hemihydrate. Anal. ($C_{20}H_{25}NO_3 \cdot C_4H_6O_6 \cdot 0.5H_2O$) C, H, N.

Intermediate **14d** was obtained in 50% yield after chromatography. Hydrogenation yielded a foam, which gave 1.4 g (88%) of crystalline **15d**, mp 195–198 °C, on trituration with EtOH. Recrystallization from EtOH gave pure **15d**, mp 210–213 °C. Anal. ($C_{25}H_{27}NO_3$) C, H, N.

Intermediate **14e** was obtained in 44% yield after chromatography. Hydrogenation of crude material containing **14e** gave a 36% yield of **15e**. The HCl salt was obtained in crystalline form, mp 77–80 °C, from EtOH. After drying under high vacuum at room temperature overnight, **15e**·HCl gave a mp of 105–115 °C. Anal. ($C_{23}H_{31}NO_3 \cdot HCl$) C, H, N.

Intermediate **14f** was not purified but directly reduced to **15f**, which was obtained in 50% yield after chromatography. The HCl salt, mp 191–195 °C, was obtained as the EtOH solvate from EtOH–$Et_2O$. Analysis, after drying at 80 °C under high vacuum, of **15f**·HCl indicated the presence of 0.7 mol of EtOH: mass spectrum, *m/e* 369 ($M^+$, 81), 312 ($C_4H_9$, 100). Anal. ($C_{23}H_{31}NO_3 \cdot HCl \cdot 0.7C_2H_6O$) C, H, N.

**7-(2-Ethoxypropenylidene)dihydrocodeinone (17).** α-Ethoxyvinyllithium was prepared under argon by the dropwise addition of *t*-BuLi (18 mmol) to ethyl vinyl ether (2.34 g, 32.4 mmol) in THF (25 mL) at −55 °C. The mixture was warmed to 0 °C while the yellow precipitate which formed dissolved to give a clear solution. The solution was recooled to −60 °C and added slowly to a solution of **11** (5.3 g, 15 mmol) in THF (300 mL) kept at −30 °C under argon. Stirring was continued for 30 min at this temperature, and the mixture was then allowed to warm to 0 °C. The mixture was quenched and processed in the usual manner to give **17** (5.3 g, 93%) as a foam, which contained traces of impurities by TLC: NMR δ 6.70 (wide s, 3 H, aromatic and =CH), 4.57 (s, 1 H, H-5), 4.44 (br, 2 H, $=CH_2$), 1.30 (t, $OCH_2CH_3$).

**17,19-Dimethyl-4,5-epoxy-3-methoxyfuro[*b*-6,7]- (18) and -18*H*-pyrrolo[*b*-6,7]morphinan (19).** To a solution of **17** (3.00 g, 7.86 mmol) in EtOH (60 mL) was added 1 N HCl (18 mL) and 10% Pd/C (0.6 g), and the mixture was hydrogenated at an initial pressure of 50 psi for 2 h. The catalyst was removed by filtration, and the filtrate was made basic with $NH_4OH$ and extracted with $CHCl_3$. The $CHCl_3$ extracts were processed in the usual fashion and evaporated to give 2.7 g of a foam, which was chromatographed. First eluted was **18** (792 mg, 30%). Crystallization from EtOH gave pure **18**: mp 140–141 °C; NMR δ 6.72 (s, aromatic), 5.72 (br s, 1 H, H-18), 5.45 (br s, 1 H, H-5), 3.86 ($OCH_3$), 2.47 ($NCH_3$), 2.25 (s, 19-$CH_3$). Anal. ($C_{21}H_{23}NO_3$) C, H, N. Next eluted was **19** (807 mg, 31%), which gave crystals containing 0.5 mol of solvent, mp 185–189 °C, from ethanol: NMR δ 8.30 (br s, exchangeable, NH), 6.70 (s), 5.58 (unsymmetrical s, 2 H, H-5 and H-18), 2.13 (s, 19-$CH_3$). Anal. ($C_{21}H_{24}N_2O_2 \cdot 0.5C_2H_6O$) C, H, N.

**17-(2-Ethoxypropenylidene)dihydrocodeine (20).** A solution of **17** (2.0 g, 5.2 mmol) in MeOH (50 mL) was cooled in an ice bath, and $NaBH_4$ (0.1 g, 2.6 mmol) was added in one portion. The mixture was stirred in the cold for 20 min; then the excess of borohydride was destroyed by the careful, dropwise addition of HOAc so that the mixture remained basic to moist pH paper. The solvent was evaporated and the residue processed in the usual fashion to give a light yellow foam (2.0 g), which was shown by TLC to be an ~9:1 mixture of 6α/6β **20**.

**7-(2-Oxopropyl)dihydrocodeine (21).** The foam obtained above was dissolved in MeOH (20 mL), and 1 N HCl (8 mL) was added. The solution was stirred for 20 min and then made basic with concentrated $NH_4OH$, and the mixture was evaporated. Processing in the usual fashion gave 1.84 g of a foam, which showed one major spot on TLC. The foam was dissolved in 95% EtOH (25 mL), 1 N HCl (8 mL) and 10% Pd/C (0.3 g) were added, and the mixture was hydrogenated at 50 psi for 1 h. Workup in the usual fashion gave a foam, which was chromatographed to give 838 mg (45%) of **21**. Two crystallizations from EtOH gave pure **21**: mp 71–73 °C; NMR δ 4.62 (d, 1 H, H-5, $J$ = 6 Hz). Anal. ($C_{21}H_{27}NO_4$) C, H, N.

**7-(2-Hydroxy-2-methylpropyl)dihydrocodeine (22).** A solution of **21** (1.07 g, 3.0 mmol) in toluene (15 mL) was added dropwise to a 0 °C solution of MeLi (7.5 mmol) in $Et_2O$ (30 mL) under argon. Stirring was continued for 20 min and the mixture was quenched with water and processed in the usual manner to give a foam, which was chromatographed. Pure fractions were combined to give 824 mg (74%) of **22** as a foam. The tartrate salt of **22** could not be obtained in crystalline form. Anal. ($C_{22}H_{31}NO_4 \cdot C_4H_6O_6 \cdot H_2O$) C, H, N.

***N*-(Cycloalkylmethyl)-7α-methyl-14-hydroxydihydromorphinone (26).** A mixture of **23** (10 mmol) and DMF-DMA (10 mL) was refluxed in an oil bath for 3–4 h. The crystals which formed on cooling the mixture in ice were collected and washed with $Et_2O$ to give **25H** (37% yield), mp 253–258 °C dec, or **25P** (40% yield), mp 223–226 °C. **25B** was not isolated from the mixture but directly hydrogenated. Intermediates **25** were hydrogenated in 95% EtOH as above to give **26H** directly in 95% yield as impure crystals, mp 220–226 °C. Chromatography, followed by crystallization from EtOH, gave **26H**·0.5$H_2O$, mp 230–233 °C dec (lit.[5] mp 226–228 °C). Anal. ($C_{19}H_{23}NO_4 \cdot 0.5H_2O$) C, H, N. **26P** was obtained in 62% yield after chromatography and obtained as crystals, mp 113–114 °C, from EtOH. Anal. ($C_{22}H_{27}NO_4$) C, H, N. **26B** was obtained in 24% overall yield from **23B** and was converted to the *d*-tartrate monohydrate, mp 200–203 °C. Anal. ($C_{23}H_{29}NO_4 \cdot C_4H_6O_6 \cdot H_2O$) C, H, N.

Compounds **26** were O-demethylated to **27** by use of $BBr_3$ in $CHCl_3$ as reported for **8** above. Chromatography gave **27P** in 50% yield, which gave a crystalline hemisolvate from EtOH. Anal. ($C_{21}H_{25}NO_4 \cdot 0.5C_2H_6O$) C, H, N. **27B** was obtained in 47% yield as a crystalline solid, mp 194–197 °C, from EtOH. Anal. ($C_{22}H_{27}NO_4$) C, H, N.

**Acknowledgment.** The authors thank Drs. R. N. Schut and J. E. Villarreal for their continued interest and encouragement.

# Methotrexate Analogues. 14. Synthesis of New γ-Substituted Derivatives as Dihydrofolate Reductase Inhibitors and Potential Anticancer Agents

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The γ-*tert*-butyl ester (**1**), γ-hydrazide (**2**), γ-*n*-butylamide (**3**), and γ-benzylamide (**4**) derivatives of methotrexate (MTX) were synthesized from 4-amino-4-deoxy-$N^{10}$-methylpteroic acid (APA) and the appropriate blocked L-glutamic acid precursors with the aid of the peptide bond forming reagent diethyl phosphorocyanidate. The affinity of these side chain modified products for dihydrofolate reductase (DHFR) from *Lactobacillus casei* and L1210 mouse leukemic cells was determined spectrophotometrically or by competitive radioligand binding assay, and their cytotoxicity was evaluated against L1210 leukemic cells in culture. The results provide continuing support for the view that the "γ-terminal region" of the MTX side chain is an attractive site for molecular modification of this anticancer agent.

Previous work in this laboratory[1,2] and others[3,4] has shown that the γ-terminus of the glutamate side chain in methotrexate (MTX) is a region of significant "bulk tolerance"[5]—i.e., that large changes in chemical structure

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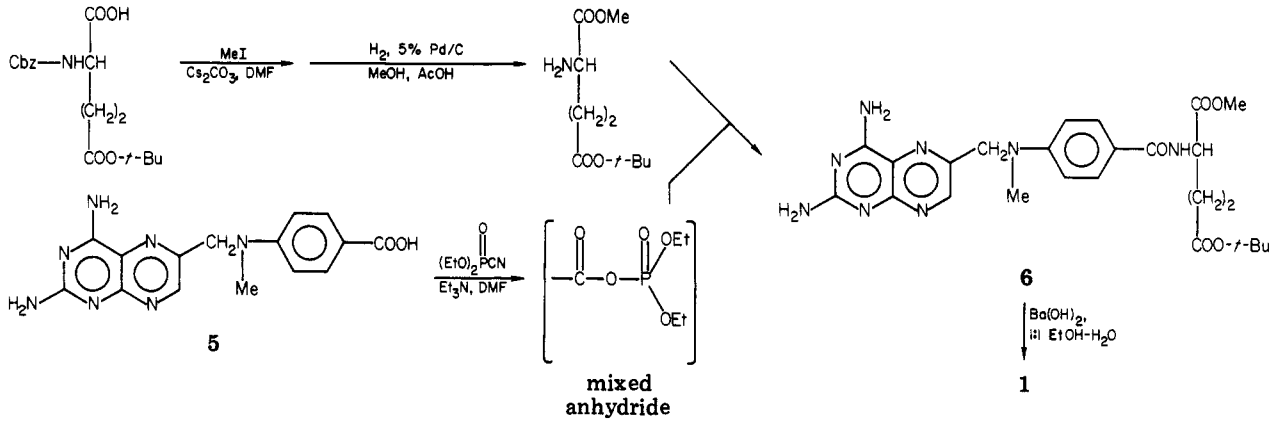
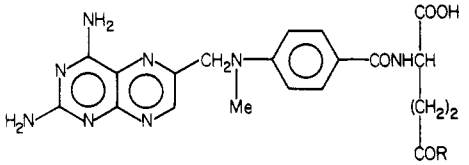
Scheme I




can be made in this portion of the molecule without greatly altering its affinity for the target enzyme dihydrofolate reductase (DHFR).

On this basis, a reasonable approach to the design of new MTX analogues with increased antitumor selectivity, a qualitatively modified therapeutic spectrum, or a more prolonged duration of pharmacological action might be to replace the γ-COOH group by other functional groups, such as esters or amides. Depending on whether cleavage of the ester or amide bond occurs in vivo, such compounds could either act as antifols by themselves or else behave as prodrugs of MTX with potentially useful sustained release properties.[6,7] An important difference between the parent compound MTX and its γ-substituted derivatives would be the inability of the latter to give polyglutamates.[8-10] The latter are known to form in significant amounts from MTX in certain organs, such as the liver and kidney, where they may give rise to unwanted toxicity due to prolonged intracellular retention.

The present paper reports the chemical synthesis and in vitro biological activity of three new γ-substituted MTX derivatives: the γ-*tert*-butyl ester **1**, the γ-hydrazide **2**,




**1**, R = O-*t*-Bu
**2**, R = $NHNH_2$
**3**, R = NH-*n*-Bu
**4**, R = $NHCH_2C_6H_5$

and the γ-*n*-butylamide **3**. The γ-benzylamide **4**[3] was also prepared, as was the heretofore unknown α isomer of **1**. All five compounds and several of the intermediates were tested for their ability to bind to DHFR from *L. casei* and L1210 mouse leukemia cells in culture and were assayed for cytotoxicity to intact L1210 cells in culture.

Compounds **1**–**4** were prepared from 4-amino-4-deoxy-$N^{10}$-methylpteroic acid (APA, **5**), which is accessible via any of three known methods of de novo chemical synthesis[11-13] or, more expeditiously, by cleavage of MTX with carboxypeptidase $G_1$.[14,15] Attachment of C-protected amino acids to APA has, until now, relied mainly on the traditional alkyl chloroformate coupling method.[1,16,17] Diphenylphosphoryl azide[18] has been found useful in converting APA into simple amides,[17] but the intermediate acyl azide is apparently too chemically inert to react with α-amino acid esters. Further complications are introduced, as well, by the tendency of the azide to undergo Curtius rearrangement to an isocyanate that can react with amino acid esters to give subsituted ureas.[15] We have now found, however, that the coupling reagent diethyl phosphorocyanidate[19,20] is much more effective than alkyl chloroformates or diphenylphosphoryl azide in bringing about condensation of APA with C-protected amino acids, including the glutamic acid derivatives described here. Use of this reagent thus represents a significant methodologic advance in the area of MTX analogue synthesis.

*N*-Carbobenzoxy-L-glutamic acid γ-*tert*-butyl ester was treated with cesium carbonate and excess methyl iodide in DMF,[21] and the Cbz group was removed by catalytic

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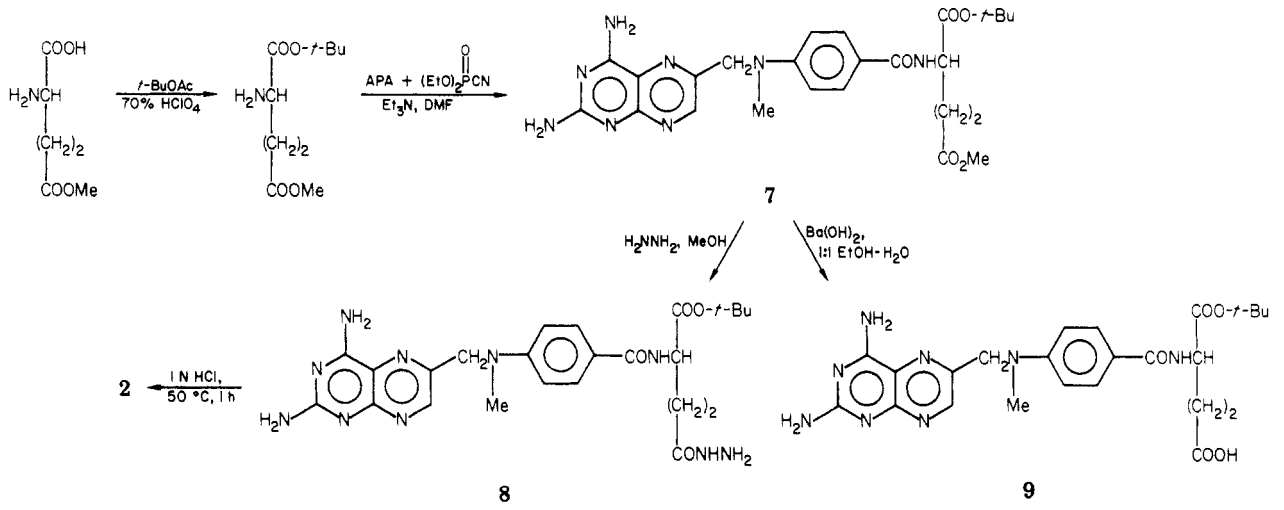
Scheme II

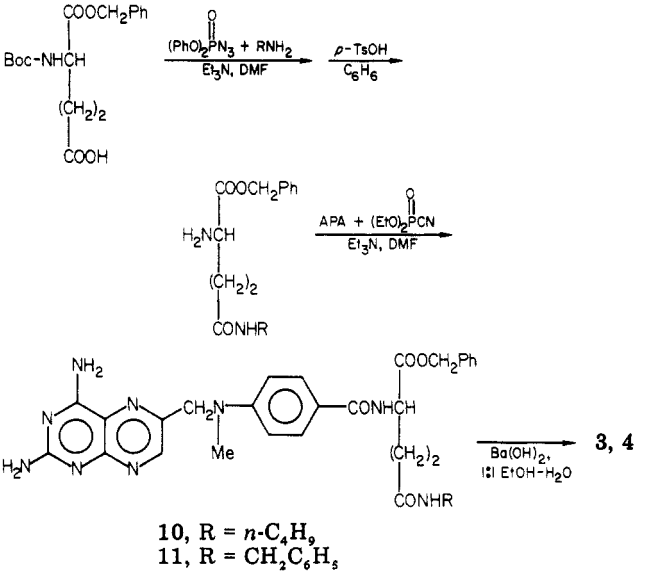


hydrogenolysis over 5% Pd/C to obtain L-glutamic acid γ-*tert*-butyl α-methyl ester (85%) (Scheme I). This was a noncrystalline product but was TLC homogeneous and fully characterized on the basis of IR and NMR spectra. The oily amino ester was added directly at room temperature to the putative carboxylic–diethylphosphoric anhydride generated in situ from APA and diethyl phosphorocyanidate[19,20] on heating at 80 °C for 2 min in DMF containing triethylamine. Heating at 80 °C for another 2 h, followed by solvent evaporation under reduced pressure and column chromatography on silica gel, afforded MTX γ-*tert*-butyl α-methyl ester (**6**, 67%). Selective hydrolysis of the α-methyl ester by overnight stirring with barium hydroxide (1 equiv) in 50% aqueous ethanol then led to the γ-ester **1** (92%).

Esterification of L-glutamic acid γ-methyl ester with *tert*-butyl acetate in the presence of 70% perchloric acid (Scheme II) led to the oily α-*tert*-butyl γ-methyl ester (81%), which on direct condensation with APA as described above produced MTX α-*tert*-butyl γ-methyl ester (**7**, 76%). Reaction of the diester with hydrazine in methanol solution at 4 °C for 60 h yielded the α-*tert*-butyl γ-hydrazide **8** (60%), and acidolysis of the *tert*-butyl ester with 1 N HCl at 50 °C for 1 h, followed by ion-exchange chromatography on DEAE-cellulose, gave the desired γ-hydrazide **2** (45%). Gentle barium hydroxide treatment converted **7** to MTX α-*tert*-butyl ester (**9**, 81%).

For the synthesis of the γ-*n*-butylamide **3** (Scheme III), *N*-(*tert*-butyloxycarbonyl)-L-glutamic acid α-benzyl ester was condensed with *n*-butylamine with the aid of diphenylphosphoryl azide in DMF solution containing triethylamine[18] to obtain the *N*-(*tert*-butyloxycarbonyl)-α-benzyl ester γ-*n*-butylamide (83%), which on reaction with *p*-toluenesulfonic acid (1 equiv) in refluxing benzene afforded L-glutamic acid α-benzyl ester γ-*n*-butylamide tosylate salt (98%). Condensation via the diethyl phosphorocyanidate procedure as described above yielded MTX α-benzyl ester γ-*n*-butylamide (**10**, 77%). Finally, saponification with barium hydroxide (1 equiv) in 50% aqueous ethanol gave the desired γ-*n*-butylamide **3** (73%). The same sequence of steps starting from *N*-(*tert*-butyloxycarbonyl)-L-glutamic acid α-benzyl ester and benzylamine led to the γ-benzylamide **4** with the following yields: γ-amide formation, 97%; Boc cleavage, 89%; APA coupling to **11**, 78%; α-ester hydrolysis, 88%.

Scheme III



**10**, R = *n*-$C_4H_9$
**11**, R = $CH_2C_6H_5$

Table I. Binding Affinity of Side Chain Modified MTX Derivatives for *L. casei* and L1210 Mouse Leukemia DHFR

| | $ID_{50}$,[a] μM | | |
|---|---|---|---|
| no. | *L. casei*[b] | *L. casei*[c] | L1210[c] |
| 1 | 0.025 (1.9) | 0.012 (1.9) | 0.0029 (1.0) |
| 2 | 0.0021 (0.34) | 0.013 (0.8) | 0.012 (3.5) |
| 3 | 0.053 (4.1) | 0.036 (5.8) | 0.0033 (1.2) |
| 4 | 0.055 (4.2) | 0.022 (3.5) | 0.0030 (1.1) |
| 6 | 0.33 (35) | 3.9 (160) | 0.011 (5.2) |
| 7 | 0.20 (21) | 2.2 (92) | 0.019 (9.0) |
| 8 | 0.17 (18) | 2.2 (92) | ND |
| 9 | 0.036 (5.8) | 0.21 (13) | 0.035 (10) |
| 10 | ND | 0.25 (36) | ND |

[a] Numbers in parentheses represent the ratio of the $ID_{50}$ value for a given compound relative to MTX in the same experiment. [b] Spectrophotometric assay at 340 nm.[2,22] [c] Competitive [$^3$H]MTX-binding assay.[2,23] [d] ND = not determined.

The ability of compounds **1**–**4** to bind to *L. casei* DHFR was measured by spectrophotometric assay of the kinetics of reduction of dihydrofolate[22] and also via a competitive

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[$^3$H]MTX-binding assay,[23] which we recently used with slight modification in studies on MTX γ-hydroxamic acid.[2] Binding affinities were also determined for a DHFR extract from L1210 cells[24] by means of the radioligand assay, which requires smaller amounts of enzyme than the spectrophotometric assay. The $ID_{50}$ values obtained from these measurements, as well as data on some of the intermediate methyl, *tert*-butyl, and benzyl esters, are given in Table I.

Examination of the relative enzyme affinity data against both enzymes revealed that γ-substituted compounds bind more tightly than those in which the α-COOH group is blocked in the form of an ester; however, the effect appears to depend on the nature of the ester group and is probably steric. Thus, while the $ID_{50}$ of the γ-*tert*-butyl ester **1** against *L. casei* DHFR in the spectrophotometric assay was 1.9 times higher than that of MTX, the corresponding difference between the γ-*tert*-butyl α-methyl ester **6** and MTX was 35-fold (i.e., the effect of the α-methyl group was to decrease binding by a factor of 18 when the data are normalized with respect to MTX). Similarly, with the γ-*n*-butylamide **3** and γ-*n*-butylamide α-benzyl ester **10** in the ligand-binding *L. casei* assay, the effect of the α-benzyl group on binding could be calculated to be ca. 30-fold. A more pronounced effect was observed with *L. casei* DHFR for the γ-hydrazide **2** and γ-hydrazide α-*tert*-butyl ester **8**, with the calculated effect of the α-*tert*-butyl group being ca. 50-fold in the spectrophotometric assay and >100-fold in the ligand-binding assay. Therefore, while an α-methyl group seemed to cause some decrease in binding to the bacterial enzyme, the sterically more demanding α-benzyl and α-*tert*-butyl groups had a larger effect. It was noted that α-esterification likewise decreased binding to the L1210 enzyme, with the $ID_{50}$ of the γ-*tert*-butyl ester **1** and γ-*tert*-butyl α-methyl ester **6** differing in their relative binding affinities by a factor of 5. Once again, however, the effect of the small methyl group appeared to be relatively minor.

The finding that the γ-*tert*-butyl ester **1**, the γ-*n*-butylamide **3**, and the γ-benzylamide **4** all displayed DHFR-inhibiting activity comparable to that of MTX against the L1210 enzyme reinforces earlier conclusions[1-4] that γ-substitution in the MTX side chain has only a slight effect on binding to this enzyme. Compound **1** is of potential pharmacological importance as an example of a sterically hindered γ-ester that ought to be stable to the action of serum esterases, which are known to rapidly convert straight-chain MTX esters to MTX in the mouse.[1,25] Cell culture and in vivo studies with this compound in mice would therefore be expected to yield information on its inherent cytotoxic and antitumor activity with no complicating added effect arising from concomitant formation of free MTX. Compound **3** is noteworthy as a bioisostere of the γ-*n*-butyl ester, which we have observed to be the major esterase cleavage product from the di-*n*-butyl ester.[1,25] Compound **4**, on the other hand, is of interest as a possible active metabolite of MTX bis(benzylamide), whose antitumor effect was reported in a previous paper.[26] Of particular interest was the finding that the γ-hydrazide **2** has somewhat better inhibitory activity against both the *L. casei* and L1210 enzyme. Compound **2** is closely related in structure to MTX γ-hydroxamic acid, another analogue we recently found to be somewhat more active than the parent drug in the ligand-binding assay against L1210 DHFR.[2]

Table II. Growth Inhibitory Activity of Side Chain Modified MTX Derivatives against L1210 Mouse Leukemia Cells in Culture

| no. | $ID_{50}$, μM |
|---|---|
| 1 | 0.02[a] |
| 2 | 0.02 |
| 3 | 0.09 |
| 4 | 0.03 |
| 6 | 4.9 |
| 7 | 9.7 |
| 8 | 11 |
| 9 | 5.2 |
| MTX | 0.01 |

[a] Data obtained by Dr. Jean Idriss (SFCI); the $ID_{50}$ for MTX in this experiment was 0.02 μM.

Several of the compounds reported in this paper were tested as inhibitors of the growth of L1210 cells in culture (Table II). The γ-*tert*-butyl ester **1** and γ-hydrazide **2** exhibited activity nearly comparable to that of MTX, and the γ-*n*-butylamide **3** and γ-benzylamide **4** were only slightly less active. The activity of the γ-*tert*-butyl ester **1** is notable in view of our earlier finding that the straight-chained γ-*n*-butyl analogue is 100-fold less toxic to cells in culture than MTX.[1] Since the DHFR-inhibiting effect of the two esters is similar, the greater cytotoxicity of **1** is likely to be due to more efficient uptake into cells or to a slower rate of efflux. On the basis of the promising data obtained in these experiments, compounds **1–4** seem to merit further preclinical evaluation.

## Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Model 137B double-beam recording spectrophotometer, and NMR spectra were measured with a Varian T60A instrument relative to tetramethylsilane as the internal reference. TLC was performed on Eastman 13181 silica gel or Eastman 13254 cellulose sheets containing a fluorescent indicator, and spots were visualized in an ultraviolet viewing chamber at 254 nm or with the aid of ninhydrin or iodine staining as appropriate. Column chromatography was carried out on Baker 3405 silica gel (60–200 mesh) or Whatman DE-52 cellulose (preswollen). Melting points were measured in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, MA) and are not corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Diethyl phosphorocyanidate[19,20] was prepared in 68% yield by adding cyanogen bromide in small portions with cooling and stirring to an equimolar amount of triethyl phosphite. When addition was complete, the mixture was warmed gradually and then distilled [bp 96–100 °C (15 mm)]. The product should be stored in a well-ventilated hood, with care being taken to avoid inhalation and skin exposure as much as possible during handling.

**Preparation of Amino Acid Derivatives. L-Glutamic Acid α-Methyl γ-*tert*-Butyl Ester.** A mixture of *N*-(carbobenzoxy)-L-glutamic acid γ-*tert*-butyl ester (3.37 g, 0.01 mol) (Vega Biochemicals, Tucson, AZ), cesium carbonate (3.26 g, 0.01 mol), and methyl iodide (2.84 g, 0.02 mol) in dry DMF (100 mL) was left to stir overnight at room temperature. After solvent evaporation, the residue was taken up in benzene, and the solution was washed with $H_2O$, dried, and concentrated to an oil: yield 3.51 g (~100%); NMR ($CDCl_3$) δ 1.44 (s, 9 H, *t*-$C_4H_9$), 1.9–2.4 (m, 4 H, $CH_2CH_2$), 3.73 (s, 3 H, $OCH_3$), 4.2–4.6 (broad, 1 H, NH), 5.14 (s, 2 H, benzylic $CH_2$), 5.3–5.6 (m, 1 H, α-CH), 7.36 (s, 5 H, aromatic protons). The oily Cbz derivative was dissolved in a mixture of MeOH (200 mL) and glacial AcOH (5 mL) and hydrogenated overnight in a Parr apparatus (3–4 atm) in the

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presence of 5% Pd/C. After the catalyst was removed by filtration through Celite, the solution was diluted with a large volume of $CH_2Cl_2$. Washing with 5% $NaHCO_3$ and solvent evaporation gave the product[27] as an oil: yield 1.85 g (85%); NMR ($CDCl_3$) $\delta$ 1.42 (s, 9 H, $t$-$C_4H_9$), 1.7–2.5 (m, 4 H, $CH_2CH_2$), 3.3–3.6 (m, 1 H, $\alpha$-CH), 3.70 (s, 3 H, $OCH_3$). This material was coupled directly to APA as described below.

**L-Glutamic Acid $\alpha$-*tert*-Butyl $\gamma$-Methyl Ester.** A mixture of L-glutamic acid $\gamma$-methyl ester (Aldrich Chemical Co., Milwaukee, WI) (1.29 g, 0.008 mol), $t$-BuOAc (60 mL), and 70% $HClO_4$ (1.26 g, 0.0088 mol) was stirred at room temperature for 3 days, cooled to 0 °C, and extracted with cold 0.5 N HCl. The acidic solution was neutralized with powdered $NaHCO_3$ (**caution**: $CO_2$ evolution), and extracted with $Et_2O$. Washing with saturated NaCl, drying, and solvent evaporation yielded the product[28] as a semisolid, which was coupled directly to APA as described below: yield 1.40 g (81%); NMR ($CDCl_3$) $\delta$ 1.46 (s, 9 H, $t$-$C_4H_9$), 1.7–2.6 (m, 4 H, $CH_2CH_2$), 3.32 (m, 1 H, $\alpha$-CH), 3.64 (s, 3 H, $OCH_3$).

***N*-(*tert*-Butyloxycarbonyl)-L-glutamic Acid $\alpha$-Benzyl Ester $\gamma$-*n*-Butylamide.** To a stirred ice-cold solution of *N*-(*tert*-butyloxycarbonyl)-L-glutamic acid $\alpha$-benzyl ester (1.7 g, 0.005 mol) (Bachem, Torrance, CA) and *n*-butylamine (0.4 g, 0.0055 mol) in dry DMF (20 mL) was added a solution of diphenylphosphoryl azide (1.5 g, 0.0055 mol) in DMF (5 mL), followed by $Et_3N$ (1.5 mL, 0.011 mol). After being stirred for 6 h at 0 °C and overnight at room temperature, the solution was poured onto a large volume of ice. The oil which separated out gradually hardened on standing. The crude product was dried in vacuo for 3 h before being recrystallized from a mixture of hexane and EtOAc to obtain a microcrystalline white solid: yield 1.6 g (83%); mp 85–86 °C; IR ($CHCl_3$) $\nu$ 3405 (NH), 1700–1650 (C=O) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ ~0.9 (br m, 7 H, $CH_2CH_2CH_3$), 1.41 (s, 9 H, $t$-$C_4H_9$), 2.11 (m, 2 H, $CH_2$ adjacent to C=O), 3.19 (m, 2 H, $CH_2$ adjacent to NH), 5.11 (s, 2 H, benzylic $CH_2$), 7.25 (s, 5 H, aromatic protons). Anal. ($C_{21}H_{32}N_2O_5$) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)-L-glutamic acid $\alpha$-benzyl ester $\gamma$-benzylamide** was prepared as in the preceding experiment, using *N*-(*tert*-butyloxycarbonyl)-L-glutamic acid $\alpha$-benzyl ester (3.4 g, 0.01 mol), benzylamine (1.2 g, 0.011 mol), diphenylphosphoryl azide (3 g, 0.011 mol), and $Et_3N$ (2.1 g, 0.021 mol) in dry DMF (10 mL): yield 4.13 g (97%); mp 92–93 °C; IR (KCl) $\nu$ 3330, 1725 (ester C=O), 1640 (amide C=O), 1525 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.4 (s, 9 H, $t$-$C_4H_9$), 2.2 (br m, 4 H, glutamyl $CH_2CH_2$), 4.4 (d, $J$ = 7 Hz, 3 H, $CH_2$ adjacent to NH and $\alpha$-CH), 5.15 (s, 2 H, $CH_2O$), 6.2 (broad, 1 H, NH), 7.28 (s, 5 H, aromatic protons), 7.33 (5 H, aromatic protons). Anal. ($C_{24}H_{30}N_2O_5$) C, H, N.

**L-Glutamic Acid $\alpha$-Benzyl Ester $\gamma$-*n*-Butylamide *p*-Toluenesulfonate Salt.** A solution of the *N*-Boc derivative (0.39 g, 0.001 mol) and *p*-toluenesulfonic acid monohydrate (0.19 g, 0.001 mol) in benzene (10 mL) was heated under reflux for 45 min. The product which precipitated on cooling was collected and washed with benzene to obtain a white solid: yield 0.45 g (98%); mp 115–125 °C; IR ($CHCl_3$) $\nu$ 2800–3200 ($NH_3^+$), 1735 (ester C=O), 1650 (amide C=O) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.7–1.5 (m, 7 H, $CH_2CH_2CH_3$), 2.25 (s, 5 H, $CH_3$ and $CH_2$ adjacent to C=O), 2.95 (m, 2 H, $CH_2$ adjacent to NH), 4.98 (s, 2 H, benzylic $CH_2$), 6.95 (d, $J$ = 8 Hz, 2 H, aromatic protons), 7.16 (s, 5 H, aromatic protons), 7.60 (d, $J$ = 8 Hz, 2 H, aromatic protons), 8.30 (broad, 3 H, $NH_3^+$). Anal. ($C_{16}H_{24}N_2O_3 \cdot C_7H_8O_3 \cdot 0.5H_2O$) C, H, N.

**L-Glutamic acid $\alpha$-benzyl ester $\gamma$-benzylamide *p*-toluenesulfonate salt** was prepared as described in the preceding experiment, using the *N*-Boc derivative (2.56 g, 0.006 mol) and *p*-toluenesulfonic acid monohydrate (1.14 g, 0.006 mol) in dry benzene (60 mL, 45-min reflux): yield 2.65 g (89%); mp 125 °C (softening); IR (KCl) $\nu$ 3330, 3015, 2940, 1745 (ester C=O), 1665 (amide C=O), 1530 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.3 (m, 7 H, glutamyl $CH_2CH_2$ and aromatic $CH_3$), 4.20 (m, 3 H, benzylic $CH_2$ of the amide and $\alpha$-CH), 5.00 (s, 2 H, benzylic $CH_2$ of the ester), 7.0–8.0 (m, 10 H, aromatic protons), 8.4 (broad, 3 H, $NH_3^+$). Analytically pure material was obtained by passing the product through a silica gel column with 9:1 $CHCl_3$–MeOH as the eluent. Anal. ($C_{19}H_{22}N_2O_3 \cdot C_7H_8O_3S$) C, H, N, S.

**APA Coupling Reactions. MTX $\gamma$-*tert*-Butyl $\alpha$-Methyl Ester (6).** APA (2.67 g, 0.008 mol)[29] was added in small portions with stirring to a solution of $Et_3N$ (2.5 g, 0.024 mol) and diethyl phosphorocyanidate (3.92 g, 0.024 mol) in dry DMF (250 mL). When all the solids dissolved, the mixture was heated to 80 °C for 2 min and cooled back to room temperature before adding another portion of $Et_3N$ (0.85 g, 0.008 mol) and the freshly prepared amino diester (1.85 g, 0.008 mol). Heating was resumed at 80 °C for 2 h, the solvent was removed by rotary evaporation (vacuum pump, dry ice/acetone cooled receiver), and the residue was taken up in $CHCl_3$. Washing with 5% $NaHCO_3$, solvent evaporation, and column chromatography on silica gel with 95:5 $CHCl_3$–MeOH as the eluent gave a bright yellow powder: yield 2.91 g (67%); mp 144–154 °C; IR (KCl) $\nu$ 1730 (ester C=O) $cm^{-1}$. Anal. ($C_{25}H_{33}N_5O_5 \cdot 0.5H_2O$) C, H, N.

**MTX $\alpha$-*tert*-butyl $\gamma$-methyl ester (7)** was prepared from APA (2.20 g, 0.006 mol), diethyl phosphorocyanidate (2.94 g, 0.018 mol), $Et_3N$ (2.4 g total in two portions, 0.024 mol), and freshly prepared L-glutamic acid $\alpha$-*tert*-butyl $\gamma$-methyl ester (1.30 g, 0.006 mol) in dry DMF (200 mL): yield 2.42 g (76%); mp 136–143 °C; IR (KCl) $\nu$ 1730 (ester C=O) $cm^{-1}$. Anal. ($C_{25}H_{32}N_8O_5$) C, H, N.

**MTX $\alpha$-benzyl ester $\gamma$-*n*-butylamide (10)** was prepared from APA (110 mg, 0.3 mmol), diethyl phosphorocyanidate (147 mg, 0.9 mmol), $Et_3N$ (122 mg total in two portions, 1.2 mmol), and L-glutamic acid $\alpha$-benzyl ester $\gamma$-*n*-butylamide *p*-toluenesulfonate salt (133 mg, 0.3 mmol) in dry DMF (10 mL): yield 138 mg (77%); mp 105–116 °C; IR (KCl) $\nu$ 1735 (ester C=O), 1610–1640 (amide C=O) $cm^{-1}$. Anal. ($C_{31}H_{39}N_9O_5 \cdot H_2O$) C, H, N.

**MTX $\alpha$-benzyl ester $\gamma$-benzylamide (11)** was prepared from APA (1.1 g, 0.003 mol), diethyl phosphorocyanidate (1.47 g, 0.009 mol), $Et_3N$ (1.51 g total in two portions, 0.015 mol), and L-glutamic acid $\alpha$-benzyl ester $\gamma$-benzylamide *p*-toluenesulfonate salt (1.66 g, 0.003 mol) in dry DMF (100 mL): yield 1.52 g (78%); mp 113–125 °C; IR (KCl) $\nu$ 1740 (ester C=O), 1615–1640 (amide C=O) $cm^{-1}$. Anal. ($C_{34}H_{37}N_9O_5 \cdot H_2O$) C, H, N.

**Alkaline Hydrolysis Reactions. MTX $\gamma$-*tert*-Butyl Ester (1).** $Ba(OH)_2 \cdot 8H_2O$ (63 mg, 0.2 mmol) was added to a solution of the diester **6** (216 mg, 0.4 mmol) in 50% EtOH (8 mL), and the mixture was left to stir in an open flask at room temperature in the hood overnight. To the hydrolysis mixture, from which some of the alcohol had evaporated on standing, was added $Na_2SO_4$ (29 mg, 0.2 mmol) in a small volume of $H_2O$, and the $BaSO_4$ precipitate was removed by filtration. The filtrate was adjusted to pH 4–5 with 10% AcOH, and after overnight cooling at 4 °C, the gelatinous precipitate was collected. Removal of water entrapped in this material was accomplished best by freeze-drying: yield 200 mg (92%). Anal. ($C_{24}H_{30}N_8O_5 \cdot 2H_2O$) C, H, N.

**MTX $\alpha$-*tert*-butyl ester (9)** was prepared from the diester **7** (1.55 g, 0.003 mol) and $Ba(OH)_2 \cdot 8H_2O$ (0.57 g, 0.0018 mol) in 50% EtOH (60 mL) as in the preceding experiment. The product was purified by ion-exchange chromatography on DEAE-cellulose with 3% $NH_4HCO_3$ as the eluent: yield 1.28 g (81%). Anal. ($C_{24}H_{30}N_8O_5 \cdot 1.5H_2O$) C, H, N.

**MTX $\gamma$-*n*-butylamide (3)** was prepared from amide ester **10** (2.3 g, 0.0038 mol) and $Ba(OH)_2 \cdot 8H_2O$ (1.2 g, 0.0038 mol) in a mixture of 95% EtOH (60 mL) and $H_2O$ (40 mL) as described in the preceding experiment: yield 2.0 g (73%). Anal. ($C_{24}H_{31}N_9O_4 \cdot 2H_2O$) C, H, N.

**MTX $\gamma$-benzylamide (4)** was prepared from amide ester **11** (4.2 g, 0.0064 mol) and $Ba(OH)_2 \cdot 8H_2O$ (2.0 g, 0.0064 mol) in a mixture of 95% EtOH (125 mL) and $H_2O$ (100 mL): yield 3.2 g (88%). Anal. ($C_{27}H_{29}N_9O_4 \cdot 2H_2O$) C, H, N.

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(29) APA was obtained from MTX as previously described,[15] except that AcOH was used instead of HCl in the final acidification step. This resulted in a product which was HCl free and showed *greatly improved DMF solubility*. Microanalysis of material dried in vacuo and then left to stand in the open until a constant weight was achieved indicated a dihydrate. In this work, therefore, the number of moles of APA in coupling reactions is based on the empirical formula $C_{15}H_{15}N_7O_2 \cdot 2H_2O$. High yields in the coupling reaction require that all the APA be in solution in the DMF prior to addition of the amino ester.

**MTX α-*tert*-Butyl Ester γ-Hydrazide (8).** Hydrazine hydrate (0.5 mL) in MeOH (5 mL) was added to a solution of the diester 7 (0.52 g, 0.001 mol) in MeOH (15 mL), and the solution was kept at 4 °C for 3 days. After vacuum evaporation of most of the solvent, $CHCl_3$ was added with just enough MeOH to bring the solid into solution. Extraction with 5% $NaHCO_3$, evaporation of the organic layer, and purification of the residue by column chromatography on silica gel (9:1 $CHCl_3$–MeOH) gave a bright yellow powder: yield 0.33 g (60%): mp ~140 °C (foaming); IR (KCl) ν 1720 (ester C=O) $cm^{-1}$. Anal. ($C_{24}H_{32}N_{10}O_4 \cdot CH_3OH$) C, H, N.

**MTX γ-Hydrazide (2).** A solution of the γ-*tert*-butyl ester 8 (1.56 g, 0.003 mol) in 1 N HCl (25 mL) was kept at 50 °C (bath temperature) for 1 h, then cooled, and basified to pH >9 with 5% NaOH. Some unchanged starting material which came out of solution was collected and treated again with acid. The combined basic solutions were adjusted to pH ~8 with AcOH and $NH_4OH$ and then freeze-dried. The product was purified by chromatographing it twice on a DEAE-cellulose column which was eluted first with 0.5% $NH_4HCO_3$ and then with 3% $NH_4HCO_3$: yield 0.64 g (45%). Anal. ($C_{20}H_{24}N_{10}O_4$) C, H, N.

**Acknowledgment.** This work was supported by Project Grant CA 25394 and Cancer Center Support Grant CA06516 from the National Cancer Institute, National Institutes of Health. The technical assistance of Carol Ginty (enzyme inhibition assay) and Gerda Swedowsky (cytotoxicity assays) is gratefully acknowledged.

# Antihypertensive Pyrrolo[1,2-*c*]quinazolines and Pyrrolo[1,2-*c*]quinazolinones

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The synthesis of a variety of pyrrolo[1,2-*c*]quinazolines and pyrrolo[1,2-*c*]quinazolinones is described. Several of these compounds have exhibited antihypertensive properties in the spontaneously hypertensive rat (SHR). Structure–activity comparisons have indicated that optimal activity is obtained in both the 2-carbethoxydihydroquinazoline series (C) and 2-carbethoxyquinazolinone series (D) when there is either a carbethoxy or cyanoethyl group at position 6 and no substitution in the benzene ring, while optimal activity is obtained in the 2-methylquinazolinone series (D) when both position 6 and the benzene ring are unsubstituted.

A variety of biological activities have been observed for compounds containing the quinazoline and quinazolinone ring systems.[1] For example, the quinazolinone alkaloids febrifugin[2] and vasicinone[3] were reported to possess antimalarial and bronchodilator activity, respectively. Other quinazolinones have been found to have diuretic,[4] antiinflammatory,[5] antimitotic,[6] antihistaminic,[7] and hypotensive[8] activities. In contrast, pyrrolo[1,2-*c*]quinazoline and pyrrolo[1,2-*c*]quinazolinone derivatives have received only limited attention.[9] This paper summarizes the synthesis and antihypertensive activity of such tricyclic quinazoline derivatives.

**Synthesis.** Substituted pyrrolo[1,2-*c*]quinazolines and pyrrolo[1,2-*c*]quinazolinones were prepared by condensing appropriate quinazolines[10] and quinazolinones[10] with α-halopyruvates (AHP) and α-halo ketones (AHK).

The general reaction sequence for the formation of the tricyclic products using α-halopyruvates (AHP) is shown in Scheme I (series A, compounds 1–5; series B, compounds 6–14; series D, compounds 35–49). Catalytic or chemical reduction of series B affords the dihydro system (series C, compounds 15–22). Chemical transformation of series C and D (e.g., Michael addition, formylation, and acylation) give series E (compounds 23–34) and series F (compounds 50–57), respectively.

The mechanism for the formation of compound **43** utilizing α-chloroacetone (AHK) proceeds by essentially the mechanism shown in Scheme I. The formation of the chlorine-containing byproducts **44** and **46** is the result of a secondary reaction between intermediate **43b** and AHK, as illustrated for **44** in Scheme II.

The formation of byproducts **36**, **37**, and **48** results when a quinazoline reacts with AHK by the alternate route as illustrated for **36** in Scheme III.

Within all series, we have executed further chemical transformations. For instance, treatment of bromo compound **15** with CuCN[11] gave three products: cyano compounds **8** and **17** and bromo product **6**. Hydrolysis of ester **12** gave acid **14**. Reaction of *N*-formyl compound **30** with diborane yielded the *N*-methyl product **31**, which was re-

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0022-2623/81/1824-1455$01.25/0 