4″,5-Tetracarbethoxy-3′,3″,4,5′,5″-pentamethyl)tripyrrylmethene. A 0.9 g. sample of 2,2′,2″-(3,4′,4″,5-tetracarbethoxy-3,3″,4,5′,5″-pentamethyl)tripyrrylmethane in 2.5 ml. of acetone was oxidized with 0.1668 g. of potassium permanganate in 5.85 ml. of aqueous solution as in the foregoing examples. 2,2′,2″-(3′,4′,4″,5-Tetracarbethoxy-3′,3″,4,5′,5″-pentamethyl)tripyrrylmethene, 0.3198 g. (36%), was obtained as red-orange crystals from a mixture of alcohol and water. When heated, the crystals reddened and appeared to soften, especially around 173–174°, and melted with decomposition at 176.0–177.9°.

(17) Kindly synthesized by P. E. Berteau by the method of H. Fischer and H. Orth, *Ann.*, **489**, 78 (1931).

Anal. Calcd. for $C_{30}H_{37}O_8N_3$: C, 63.47; H, 6.57; N, 7.40. Found: C, 63.47; H, 6.69; N, 7.27.

2,2′,2″-(3,4′,4″,5-Tetracarbethoxy-4,5′,5″-trimethyl)tripyrrylmethene. A 0.3216 g. sample of 2,2′,2″-(4,5′,5″-trimethyl-3,4′,4″,5-tetracarbethoxy)tripyrrylmethane in 20 ml. of acetone was oxidized with 0.06255 g. of potassium permanganate in 1.95 ml. of water. Crystallization of the reaction product from 95% ethyl alcohol yielded a mixture of red and yellow colored solids. After stirring the mixture twice with acetone and three times with 95% ethyl alcohol most of the yellow solid was dissolved. The red solid that remained and that obtained upon concentration of the combined extracts were combined and crystallized from 95% ethyl alcohol yielding 0.0210 g. of the red crystalline methene, m.p. 221.9–223.0° (dec.). Considering the recovered tripyrrylmethane (below) the yield of methene is 11%.

Anal. Calcd. for $C_{28}H_{33}O_8N_3$: C, 62.32; H, 6.16; N, 7.79. Found: C, 62.45; H, 6.37; N, 8.37.

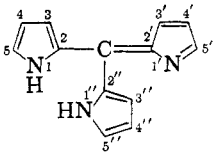
The residue from the tripyrrylmethene mother liquors in 95% ethyl alcohol was applied to a column of Woelm's Alumina (non-alkaline, activity grade I) and the chromatogram was developed with ethyl ether. The lower, broad, tan colored zone was eluted with ether, the solution was evaporated, and the residue was crystallized from 95% ethyl alcohol yielding 0.1305 g. of orange-tan crystals of the methane, m.p. 197.0–198.3° (dec.). The product when crushed appeared as a white powder. The infrared spectrum of this compound is identical with that of the starting methane.

Anal. Calcd. for $C_{28}H_{35}O_8N_3$: C, 62.09; H, 6.51; N, 7.76. Found: C, 62.31; H, 6.55; N, 7.68.

Ultraviolet-Visible Absorption Spectra. Solutions of the tripyrrylmethenes in isopropyl alcohol were examined. Measurements were made with a Beckman Model DU or a Cary Model 11M Spectrophotometer. The results are presented in the following table.

TABLE II

ULTRAVIOLET-VISIBLE ABSORPTION SPECTRA FOR 2,2′,2″-TRIPYRRYLMETHENES



Substituents	Isopropyl Alcohol λ_{max}	Isopropyl Alcohol $\epsilon \times 10^{-3}$	Isopropyl alcohol plus $HClO_4$[a] λ_{max}	Isopropyl alcohol plus $HClO_4$[a] $\epsilon \times 10^{-3}$
4,4′,4″-Tricarbethoxy-5,5′,5″-trimethyl	490	43.1	487	115.7
	465–470	42.0		
	435–440[b]	33.1		
	245–250[c]	14.7		
	220[d]	38.3		
3,3′,3″,5,5′,5″-Hexamethyl-4,4′,4″-tricarbethoxy	486	38.3	497	82.1
	255[e]	13.3		
	224	39.3		
3,4′,4″,5-Tetracarbethoxy-3′,3″,4,5′,5″-pentamethyl	475	40.0	524	51.2
	264	23.1	486[f]	26.1
	220	48.4		
3,4′,4″,5-Tetracarbethoxy-4,5′,5″-trimethyl	460–466	36.1	512	71.9
	262	20.2		
	220[d]	39.8		

[a] One milliliter of 10% aqueous perchloric acid per 100 ml. of solution. [b] Only long wave length maximum recorded. [c] Shoulder on ascending limb. [d] End absorption, not necessarily a maximum. [e] Inflection on ascending limb. [f] Inflection on descending limb.

SANTA CLARA, CALIF.

[FROM THE CLAYTON FOUNDATION BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

O-(Substituted)-α-amino-β-hydroxybutyric Acids

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The *O*-carbamyl derivatives of DL-threonine and DL-allothreonine, and *O*-carbazyl-DL-threonine were prepared from the corresponding carbobenzoxy-amino acid benzyl esters by condensation with phosgene followed by ammonia or *N*-carbobenzoxyhydrazine, and then hydrogenolysis, to produce the carbamyl- and carbazyl- derivatives, respectively. In contrast to the comparable serine derivatives, these compounds were not effective metabolic antagonists in several microbiological assays.

Both *O*-carbamyl- and *O*-carbazyl- derivatives of DL-serine have been prepared and found to be competitive antagonists of glutamine in several microörganisms.[1,2] The sulfur analogue of the former compound, *S*-carbamylcysteine,[3] is also an inhibitory amino acid derivative; however, glutamine does not competitively reverse its toxicity, and in this respect it is similar to azaserine[4] an antitumor agent.[5] The antitumor activity of several of these analogs[6] prompted the synthesis and biological testing of a number of additional *O*-(substituted carbamyl)serine derivatives.[7]

In the present investigation, the *O*-carbamyl- derivatives of both threonine and allothreonine,

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