mixture of 0.6 g (0.002 mol) of 1-[4-(*tert*-butoxycarbonyl)-phenyl]-3-(aminomethylene)-4-piperidone (**18**) and 0.29 g (0.002 mol) of 2,4-diamino-6(1*H*)-pyrimidinone was dissolved in 10 mL of glacial acetic acid containing 5 mL of water. One drop of piperidine was added, and the mixture was heated under reflux in a nitrogen atmosphere for 2 h, cooled to room temperature, diluted with 10 mL of water, and filtered. The collected solid was washed with water followed by methanol and acetone: yield 0.4 g (51%); mp >250 °C; NMR (TFA) δ 1.7 (s, 9 H), 3.8–4.05 (m, 2 H), 4.4–4.55 (m, 2 H), 5.3 (s, 2 H), 7.95 and 8.55 (ABq, 4 H, J = 9 Hz), 8.8 (s, 1 H).

2-Acetamido-7-[4-(*tert*-butoxycarbonyl)phenyl]-5-deaza-6,7,8,9-tetrahydro-4(3*H*)-pyrido[3,4-*g*]pteridinone (20). A mixture of 1.0 g of 2-amino-7-[4-(*tert*-butoxycarbonyl)phenyl]-5-deaza-6,7,8,9-tetrahydro-4(3*H*)-pyrido[3,4-*g*]pteridinone (**19**) and 10 mL of acetic anhydride containing 5 drops of 4-(dimethylamino)pyridine was heated under reflux for 1 h and cooled to room temperature, and 10 mL of ether added. Filtration then gave 0.84 g (76%) of **20**: mp >250 °C; NMR (TFA) δ 1.75 (s, 9 H), 2.65 (s, 3 H), 4.1–4.3 (m, 2 H), 4.5–4.75 (m, 2 H), 5.4 (s, 2 H), 7.95 and 8.58 (ABq, 4 H, J = 9 Hz), 9.25 (s, 1 H).

2-Acetamido-7-(4-carboxyphenyl)-5-deaza-6,7,8,9-tetrahydro-4(3*H*)-pyrido[3,4-*g*]pteridinone (21). Method A. Hydrogen chloride was bubbled for 2 min through a suspension of 50 mg of 2-acetamido-7-[4-(*tert*-butoxycarbonyl)phenyl]-5-deaza-6,7,8,9-tetrahydro-4(3*H*)-pyrido[3,4-*g*]pteridinone (**20**) in 5 mL of nitromethane at room temperature. The reaction mixture was stirred for 1 h, the solvent evaporated under reduced pressure, and the residual solid triturated with ether and filtered: yield 44 mg (96%); mp >250 °C.

Anal. Calcd for $C_{19}H_{17}N_5O_4 \cdot H_2O$: C, 57.43; H, 4.79; N, 17.63. Found: C, 57.76; H, 4.43; N, 16.98.

Method B. Hydrogen chloride gas was bubbled for 2 min through a suspension of 2.0 g of 2,4-diamino-7-[4-(*tert*-butoxycarbonyl)phenyl]-5-deaza-6,7,8,9-tetrahydropyrido[3,4-*g*]pteridine (**10b**) in 50 mL of nitromethane, cooled by an external ice bath. The resulting solution was stirred for 1 h at room temperature, 50 mL of ether added, and the resulting solid precipitate collected by filtration and washed well with ether. This solid (**10c**) was suspended in 70 mL of 1 N sodium hydroxide solution, and the mixture was heated under reflux under nitrogen for 4 h. The resulting yellow homogeneous solution was filtered, and the filtrate was acidified with acetic acid. The resulting gellatinous precipitate was collected by centrifugation, washed with water and methanol, and dried at 100 °C (100 mm) to give 1.6 g (86%) of **22**. This compound was suspended in 15 mL of acetic anhydride, 0.1 g of 4-(dimethylamino)pyridine added, and the reaction mixture heated under nitrogen at 130 °C for 4 h. The mixture was then cooled to room temperature, 20 mL of diethyl ether added, and the mixture filtered to give 2.0 g (93%) of **23**. This compound was dissolved in 20 mL of 1 N sodium hydroxide solution and quickly filtered and the filtrate acidified with acetic acid. The solid which precipitated was collected by filtration and dried at 80 °C (0.1 mm) to give 1.68 g (92%) of **21**, identical in every respect with the compound obtained by Method A as described above.

Diethyl *N*-[4-[7-(2-Acetamido-5-deaza-4(3*H*)-oxo-6,7,8,9-tetrahydropyrido[3,4-*g*]pteridino)]benzoyl]-L-glutamate (24). To a solution of 0.37 g (0.001 mol) of 2-acetamido-7-(4-carboxyphenyl)-5-deaza-6,7,8,9-tetrahydro-4(3*H*)-pyrido[3,4-*g*]pteridinone (**21**) in 5 mL of hot *N*-methylpyrrolidone was added 0.14 mL (0.0012 mol) of triethylamine, the mixture was cooled to room temperature, and 0.27 g (0.001 mol) of phenyl *N*-phenylphosphoramidochloridate added. After 30 min of stirring at room temperature, 0.24 g (0.001 mol) of L-diethyl glutamate hydrochloride and 0.14 mL (0.0012 mol) of triethylamine in 5 mL of *N*-methylpyrrolidone were added, and the reaction mixture was stirred at room temperature overnight. Evaporation of the solvent gave a tan solid which was triturated with 50 mL of water, air dried, dissolved in 100 mL of chloroform/methanol (4:1), and filtered through Celite. Silica gel (5 g) was added, the solvent evaporated, and the impregnated silica gel applied to the top of a silica gel column prepared from 15 g of Merck Kieselgel-60, 230–240 mesh. The product was eluted with chloroform/methanol (95:5); evaporation of the solvent gave 0.31 g (55%) of **24** as a brown powder: mp 185–190 °C; NMR (Me_2SO-d_6) δ 1.25 (2 t, 6 H, J = 7 Hz), 2.3 (s, 3 H), 1.7–2.6 (m, 4 H), 3.0–2.25 (m, 2 H), 2.7–2.95 (m, 2 H), 4.1 (2 q, 4 H, J = 7 Hz), 4.3–4.5 (m, 1 H), 4.65 (s, 2 H), 7.05 and 7.8 (ABq, 4 H, J = 9 Hz), 8.3 (s, 1 H).

Anal. Calcd for $C_{28}H_{32}N_6O_7 \cdot 0.5H_2O$: C, 58.64; H, 5.76; N, 14.66. Found: C, 58.65; H, 5.52; N, 14.73.

L-7,10-Ethano-5-deazafolic Acid (5). Hydrogen chloride gas was passed for a few minutes through a suspension of 0.7 g of diethyl *N*-[4-[7-(2-acetamido-5-deaza-4(3*H*)-oxo-6,7,8,9-tetrahydropyrido[3,4-*g*]pteridino)]benzoyl]-L-glutamate (**24**) in 20 mL of nitromethane at 0 °C. The resulting pink emulsion was stirred at room temperature for 1 h, 20 mL of diethyl ether added, the suspended solid collected by filtration and suspended in water, and 1 N sodium hydroxide solution added until a homogeneous solution resulted. This solution was filtered and the filtrate acidified with acetic acid to give an orange precipitate which was collected by centrifugation and washed well with water, methanol, and ether: yield 0.49 g (88%) of **4**; mp >250 °C. The insolubility of this compound, even in TFA, precluded determination of its NMR spectrum.

Anal. Calcd for $C_{22}H_{22}N_6O_6 \cdot H_2O$: C, 54.55; H, 4.96; N, 17.35. Found: C, 54.19; H, 4.70; N, 17.00.

Synthesis of 4-Amino-4-deoxy-7,10-methano-5-deazapteroic Acid and 7,10-Methano-5-deazapteroic Acid[1]

Edward C. Taylor,* Stephen R. Fletcher, and Steven Fitzjohn

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Received August 1, 1984

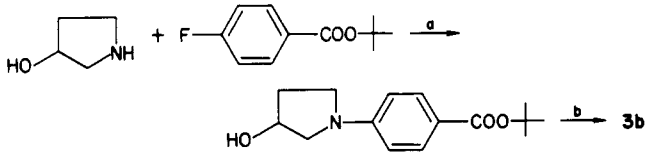
The 5-deazapteroic acid analogues **1** and **2** have been prepared by several different strategies starting from 1-[4-(*tert*-butoxycarbonyl)phenyl]-3-pyrrolidinone (**3b**).

A major objective in our laboratories over the past few years has been the synthesis of structural analogues of folic acid, methotrexate, and aminopterin which we hope will exhibit enhanced binding to dihydrofolate reductase and/or thymidylate synthetase and thus greater selectivity for a broader range of human tumors. Arguments supporting the synthesis of "tied-back" analogues of the above pteridines in which C-7 (the site of metabolic inactivation of methotrexate itself) is blocked by a bridge to N-10 have been presented elsewhere.[2] We describe in the present

(1) This work was supported by a grant (#R01 CA 28351) to Princeton University from the National Cancer Institute, National Institutes of Health.

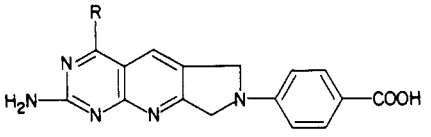
0022-3263/85/1950-1010$01.50/0

Scheme I[a]



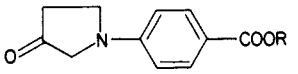
[a] (a) $Na_2CO_3/Me_2SO/120\ °C/7$ h; (b) DCC/Me_2SO/TFA/pyridine.

paper the synthesis of the "tied-back" 5-deazapteroic acid analogues **1** and **2**.



1, R=NH_2
2, R=OH

Synthetic methodology previously developed for the synthesis of 7,10-ethano analogues of 5-deazaaminopterin and 5-deazafolic acid[2] suggested that the fused pyrroline systems **1** and **2** might be accessible by an analogous strategy starting from a 1-[4-(alkoxycarbonyl)phenyl]-3-pyrrolidinone (**3**). Although it was anticipated that the

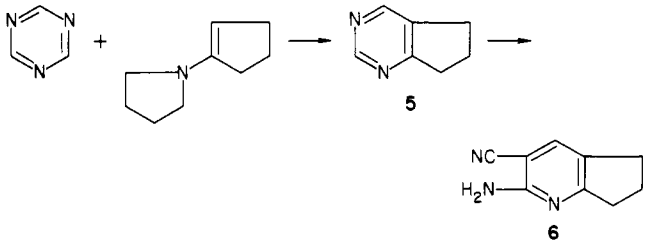


3a, R=CH_3
b, R=*t*-Bu

tert-butyl ester **3b** might ultimately prove to be the more versatile intermediate for ultimate conversion to the desired target compounds, exploratory chemistry should be facilitated by use of the more stable methyl ester **3a**. Synthetic routes to both esters were developed as follows.

An efficient synthesis of *N*-[4-(methoxycarbonyl)-phenyl]-4-(methoxycarbonyl)-3-pyrrolidinone has been reported,[3] and we have now found that this compound is converted to **3a** in 59% yield by heating in 60% aqueous acetic acid under nitrogen for 12 h.[4] This sequence is clearly unsuitable, however, for preparation of the acid-sensitive *tert*-butyl ester **3b**. Attempts to convert **3a** to **3b** by hydrolysis and reesterification of the resulting carboxylic acid led to decomposition during the hydrolysis step. Ester exchange of **3a** with *tert*-butyl alcohol in the presence of molecular sieves was also unsuccessful. Compound **3b** was therefore synthesized as outlined in Scheme I by a procedure modeled after an analogous synthesis of the corresponding 3-piperidinone.[5]

A one-step synthesis of 4,5-trimethylenepyrimidine (**5**) by cycloaddition of *s*-triazine with 1-pyrrolidinocyclopentene has recently been described.[6] In a model experiment, we subjected **5** to the Albert–Pendergast reaction[7] and obtained, as expected, the aminonitrile **6**. We



5

6

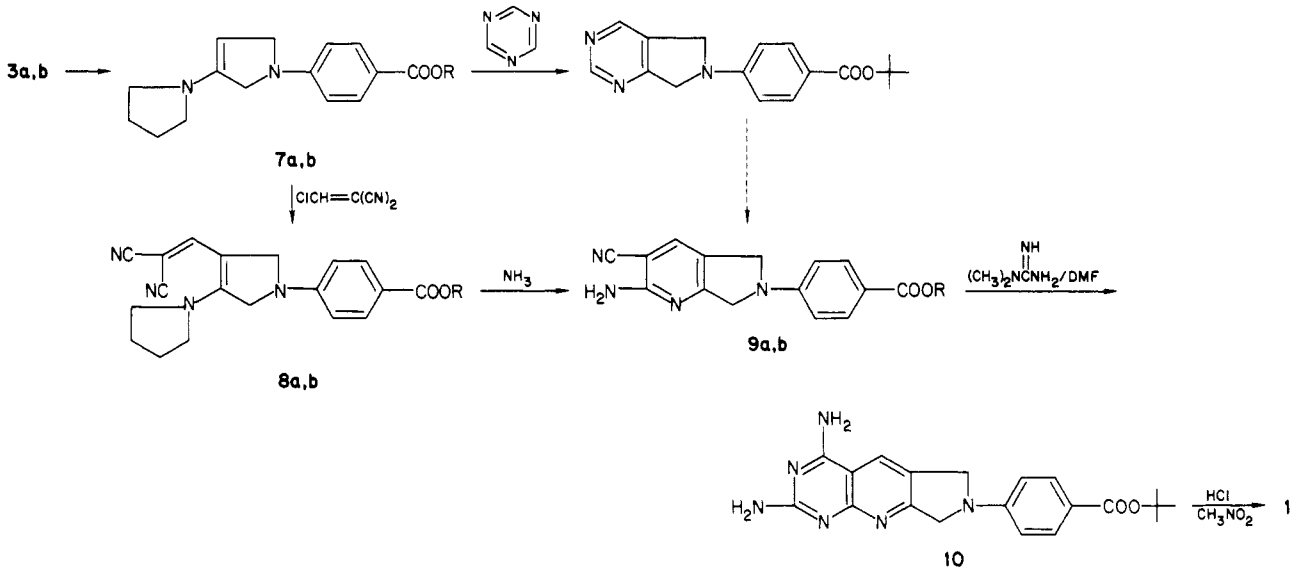
then attempted to extrapolate this reaction sequence to the 3-pyrrolidinones **3a** and **3b** (see Scheme II). Each was converted into its pyrrolidine enamine (**7a,b**, respectively) by reaction with an excess of pyrrolidine in THF in the presence of anhydrous magnesium sulfate under nitrogen at room temperature. To our disappointment, **7b** underwent the desired cycloaddition reaction with *s*-triazine only in very poor yield (3%); as a consequence, no further work was done on this reaction pathway. Instead, **7a,b** were alkylated with (chloromethylene)malononitrile and the resulting adducts were converted to **9a,b** with methanolic ammonia. Cyclization of **9b** to the *tert*-butyl ester of 4-deoxy-4-amino-7,10-methano-5-deazapteroic acid (**10**) was then achieved by reaction with *N,N*-dimethylguanidine free base in DMF under reflux. 4-Deoxy-4-amino-7,10-methano-5-deazapteroic acid (**1**) was then readily prepared from **10** by selective hydrolysis with dry HCl in nitromethane.

The 5-deazapteroic acid analogue **2** was prepared by a different strategy starting once again, however, with 1-[4-(*tert*-butoxycarbonyl)phenyl]-3-pyrrolidinone (**3b**). We have shown previously that the reaction of 2,4-diamino-6(1*H*)-pyrimidinone (**11**) with 2-(aminomethylene)[or [(dimethylamino)methylene]]cyclopentanone (**12**, R = H, CH_3) yields the 5-deazapterin derivative **13** in which the cyclopentene ring is fused across positions 6 and 7,[9] not across positions 5 and 6 as previously claimed.[10] We therefore prepared the (dimethylamino)methylene derivative **14** from **3b** by reaction with DMF acetal, and have found that this compound likewise cyclizes with 2,4-diamino-6(1*H*)-pyrimidinone (**11**) to give a 6,7-fused 5-deazapterin (i.e., **15**) (see Scheme III). The structure of **15** was unambiguously established by acetylation at N-2 to give **16** followed by hydrolysis of the *tert*-butyl ester grouping with dry HCl in nitromethane. The resulting 2-acetyl derivative of 7,10-methano-5-deazapteroic acid (**17**) was identical in every respect with an authentic sample of **17** prepared by alkaline hydrolysis of **1** (prepared unambiguously as described above) to 7,10-methano-5-deazapteroic acid **2**, followed by acetylation at N-2. An independent synthesis of **2** was achieved by hydrolysis of **15** with dry HCl in nitromethane.

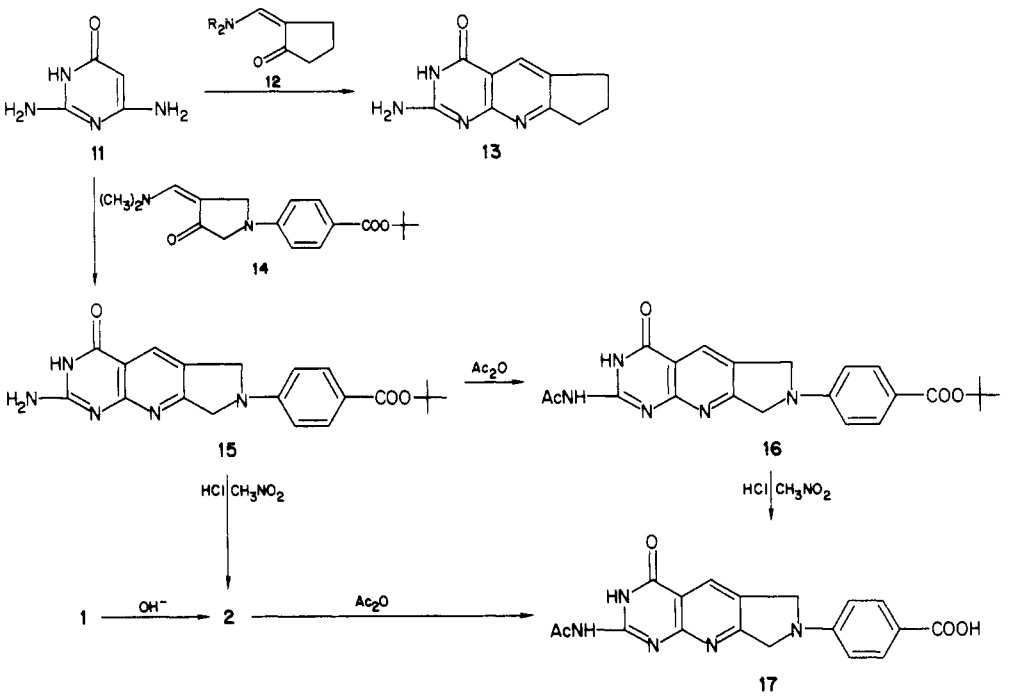
The extraordinary insolubility of the pteroic acid analogues **1** and **2** has thus far frustrated all attempts to effect coupling with diethyl L-glutamate. In fact, **2** proved to be so insoluble that the only way found to compare the sample of **2** prepared from **1** with that prepared from **15** was to convert each into the somewhat more soluble 2-acetyl derivative **17**, which permitted an FT NMR spectrum to be obtained. We have not even been able to acetylate **1** because of its insolubility, and the acetyl derivative **17** was too insoluble to be coupled with diethyl L-glutamate. Some method for solubilizing these extremely insoluble fused 2-amino-4(3*H*)pyrimidinones and 2,4-diaminopyrimidines must be found, and this is an important current object of

(2) Taylor, E. C.; Skotnicki, J. S.; Fletcher, S. R. *J. Org. Chem.*, preceding paper in this issue.
(3) Southwick, P. L.; Madhav, R.; Fitzgerald, J. A. *J. Heterocycl. Chem.* **1969**, *6*, 507.
(4) We have developed an alternative synthesis of **3a** which employs a totally different strategy (cycloaddition of 2-methoxy-1,3-butadiene with methyl *p*-nitrosobenzoate followed by acid hydrolysis of the resulting enol ether, hydrogenolysis of the N–O bond, and final intramolecular dehydrative cyclization). Details of this independent synthesis of **3a** have been described independently: Taylor, E. C.; McDaniel, K.; Skotnicki, J. S. *J. Org. Chem.* **1984**, *49*, 2500.
(5) Taylor, E. C.; Skotnicki, J. S. *Synthesis* **1981**, 606.
(6) Boger, D. L.; Schumacher, J.; Millican, M. D.; Patel, M.; Panek, J. S. *J. Org. Chem.* **1982**, *47*, 2673.
(7) Albert, A.; Pendergast, W. *J. Chem. Soc., Perkin Trans. 2*, **1973**, 1794.
(8) Josey, A. D.; Dickinson, C. L.; Dewhirst, K. C.; McKusick, B. C. *J. Org. Chem.* **1967**, *32*, 1940.
(9) Taylor, E. C.; Fletcher, S. R. *J. Org. Chem.* **1984**, *49*, 3226.
(10) Stark, E.; Breitmaier, E. *Tetrahedron* **1973**, *29*, 2209.

Scheme II



Scheme III



our research program in this field of heterocyclic chemistry.

Experimental Section

***N*-[4-(Methoxycarbonyl)phenyl]-3-pyrrolidinone (3a).** A solution of 20 g of *N*-[4-(methoxycarbonyl)phenyl]-4-(methoxycarbonyl)-3-pyrrolidinone[3] in 100 mL of 60% aqueous acetic acid was heated under reflux under N_2 for 18 h. The reaction mixture was then cooled to room temperature and the resulting yellow crystals collected by filtration and recrystallized from toluene to give 9.38 g (59%) of **3a** as a beige solid: mp 163–165 °C; NMR ($CDCl_3$) δ 2.8 (t, 2 H, J = 7 Hz), 3.7–3.9 (t + s, 4 H), 3.9 (s, 3 H), 6.64 and 8.0 (ABq, 4 H, J = 9 Hz).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.94; N, 6.39. Found: C, 65.60; H, 5.94; N, 6.41.

***N*-[4-(*tert*-Butoxycarbonyl)phenyl]-3-pyrrolidinol (4).** Finely ground potassium carbonate (10 g) was added to a solution of 10 g (0.051 mol) of *tert*-butyl 4-fluorobenzoate and 5.0 g (0.057 mol) of 3-pyrrolidinol in 20 mL of dimethyl sulfoxide. The resulting slurry was heated at 120 °C (external temperature) under N_2 for 7 h, cooled to room temperature, and poured into 80 mL of water. The resulting white precipitate was collected by filtration and air dried to give 11.4 g (85%) of **4** as colorless needles: mp 166–168 °C; NMR ($CDCl_3$) δ 1.6 (s, 9 H), 2.0–2.5 (m, 2 H), 3.2–3.7 (m, 4 H), 4.4–4.9 (m, 1 H), 4.65–4.75 (d, 1 H, J = 3 Hz), 6.47 and 7.8 (ABq, 4 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.06; N, 5.32. Found: C, 68.18; H, 7.85; N, 5.26.

***N*-[4-(*tert*-Butoxycarbonyl)phenyl]-3-pyrrolidinone (3b).** Trifluoroacetic acid (0.8 mL) was added dropwise to a solution of 3.8 g (0.014 mol) of *N*-[4-(*tert*-butoxycarbonyl)phenyl]-3-pyrrolidinol (**4**), 9 g (0.044 mol) of *N*,*N*′-dicyclohexylcarbodimide, and 1.6 mL of pyridine in a mixture of 40 mL of Me_2SO and 60 mL of benzene cooled below 5 °C under N_2. The resulting reaction mixture was allowed to attain room temperature, and it was then stirred for 24 h. Ethyl acetate (200 mL) was added, and the mixture was filtered to remove precipitated *N*,*N*′-dicyclohexylurea. The filtrate was washed with brine (3 × 50 mL), dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. Trituration of the resulting gummy solid with diethyl ether/hexane followed by filtration gave 2.1 g (57%) of **3b** as colorless needles: mp 172–174 °C; NMR ($CDCl_3$) δ 1.6 (s, 9 H), 2.75 (t, 2 H, J = 7 Hz), 3.77 (s, 2 H), 3.77 (t, 2 H, J = 7 Hz), 6.6

and 7.95 (ABq, 4 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.58; H, 7.49; N, 5.76.

2-Amino-3-cyano-5,6-trimethylenepyridine (6). A solution of 120 mg (1 mmol) of 4,5-trimethylenepyrimidine[6] and 66 mg (1 mmol) of malononitrile in 0.5 mL of anhydrous tetrahydrofuran was heated under reflux for 10 h. The resulting dark oily mass was removed by filtration, and the resulting solid was washed with 2 × 2-mL portions of methylene chloride. Recrystallization from ethanol gave 40 mg (25%) of **6** as a yellow-brown solid, mp 212–214 °C (lit.[11] mp 219 °C).

***N*-[4-(Methoxycarbonyl)phenyl]-4-(*N*-pyrrolidino)-3-pyrroline (7a).** A solution of 0.75 g (3 mmol) of *N*-[4-(methoxycarbonyl)phenyl]-3-pyrrolidinone (**3a**) and 0.55 mL (6.6 mmol) of pyrrolidine in 50 mL of anhydrous tetrahydrofuran was slurried with 5 g of anhydrous magnesium sulfate at room temperature for 18 h. The mixture was then filtered and the filtrate evaporated under reduced pressure to give 0.72 g (87%) of **7a** as a yellow solid: mp 140–145 °C; NMR ($CDCl_3$) δ 1.8–2.0 (m, 2 H), 2.8–3.2 (m, 2 H), 3.6–4.0 (m, 5 H), 4.2 (m, 2 H), 6.5 and 7.9 (ABq, 4 H, J = 9 Hz).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.33; H, 7.27; N, 10.22.

***N*-[4-(*tert*-Butoxycarbonyl)phenyl]-4-(*N*-pyrrolidino)-3-pyrroline (7b).** A solution of 1 g (4 mmol) of *N*-[4-(*tert*-butoxycarbonyl)phenyl]-3-pyrrolidinone (**3b**) and 0.55 g (8 mmol) of pyrrolidine in 25 mL of anhydrous tetrahydrofuran was slurried with 5 g of anhydrous magnesium sulfate under N_2 at room temperature for 1.5 h. The mixture was filtered through Celite and the solvent evaporated under reduced pressure to give a yellow solid which was triturated with 10 mL of pentane to give 870 mg (70%) of crude **7b** as a yellow solid, mp 168–169 °C. This material was used without further purification, since attempted recrystallization led to extensive decomposition: NMR ($CDCl_3$) δ 1.6 (s, 9 H), 1.6–2.2 (m, 4 H), 2.64–3.30 (m, 4 H), 3.74 (m, 1 H), 4.19 (m, 4 H), 6.45 and 7.90 (ABq, 4 H, J = 9 Hz).

***N*-[4-(Methoxycarbonyl)phenyl]-3-(2,2-dicyanoethylene)-4-(*N*-pyrrolidino)-3-pyrroline (8a).** A solution of 0.35 g (0.003 mol) of (chloromethylene)malononitrile[8] in 5 mL of tetrahydrofuran was added dropwise to a solution of 0.8 g (2.9 mmol) of *N*-[4-(methoxycarbonyl)phenyl]-4-(*N*-pyrrolidino)-3-pyrroline (**7a**) and 0.5 mL (3 mmol) of triethylamine in 55 mL of tetrahydrofuran cooled to −20 °C. A precipitate rapidly formed. When the addition was complete (10 min) the reaction mixture was warmed to room temperature and stirred for 1 h. The precipitated solid was collected by filtration, washed well with water followed by methanol and ether, and then recrystallized from DMF to give 0.4 g (38%) of **8a** as an orange solid: mp 240–242 °C; NMR (Me_2SO-d_6) δ 1.8–2.0 (m, 4 H), 3.76 (s, 3 H), 3.6–3.8 (m, 4 H), 4.48 and 4.52 (2 s, 4 H), 6.55 and 7.8 (ABq, 4 H, J = 9 Hz), 7.46 (s, 1 H).

Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.96; H, 5.75; N, 16.09. Found: C, 68.60; H, 5.81; N, 15.88.

2-Amino-3-cyano-6-[4-(methoxycarbonyl)phenyl]-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine (9a). A suspension of 0.4 g of *N*-[4-(methoxycarbonyl)phenyl]-3-(2,2-dicyanoethylene)-4-(*N*-pyrrolidino)-3-pyrroline (**8a**) in 50 mL of saturated ethanolic ammonia was heated in a sealed tube for 12 h at 120 °C. The reaction mixture was then cooled to room temperature and filtered, and the collected solid recrystallized from DMF to give 0.3 g (89%) of **9a** as a beige solid: mp >250 °C; NMR (TFA) δ 4.05 (s, 3 H), 4.85 and 5.02 (2 s, 4 H), 6.8 and 8.1 (ABq, 4 H, J = 9 Hz), 8.45 (s, 1 H).

Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.76; N, 19.05. Found: C, 65.10; H, 4.58; N, 18.84.

2-Amino-3-cyano-6-[4-(*tert*-butoxycarbonyl)phenyl]-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine (9b). A solution of 3.8 g (0.034 mol) of (chloromethylene)malononitrile in 10 mL of anhydrous tetrahydrofuran was added dropwise to a cooled (−30 °C) solution of 10.7 g (0.034 mol) of *N*-[4-(*tert*-butoxycarbonyl)-phenyl]-4-(*N*-pyrrolidino)-3-pyrroline (**7b**) and 4.7 mL (0.034 mol) of triethylamine in 50 mL of anhydrous tetrahydrofuran under N_2. After addition was complete (10 min) the reaction mixture was warmed to room temperature, stirred for 2 h, and diluted with 60 mL of hexane, and the resulting precipitate collected by filtration and washed with water, methanol, and ether to give 10.5 g (81%) of crude **8b**. This material was suspended in 100 mL of saturated ethanolic ammonia and the mixture was heated in a sealed tube for 12 h at 120 °C. The reaction mixture was then cooled and filtered, and the collected solid recrystallized from DMF to give 5.7 g (49%) of **9b** as a beige solid: mp >250 °C; NMR (Me_2SO-d_6) δ 1.5 (s, 9 H), 4.5 (s, 4 H), 6.65 and 7.75 (ABq, 4 H, J = 9 Hz), 6.95 (s, 2 H), 7.85 (s, 1 H).

Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.86; H, 5.95; N, 16.67. Found: C, 68.06; H, 6.02; N, 16.55.

***tert*-Butyl 4-Deoxy-4-amino-7,10-methano-5-deazapteroate (10).** Dimethylguanidine hydrochloride (4.4 g, 0.0357 mol) was added to a solution of 4.4 g (0.04 mol) of potassium *tert*-butoxide in 50 mL of dry DMF, and after 15 min of stirring, 4.0 g (0.0119 mol) of 2-amino-3-cyano-6-[4-(*tert*-butoxycarbonyl)phenyl]-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine (**9b**) was added. The reaction mixture was heated at 100 °C for 8 h, and the yellow solid which had separated was collected by filtration and washed with DMF, hot water, methanol, acetone, and finally ether to give 3.8 g (84%) of **10** as a tan powder: mp >250 °C; NMR (TFA) δ 1.68 (s, 9 H), 5.18 (s, 4 H), 7.15 and 8.25 (ABq, 4 H, J = 9 Hz), 8.95 (s, 1 H).

Anal. Calcd for $C_{20}H_{22}N_6O_2$: C, 63.46; H, 5.87; N, 22.21. Found: C, 63.09; H, 5.93; N, 21.99.

4-Deoxy-4-amino-7,10-methano-5-deazapteroic Acid (1). A solution of 0.4 g of *tert*-butyl 4-deoxy-4-amino-7,10-methano-5-deazapteroate (**10**) in 8 mL of 88% formic acid was stirred at room temperature for 18 h. Over this period of time a thick yellow precipitate formed. The reaction mixture was diluted with 25 mL of water, the pH adjusted to 6 by addition of aqueous ammonium hydroxide, and the separated yellow solid was collected by filtration and washed well with water followed by methanol and ether to give 0.28 g (83%) of **1** as a yellow powder: mp >250 °C; NMR (TFA) δ 5.18 (s, 4 H), 7.1 and 8.3 (ABq, 4 H), 8.95 (s, 1 H); MS calcd for $C_{16}H_{14}N_6O_2$ 322 (M^+), found 322 (M^+), 278, 277.

***N*-[4-(*tert*-Butoxycarbonyl)phenyl]-3-[(*N*,*N*-dimethylamino)methylene]-4-pyrrolidinone (14).** A mixture of 0.5 mL of DMF dimethyl acetal and 0.2 g (0.77 mmol) of *N*-[4-(*tert*-butoxycarbonyl)phenyl]-3-pyrrolidinone (**3b**) in 5 mL of ethanol was heated under reflux under N_2 for 4 h. The solvent and excess reagent were then removed by evaporation under reduced pressure, and the residual solid was triturated with ether/hexane to give 0.8 g (33%) of **14** as an orange solid: mp 162–165 °C; NMR ($CDCl_3$) δ 1.6 (s, 9 H), 3.2 (s, 6 H), 3.85 and 4.1 (2 s, 4 H), 6.55 and 7.95 (ABq, 4 H, J = 9 Hz), 7.4 (s, 1 H).

Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.35; H, 7.59; N, 8.86. Found: C, 68.03; H, 7.42; N, 8.66.

***tert*-Butyl 7,10-Methano-5-deazapteroate (15).** A mixture of 2 g (6.3 mmol) of *N*-[4-(*tert*-butoxycarbonyl)phenyl]-3-[(*N*,*N*-dimethylamino)methylene]-4-pyrrolidinone (**14**) and 0.8 g (6.3 mmol) of 2,4-diamino-6(1*H*)-pyrimidinone in 20 mL of 60% aqueous acetic acid containing one drop of piperidine was heated under reflux under N_2 for 2 h. The warm reaction mixture was then filtered, and the collected solid was washed well with hot water, methanol, and finally ether to give 1.86 g (86%) of **15** as a yellow powder: mp >250 °C; NMR (TFA) δ 1.65 (s, 9 H), 5.12 (s, 4 H), 7.1 and 8.25 (ABq, 4 H, J = 9 Hz), 8.8 (s, 1 H).

7,10-Methano-5-deazapteroic Acid (2). Hydrogen chloride gas was passed for 2 min through a suspension of 0.38 g of *tert*-butyl 7,10-methano-5-deazapteroate (**15**) in 10 mL of nitromethane cooled in an ice bath. The reaction mixture was stirred at room temperature for 30 min, and 10 mL of diethyl ether was added. The resulting precipitate was collected by filtration and dried at 100 °C (0.1 mm) for 2 h to give 0.25 g (89%) of **2** as a tan solid, mp >250 °C. This material was so insoluble that an NMR spectrum in TFA solution was unobtainable.

***tert*-Butyl 2-Acetyl-7,10-methano-5-deazapteroate (16).** A suspension of 0.5 g of *tert*-butyl 7,10-methano-5-deazapteroate (**15**) in 10 mL of acetic anhydride containing 5 drops of 4-(dimethylamino)pyridine was heated under reflux for 2 h, cooled to room temperature, and diluted with 10 mL of diethyl ether, and the separated solid collected by filtration. Recrystallization from *N*-methylpyrrolidone gave 0.6 g (47%) of **16** as a tan powder, mp >250 °C. The material was so insoluble that an NMR

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spectrum, even in TFA, could not be obtained.

Anal. Calcd for $C_{22}H_{23}N_5O_4$: C, 62.69; H, 5.50; N, 16.62. Found: C, 62.38; H, 5.41; N, 16.33.

2-Acetyl-7,10-methano-5-deazapteroic Acid (17). Method A. Hydrogen chloride was bubbled for 2 min through a suspension of 0.1 g of *tert*-butyl 2-acetyl-7,10-methano-5-deazapteroate in 10 mL of nitromethane at room temperature. A yellow precipitate rapidly separated from the initially homogeneous solution. The mixture was stirred for 2 h and diluted with 10 mL of diethyl ether, and the suspended solid collected by filtration and dried at 100 °C (0.1 mm) to give 80 mg (92%) of **17** as a tan solid: mp >250 °C; NMR (Me_2SO-d_6) 2.2 (s, 3 H), 4.75 (s, 4 H), 6.7 and 7.85 (ABq, 4 H, J = 9 Hz), 8.4 (s, 1 H); LRMS 365 (M^+).

Method B. Hydrogen chloride gas was bubbled for 2 min through a suspension of 2.0 g of *tert*-butyl 4-deoxy-4-amino-7,10-methano-5-deazapteroate (**10**) in 50 mL of nitromethane cooled in an ice bath. The reaction mixture was stirred at room temperature for 3 h and diluted with 30 mL of diethyl ether, and the precipitated solid collected by filtration, dried at 70 °C (0.1 mm), and then suspended in 100 mL of 1 N sodium hydroxide solution. This suspension was heated under reflux for 6 h and acidified to pH 6 with acetic acid, and the resulting gelatinous precipitate collected by filtration to give 1.5 g (88%) of 7,10-methano-5-deazapteroic acid (**2**). A suspension of 0.2 g of **2** in 10 mL of acetic anhydride containing 3 drops of 4-(dimethylamino)pyridine was heated under reflux for 1 h, cooled, and diluted with 10 mL of ether, and the precipitated solid collected by filtration. This material was dissolved in 10 mL of 1 N sodium hydroxide solution. Neutralization with acetic acid resulted in the separation of a solid which was collected by filtration and dried to give 0.18 g (80%) of **17**, identical in every respect with the material prepared by Method A as described above.

Registry No. 1, 94943-98-3; **2**, 94930-26-4; **3a**, 90030-20-9; **3b**, 94930-27-5; **4**, 94930-28-6; **5**, 5661-00-7; **6**, 65242-18-4; **7a**, 94930-29-7; **7b**, 94930-30-0; **8a**, 94930-31-1; **8b**, 94930-32-2; **9a**, 94930-33-3; **9b**, 94930-34-4; **10**, 94930-35-5; **14**, 94930-36-6; **15**, 94930-37-7; **16**, 94930-38-8; **17**, 94930-39-9; *N*-[4-(methoxycarbonyl)phenyl]-4-(methoxycarbonyl)-3-pyrrolidinone, 23935-80-0; *tert*-butyl 4-fluorobenzoate, 58656-98-7; 2,4-diamino-6-(1*H*)-pyrimidinone, 56-06-4; 6-[*p*-(*tert*-butyloxycarbonyl)-phenyl]-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine, 94930-40-2; 3-pyrrolidinol, 40499-83-0; malononitrile, 109-77-3; (chloromethylene)malononitrile, 10472-09-0; *N*,*N*-dimethylguanidine, 6145-42-2; dimethylformamide dimethyl acetal, 4637-24-5; 1,3,5-triazine, 290-87-9.

A Theoretical Analysis of the Interaction of the Phosphonate and Sulfonyl Groups with a Carbocationic Center

Daniel J. Pasto

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

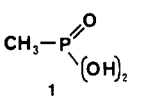
Received August 22, 1984

Solvolytic studies on derivatives of the α-hydroxy phosphonate system have indicated that the destabilizing effect of the phosphonate function on the carbocationic center is less than anticipated. An interaction between the p AO of the cationic center with a d AO on phosphorus was suggested to account for this effect. Theoretical calculations have been carried out on methanephosphonic acid and hydrogen methyl sulfone and the corresponding carbocations. Calculations have been carried out with and without a set of d AO's on phosphorus and sulfur in the STO-3G and 4-31G basis sets to assess the effect on charge delocalization and on the relative stability of the substituted cations. Very interestingly, with the parent systems no open cationic structures representing a local minimum were found in these studies; the open structures closed to form three-membered ring structures. The effect of methyl substitution at the cationic center has been briefly investigated.

Considerable interest has been shown recently in the effect of electron-withdrawing groups on the stability of carbocationic centers. Experimental results have been reported describing the effects of the carbonyl,[1] cyano,[2] phosphonate,[3] and trifluoromethyl[4] groups on the stability of carbocations. The carbonyl and cyano groups destabilize the carbocationic center to a lesser degree than would have been expected on the basis of their σ values. This attenuated destabilization has been attributed to delocalization of the π-orbitals of the carbonyl and cyano groups to the carbocationic center. The results of theoretical studies have supported this view.[5] The phosphonate group similarly destabilizes the cationic center to a lesser degree than anticipated,[3] and an interaction between the p AO of the cationic center with a d AO on phosphorus was suggested to account for this attenuated destabilization. Calculations have now been carried out on model phosphonate and sulfonyl systems in order to gain a more thorough understanding of this type of interaction.

Results and Discussion

Methanephosphonic Acid and Related Cations. Complete geometry optimization calculations on methanephosphonic acid (**1**) have been carried out at the



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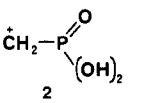

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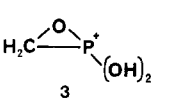

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