Conversion of 1-Benzyl-4-aminotetrahydropyridine-3-carboxylic Acid Methyl Ester to Antithrombotic Pyrido[4,3-*d*]pyrimidine-2,4-diones and to (2-Oxotetrahydropyrimidin-4-ylidene)acetic Acid Methyl Esters

H. Furrer*[a], H.-W. Fehlhaber [b] and R. Wagner [a]

[a] Preclinical Research, Medicinal Chemistry, Hoechst AG Werk Kalle-Albert, D-65174 Wiesbaden, Germany
[b] General Pharma Research, Hoechst AG, D-65926 Frankfurt/Main, Germany
Received August 8, 1994

6-Benzyl-3-methyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **2**, a representative of new antithrombotic compounds with favourable cerebral and peripheral effects has been synthesized from enamine **1** in good yield by two methods. The thermal fusion of **1** with ureas gave the pyrido[4,3-*d*]-pyrimidine-2,4-diones **5a**, **2** and **5b** and unexpectedly the esters **6** and **7**. The structure of **6** was deduced from its spectroscopic properties and was proven by ozonolysis to cleavage products **9** and **10** and by oxidative hydrolysis to pyrimidin-2-one **13**. The (*Z*)-configured **6** was converted to (*E*)-configured **7** by methylation. The products **5a**, **5b** and **5c** were synthesized by independent methods. Hydrogenolysis of **2** led to the secondary amine **15** which was alkylated to the base of **16**.

J. Heterocyclic Chem., **31**, 1569 (1994).

In the course of our studies directed towards drugs with antithrombotic and vasoactive efficiency we wished to prepare alkylated pyrido[4,3-*d*]pyrimidine-2,4-diones. This was achieved as outlined in Schemes I, II, V and VI. Results from *in vivo* evaluations have shown that some of these compounds like **2** or **16** have pronounced antithrombotic activity, promote the restoration of normal functions in ischemic muscles and have favourable effects on the energy metabolism in neuropathological syndromes [1].

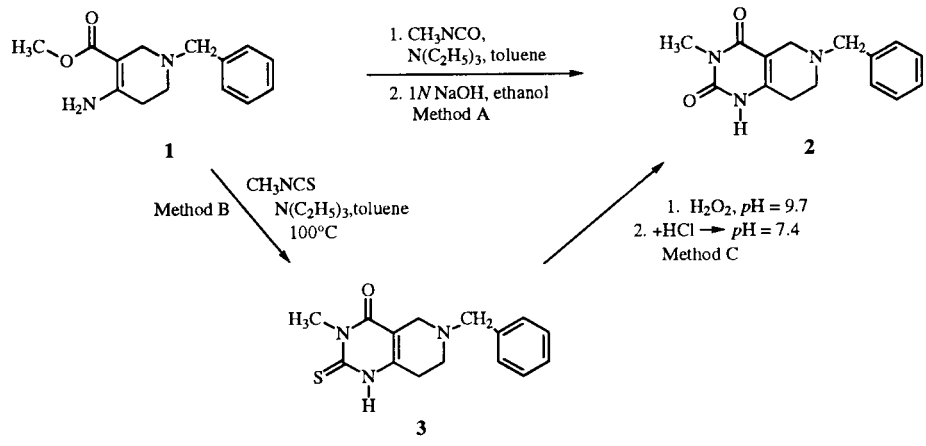
In Scheme I the synthesis of compound **2** as a representative of a 3-alkylated 5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]-pyrimidine-2,4-dione is illustrated by two different routes. Method A gave **2** by treatment of enamine **1** [2] with methyl isocyanate and triethylamine to the corresponding urea as an intermediate which was cyclized *in situ* to **2** with sodium hydroxide. The reaction of **1** with methyl isothiocyanate in the presence of triethylamine led to bicyclic thiouracil **3** (Method B). Compound **3** was oxidized to **2** by treatment with hydrogen peroxide (Method C).

As a third route to pyrido[4,3-*d*]pyrimidine-2,4-diones the thermal fusion of enamine **1** with ureas **4a** or **4b** at 180° was envisaged. Under these reaction conditions **4a** and **1** resulted not only in the expected bicyclic product **5a**, but surprisingly also in the α,β-unsaturated ester **6**. In an analogous reaction of **1** with *N*-methylurea **4b**, the bicyclic products **2** and **5b** and the unexpected compounds **6** and **7** were obtained (Scheme II).

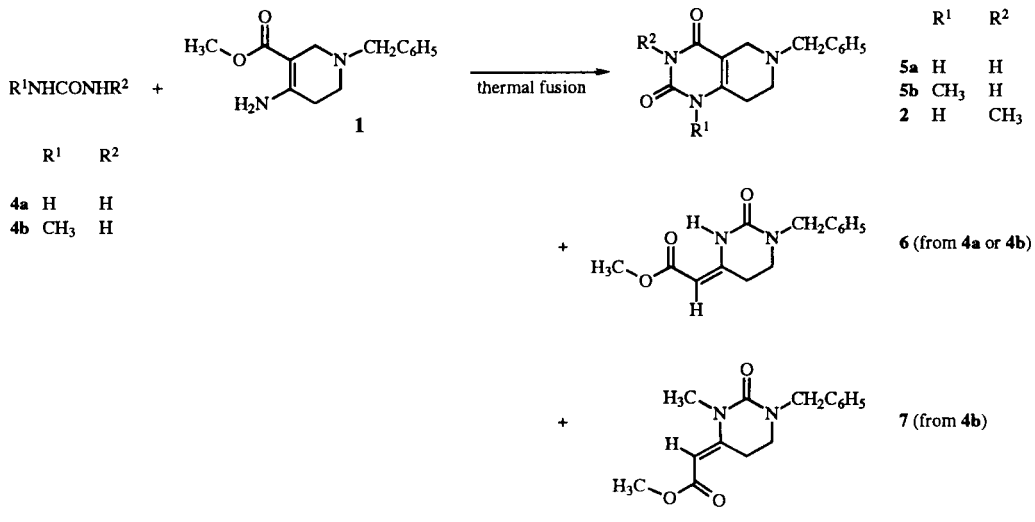
The structures of (*Z*)- and (*E*)-α,β-unsaturated esters **6** and **7** have been deduced from their spectroscopic properties and have been verified chemically by degradation reactions of **6** as well as by conversion of **6** to **7** (Scheme III).

The spectroscopic elucidation of structures **6** and **7** was achieved by ^1H nmr, ^{13}C nmr, mass and ir spectra and by selective difference nuclear overhauser effects (Δ-NOE). From the Δ-NOE measurements the clearcut assignment of the (*Z*)-configuration to structure **6** (NOE between the CH_2 group in 5-position and the olefinic hydrogen atom

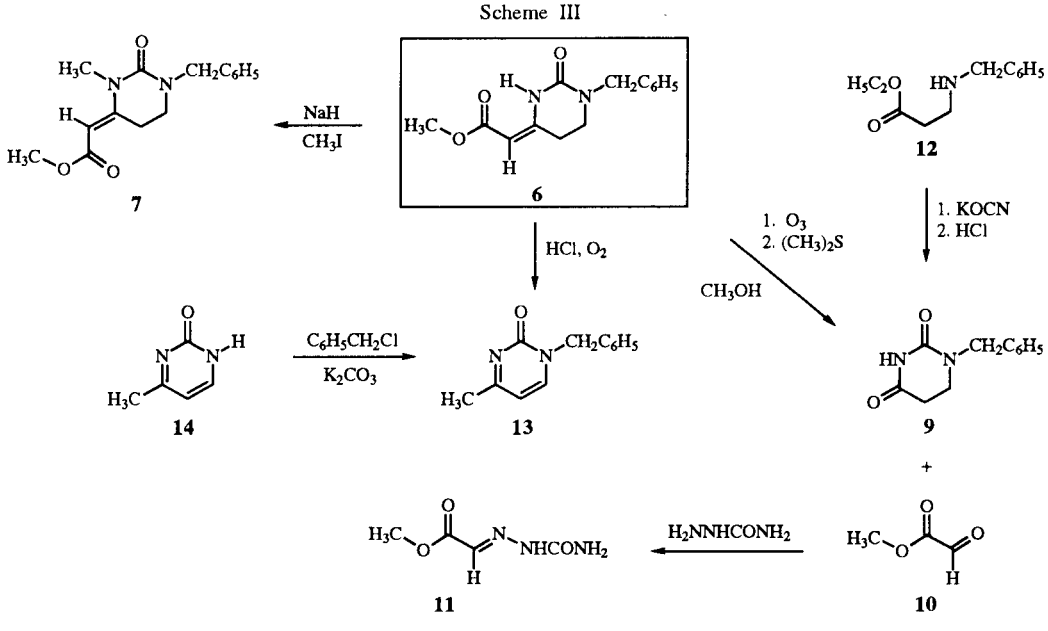
Scheme I



Scheme II



Scheme III



of the exocyclic double bond) and the (*E*)-configuration to structure **7** (NOE between the olefinic hydrogen atom and the N_3-CH_3 group) was possible.

Due to the inductive effect of the closely located carboxylic acid ester group, the CH_2 group in 5-position in the ^1H nmr spectrum of compound **7** is 0.76 ppm at lower field than the corresponding CH_2 group of compound **6**.

The degradation of **6** was performed by ozonolysis and by acid-catalyzed hydrolysis.

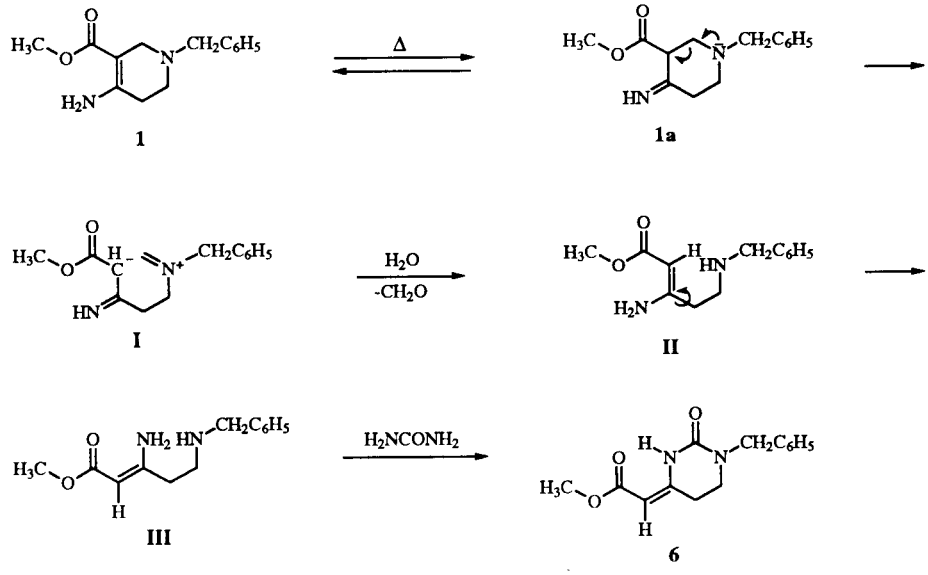
Ozonolysis of **6** led to oxidative cleavage of the exocyclic double bond furnishing dihydropyrimidin-2,4-dione **9** and oxoacetic acid methyl ester **10**. The structure of **9** was derived from spectral data and was proven by independent synthesis from amino ester **12** [3]. Product **10** was identified by conversion into its semicarbazone **11** [4].

Heating of **6** at reflux under air in 18% aqueous hydrochloric acid resulted in hydrolysis of the α,β-unsaturated ester function, decarboxylation, tautomerization and finally oxidation to pyrimidin-2-one **13**. The structure of **13** was proven spectroscopically and by synthesis from **14** which reacted regiospecifically with potassium carbonate and benzyl chloride in dimethylformamide.

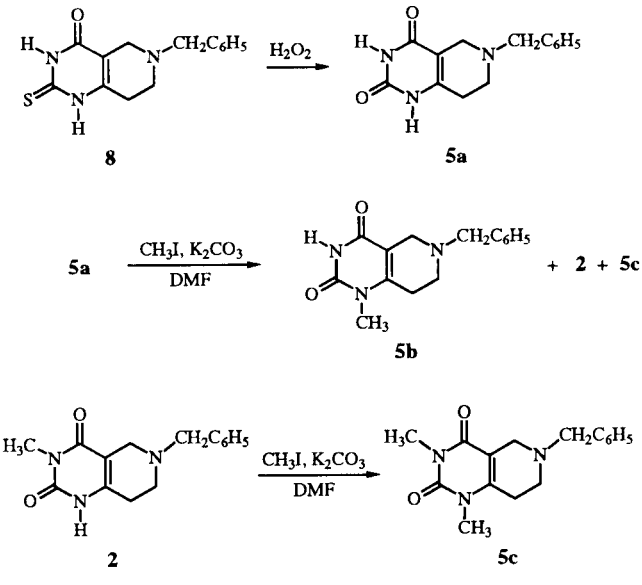
Reaction of (*Z*)-configured **6** with sodium hydride and methyl iodide led to isomerization of the α,β-unsaturated ester and conversion into the (*E*)-configured *N*-methylated product **7**.

A mechanism for the formation of (*Z*)-configured ester **6** from **1** and urea **4a** is proposed in Scheme IV. As a first step tautomerization of enamine **1** yields **1a** which under-

Scheme IV



Scheme V

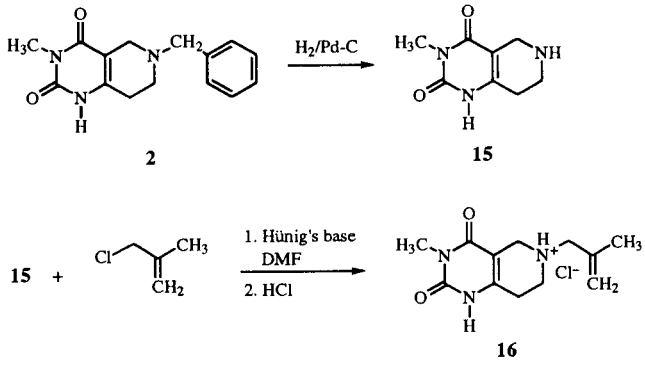


goes a ring-opening to **I** followed by hydrolysis under loss of formaldehyde and formation of **II** which results in **III** by rotation around a C-C-bond. The rotation isomer **III** finally reacts with urea under ring closure leading to the (*Z*)-configured **6**. The formation of **6** from N-methylurea **4b** and **1** should proceed in a comparable manner.

For the formation of N-methylated (*E*)-configured **7** from **1** and *N*-methylurea **4b** we suggest a similar mechanism where the incorporation of the methylamino group occurs either by replacement of the amino residue by the methylamino function through reaction with methylamine (from the thermal decomposition of **4b**) during the sequence in Scheme IV or by reaction of **III** with **4b** under elimination of 2 moles of ammonia.

The pyrido[4,3-*d*]pyrimidine-2,4-dione products of the thermal fusion (Scheme II) have been prepared independently for comparison (Scheme V). Oxidation of thioxo compound **8** [5] with hydrogen peroxide according to Method C led to **5a**. Methylation of **5a** resulted in products **2**, **5b** and **5c**. These compounds were separated by medium pressure chromatography. Compound **5c** was also obtained by methylation of **2** (Scheme V). The debenzylation of compound **2** by Pd-C catalyzed hydrogenolysis in acetic acid led to **15** which was alkylated at the 6-position with 2-methylallyl chloride in the presence of Hünigs base. The product was characterized as its hydrochloride to give compound **16** (Scheme VI).

Scheme VI



EXPERIMENTAL

Melting points were determined on a Büchi® SMP 20 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer® 841 and nuclear magnetic

resonance spectra were taken on a Varian® GEM 200 or a Bruker® JL 280, NOE-measurements were performed on a Bruker® HX 270. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Ultraviolet spectra were determined on a Pye Unicam® SP 8000. Mass spectra were performed on a Kratos® MS 30, a MS 80 RFA or a MS 902 S. The hplc were done on a liquid chromatograph PU 4850 from Philips®. For medium pressure chromatography the following were used: A pressure pump from Büchi®, columns from Büchi® filled with Matrex™ silica gel (6 nm pore diameter, 20-45 µm particle size), and a fraction collector Superrac from LKB® with a uv-detector (wave length 275 nm).

6-Benzyl-3-methyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]-pyrimidine-2,4-dione **2**. (Method A).

The mixture of **1** (24.6 g, 0.1 mole), 90% methyl isocyanate (26.2 ml, 0.38 mole) and triethylamine (3 ml) in toluene (150 ml) was heated under nitrogen for 8 hours at 100° in an autoclave. The solvent was evaporated and the residue was diluted with 1 *N* sodium hydroxide (325 ml) and ethanol (100 ml). The mixture was heated for 20 minutes at reflux. It was cooled to room temperature and the *p*H 7.5 adjusted with concentrated hydrochloric acid. It was evaporated *in vacuo* and the residue was extractively worked up with dichloromethane and water. The organic layer was dried over sodium sulfate, then the solvent was evaporated *in vacuo* and the residue was recrystallized from 2-propanol to give **2** (16 g, 59%); ^{1}H nmr (DMSO-d_6): δ = 2.45 (m, 2H, 8-H), 2.62 (m, 2H, 7-H), 3.06 (s, 2H, 5-H), 3.10 (s, 3H, N_3-CH_3), 3.63 (s, 2H, N-CH_2C$_6$H$_5$), 7.3 (m, 5H, C$_6$H$_5$), 11.1 (s, 1H, N_1H). The base was dissolved in dichloromethane, treated with ethereal hydrogen chloride and the precipitate was recrystallized from water to afford **2** hydrochloride (13.9 g, 45%), dec from 298°; ^{1}H nmr (DMSO-d_6): δ = 2.6-3.1 (m, 2H, 8-H), 3.13 (s, 3H, N_3-CH_3), 3.1-3.7 (m, 2H, 7-H), 3.8 (m, 2H, 5-H), 4.45 (m, 2H, N-CH_2C$_6$H$_5$), 7.48 (m, 3H, C$_6$H$_5$), 7.65 (m, 2H, C$_6$H$_5$), 11.05 (m, 1H, NH), 11.5 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ = 26.4, 27.7, 48.8 (5-C, 7-C), 61.5, 102.3, 126.9, 128.2, 128.7, 138.1, 150.5, 153.6, 162.8.

Anal. Calcd. for $C_{15}H_{18}ClN_3O_2$ (307.78): C, 58.54; H, 5.90; Cl, 11.52; N, 13.65. Found: C, 58.34; H, 5.84; Cl, 11.33; N, 13.61.

6-Benzyl-3-methyl-2-thioxo-2,3,5,6,7,8-hexahydro-1*H*-pyrido[4,3-*d*]pyrimidin-4-one **3**. (Method B).

Methyl isothiocyanate (447 g, 6.1 moles) and triethylamine (625 ml, 4.5 moles) were added subsequently to a stirred solution of 94% **1** (788 g, 3 moles) in toluene (2.5 ℓ). The mixture was heated for 24 hours at 100°, then cooled to 20°. The precipitate was collected and washed with toluene. Drying *in vacuo* gave crude **3** (420 g, 49%) as a yellow solid which was used directly for the preparation of **2**. A sample (15 g) was recrystallized from ethanol and dried *in vacuo* yielding **3** (13.4 g), dec from 210°; ir (potassium bromide): ν = 3215, 3170, 3045, 2950, 2920, 1660, 1630, 1550, 1460, 1410, 1280, 1125, 1110, 1060, 1020, 990, 835, 810, 760, 745, 740, 700, 660 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ = 2.50 (m, 2H, 8-H), 2.65 (m, 2H, 7-H), 3.09 (s, 2H, 5-H), 3.51 (s, 3H, N_3-CH_3), 3.65 (s, 2H, N_6-CH_2C$_6$H$_5$), 7.32 (m, 5H, C$_6$H$_5$), 12.6 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_{17}N_3OS$ (287.39): C, 62.69; H, 5.96; N, 14.62; S, 11.16. Found: C, 62.66; H, 6.03; N, 14.62; S, 11.26.

6-Benzyl-3-methyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **2**. (Method C).

To a well stirred solution of sodium hydroxide (78 g, 1.95 moles) in water (4 ℓ) was added at room temperature **3** (210 g, 0.73 mole). The resulting suspension was cooled to 0° and 30% hydrogen peroxide (3.2 ℓ, 28 moles) was added with stirring at 0° during 5.5 hours. After further 30 minutes of stirring at 0° the *p*H was adjusted from 9.7 to 7.4 with concentrated aqueous hydrochloric acid solution. The precipitate was collected, washed with water and dried *in vacuo*.

The above procedure was repeated. The precipitates were combined (396 g), suspended in water (1 ℓ) and dissolved by addition of a 33% aqueous sodium hydroxide solution. The solution of *p*H 13.5 was stirred, treated with charcoal and filtered. The *p*H of the filtrate was adjusted at room temperature to 10 by addition of concentrated aqueous hydrochloric acid solution. The resulting precipitate was collected by filtration, washed with water and dried *in vacuo*, affording **2** (192 g) as a white solid. The base was dissolved in dichloromethane, treated with ethereal hydrogen chloride and the precipitate was recrystallized from 2-propanol to afford 216.3 g (48%) of **2** hydrochloride, dec from 298°; ir (potassium bromide): ν = 3265, 3220, 2980, 2920, 2490, 1700, 1670, 1625, 1540, 1515, 1450, 1440, 1410, 1400, 1370, 1320, 1280, 1240, 1210, 1195, 1065, 1040, 980, 890, 760, 750, 705, 690, 615 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ = 2.6-3.1 (m, 2H, 8-H), 3.11 (s, 3H, N_3-CH_3), 3.1-3.7 (m, 2H, 7-H), 3.72 (m, 2H, 5-H), 4.43 (br s, 2H, N-CH_2C$_6$H$_5$), 7.48 (m, 3H, C$_6$H$_5$), 7.65 (m, 2H, C$_6$H$_5$), 11.55 (br m, 2H, N_6H and N_1H).

Anal. Calcd. for $C_{15}H_{18}ClN_3O_2$ (307.78): C, 58.54; H, 5.90; Cl, 11.52; N, 13.65. Found: C, 58.19; H, 6.02; Cl, 11.99; N, 13.66.

6-Benzyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **5a** and (*Z*)-(1-Benzyl-2-oxotetrahydropyrimidin-4-ylidene)acetic Acid Methyl Ester **6**.

Compound **1** (100 g, 0.406 mole) was added at 180° during 15 minutes with stirring to the fusion of urea (400 g, 6.6 moles), which was gasing strongly. Heating was continued for 40 minutes at 180°, then the temperature was lowered to 150° and the melt was poured carefully with stirring into water (2.5 ℓ). The aqueous solution was extractively worked up with dichloromethane (2 ℓ). During this process a white precipitate (20.3 g) occurred, which led, after several recrystallizations from ethanol, and drying *in vacuo*, to **5a** (16.5 g, 16%), dec from 291°; ir (potassium bromide): ν = 3150, 3010, 2940, 2840, 2760, 1730, 1700, 1650, 1510, 1450, 1440, 1370, 1270, 1210, 1140, 1055, 1020, 890, 850, 800, 760, 740, 700 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ = 2.43 (m, 2H, 8-H), 2.63 (m, 2H, 7-H), 3.00 (s, 2H, 5-H), 3.62 (s, 2H, N-CH_2C$_6$H$_5$), 7.33 (m, 5H, C$_6$H$_5$), 10.8 (s, 1H, NH), 10.98 (s, 1H, NH).

The above compound was identical, according to tlc, ir- and ^{1}H nmr-spectra, to **5a** synthesized independently by oxidation of **8**.

The dichloromethane phase was dried over sodium sulfate and concentrated *in vacuo*. The residue gave after a medium pressure chromatography on silica gel using *tert*-butyl methyl ether/petroleum ether (60-80°)-1/1-, recrystallization from dichloromethane-petroleum ether (60-80°) and drying *in vacuo* 13.2 g (13%) of **6**, mp 98-99°; ir (potassium bromide): ν = 3320, 3030, 2950, 1670, 1620, 1500, 1450, 1420, 1360, 1340, 1260, 1160, 1080, 1040, 800, 750, 700, 600 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.57 (dt, 2H, 5-H), 3.23 (t, 2H, 6-H), 3.69 (s, 3H, OCH_3), 4.59 (s, 2H, N-CH_2C$_6$H$_5$), 4.73 (t, 1H, =CH), 7.30 (m, 5H, C$_6$H$_5$), 9.88 (br s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ = 28.2 (5-C), 42.2 (6-C), 50.9, 51.0 (N-CH_2C$_6$H$_5$, O-CH_3), 89.5 (=CH), 128.1, 128.4, 129.1 (aromat *C*H), 137.2 (aromat *C*), 152.4, 152.5, 168.9 (4-C, 2-C, *C*OOCH$_3$); ms: (DI) m/z 260 (M$^+$); uv (methanol):

λ_{max} 269 nm (ε = 24,180), 207 nm (ε = 9,615).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$ (260.29): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.51; H, 6.19; N, 10.77.

6-Benzyl-3-methyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **2**, 6-Benzyl-1-methyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **5b**, (*Z*)-(1-Benzyl-2-oxotetrahydropyrimidin-4-ylidene)acetic Acid Methyl Ester **6** and (*E*)-(1-Benzyl-3-methyl-2-oxotetrahydropyrimidin-4-ylidene)-acetic Acid Methyl Ester **7**.

Compound **1** (100 g, 0.406 mole) was added at 180° during 15 minutes with stirring to the fusion of *N*-methylurea (490 g, 6.5 moles). Heating was continued for 1 hour at 180°, then the temperature was lowered to 120° and the melt was poured carefully with stirring into water (1.5 ℓ). The aqueous solution was extractively worked up with dichloromethane (2 ℓ). The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by medium pressure chromatography on silica gel using *tert*-butyl methyl ether/petroleum ether (60-80°)-1/1-, furnishing successively the following:

a) The *N*-Methyl-compound **7** (4.1 g, 3.7%), had mp 106° (dichloromethane/petroleum ether); ir (potassium bromide): ν = 2950, 2900, 2860, 1690, 1680, 1650, 1600, 1490, 1450, 1430, 1410, 1360, 1330, 1300, 1270, 1260, 1220, 1190, 1170, 1160, 1150, 1120, 1080, 1060, 1040, 1020, 950, 820, 760, 750, 710, 600 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 3.19 (m, 2H, 6-H), 3.21 (s, 3H, N-CH_3), 3.33 (m, 2H, 5-H), 3.65 (s, 3H, OCH_3), 4.61 (s, 2H, N-$CH_2C_6H_5$), 5.09 (s, 1H, =CH), 7.3 (m, 5H, C_6H_5); ^{13}C nmr (deuteriochloroform): δ = 24.7 (5-C), 31.4 (N-CH_3), 41.4 (6-C), 50.7, 51.8 (N-$CH_2C_6H_5$, OCH_3), 92.3 (=CH), 127.7, 128.0, 128.8 (aromat *C*H), 137.0 (aromat *C*), 153.7, 155.3, 168.3 (4-C, 2-C, *C*$OOCH_3$); ms: (FAB) m/z 275 (M^++1); uv (methanol): λ_{max} 271 nm (ε = 26,125), 208 nm (ε = 12,095).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.34; H, 6.54; N, 10.23.

b) Compound **6** (4.6 g, 4.3%), had mp 99° (dichloromethane/petroleum ether); ^1H nmr (deuteriochloroform): δ = 2.55 (dt, 2H, 5-H), 3.23 (t, 2H, 6-H), 3.69 (s, 3H, OCH_3), 4.59 (s, 2H, N*C*$H_2C_6H_5$), 4.74 (t, 1H, =CH), 7.3 (m, 5H, C_6H_5), 9.88 (br s, 1H, NH)

Anal. Calcd. for $C_{14}H_{16}N_2O_3$ (260.29): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.61; H, 6.14; N, 10.73.

The more polar eluent dichloromethane/ethanol (9/1→ 7/3) yielded: c) compound **2** (1.2 g, 1.1%) and d) compound **5b** (35 mg, 0.03%) in addition.

Compounds **2** and **5b** in fractions c) and d) respectively, were identified by comparison with authentic samples using: 1) tlc on silica gel with dichloromethane/ethanol-98/2-as eluent and 2) hplc on a C-18 column (Nucleosil), gradient elution in 10 minutes with a mixture of acetonitrile/0.1 *M* phosphoric acid, gradient from 3% to 20% acetonitrile, then isocratic elution in 10 minutes with 20% acetonitrile/80% 0.1 *M* phosphoric acid. This system was also used for quantitative determination of **2** and **5b** using benzoic acid as an internal standard.

6-Benzyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **5a**.

This compound was obtained from 6-benzyl-2-thioxo-2,3,5,6,7,8-hexahydro-1*H*-pyrido[4,3-*d*]pyrimidin-4-one **8** [5] in 67% yield by method C as a colourless powder, dec from 291°; ^1H nmr (DMSO-d_6): δ = 2.44 (m, 2H, 8-H), 2.63 (m, 2H, 7-H), 3.01 (s, 2H, 5-H), 3.63 (s, 2H, N-$CH_2C_6H_5$), 7.33 (m, 5H, C_6H_5), 10.80 (s, 1H, NH), 10.95 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$ (257.29): C, 65.35; H, 5.88; N, 16.33. Found: C, 65.06; H, 5.87; N, 16.15.

6-Benzyl-1-methyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **5b**, 6-Benzyl-1,3-dimethyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **5c**, and 6-Benzyl-3-methyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **2**.

A mixture of **5a** (15.7 g, 0.061 mole) and potassium carbonate (8.7 g, 0.063 mole) in dimethylformamide (700 ml) was stirred at 50° for 1.5 hours. Methyl iodide (8.9 g, 0.063 mole) was then added over 10 minutes. After an additional 5 hours of stirring at 50° the mixture was concentrated *in vacuo*. The residue was extractively worked up with dichloromethane and water. The organic phases were combined, dried (sodium sulfate) and evaporated. The residue was chromatographed at medium pressure (silica gel, elution with dichloromethane/ethanol 98/2) and gave successively the following:

a) Compound **5c**.

This compound was shown to be identical with an authentic product obtained by methylation of **2**, (see below) according to tlc (silica gel, elution with dichloromethane/ethanol 95/5) and hplc (column with C-18 (Nucleosil), gradient elution in 10 minutes with a mixture of acetonitrile/0.1 *M* phosphoric acid, gradient from 10% to 50% acetonitrile.

b) Compound **5b**.

The fractions with pure **5b** were combined, dissolved in dichloromethane and treated with ethereal hydrogen chloride. The precipitate was recrystallized from water and dried *in vacuo* yielding **5b** hydrochloride (2.6 g, 14%), dec from 293°; ir (potassium bromide): ν = 3000, 2790, 2700, 2645, 2580, 1710, 1700, 1480, 1425, 1400, 1340, 1230, 1220, 1190, 1110, 1090, 1060, 980, 965, 860, 745, 730, 695 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.05 (br m, 2H, 8-H), 3.27 (s, 3H, N_1-CH_3), 3.45 (br m, 2H, 7-H), 3.75 (br m, 2H, 5-H), 4.48 (br m, 2H, N-$CH_2C_6H_5$), 7.49 (m, 3H, C_6H_5), 7.68 (m, 2H, C_6H_5), 11.65 (broad s, N-H).

Anal. Calcd. for $C_{15}H_{18}ClN_3O_2$ (307.78): C, 58.54; H, 5.90; Cl, 11.52; N, 13.65. Found: C, 58.34; H, 5.92; Cl, 11.44; N, 13.58.

c) Compound **2**.

This fraction was shown to be identical with authentic **2** according to tlc (silica gel, elution with dichloromethane/ethanol 95/5) and hplc (conditions as under a).

6-Benzyl-1,3-dimethyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]-pyrimidine-2,4-dione **5c**.

To a stirred mixture of **2** (40.7 g, 0.15 mole) and potassium carbonate (20.7 g, 0.15 mole) in dimethylformamide (230 ml) was added dropwise at 40° in 10 minutes methyl iodide (9.6 ml, 0.154 mole). Stirring was continued for 8 hours at 60°, then the solvent was evaporated. The residue was taken up with water (150 ml) and the *p*H adjusted to 8 by addition of 2 *N* aqueous hydrochloric acid. The mixture was extractively worked up with dichloromethane and water. The organic phases were combined, dried (sodium sulfate) and the solvent was evaporated. The residue was chromatographed (silica gel, elution with dichloromethane/ethanol 95/5). The fractions with pure **5c** were combined, dissolved in diethyl ether and treated with a solution of hydrogen chloride in ethanol. The precipitate was recrystal-

lized from methanol/diethyl ether and dried *in vacuo*, giving **5c** hydrochloride (15.1 g, 31%), mp 141-143°; ir (potassium bromide): ν = 3490, 3420, 2930, 2685, 2580, 1695, 1660, 1620, 1495, 1435, 1375, 1340, 1015, 765, 740, 705 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.06 (br m, 2H, 8-H), 3.18 (s, 3H, N_3-CH_3), 3.33 (s, 3H, N_1-CH_3), 3.2-3.7 (m, 2H, 7-H), 3.79 (m, 2H, 5-H), 4.45 (m, 2H, N-$CH_2C_6H_5$), 7.49 (m, 3H, C_6H_5), 7.68 (m, 2H, C_6H_5), 11.75 (br s, NH); ^{13}C nmr (DMSO-d_6): δ = 22.9, 27.5, 30.7, 45.2, 46.6, 57.2, 99.7, 128.7, 129.4, 130, 131.2, 146.8, 150.8, 160.1.

Anal. Calcd. for $C_{16}H_{20}ClN_3O_2$ (321.81) with 1.2 H_2O: C, 55.96; H, 6.57; Cl, 10.32; N, 12.24. Found: C, 56.09; H, 6.39; Cl, 10.15; N, 12.17. The water content was determined by Karl Fischer titration.

Ozonolysis of **6**.

1-Benzyldihydropyrimidine-2,4-dione **9**.

The colourless solution of **6** (5.21 g, 0.020 mole) in methanol/dichloromethane 1/1 (180 ml) was ozonized at -78° until it turned blue. Excess ozone was washed out by bubbling with nitrogen. Dimethyl sulfide (10 ml) was added over 10 minutes with no further cooling. After the solution had reached room temperature the solvent was evaporated *in vacuo* and the residue was taken up and stirred with a (1:1)-mixture of methanol/water (40 ml). The precipitate was recrystallized from 2-propanol and dried *in vacuo*, giving **9** (2.4 g, 59%), mp 125° (mixed mp with authentic **9** (synthesized for comparison [3]): 125°); ir (potassium bromide): ν = 3185, 3060, 2960, 2940, 2870, 1710, 1700, 1495, 1460, 1450, 1410, 1380, 1360, 1330, 1320, 1280, 1240, 1210, 1020, 810, 755, 730, 695 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.62 (t, 2H, 5-H), 3.32 (t, 2H, 6-H), 4.62 (s, 2H, N-$CH_2C_6H_5$), 7.33 (m, 5H, C_6H_5), 7.85 (br s, NH).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.86; H, 6.01; N, 13.72.

The ir and ^1H nmr spectra, mp and combustion analysis were in agreement with those obtained with **9** synthesized from aminoester **12** according to Scheme III [3].

Oxoacetic Acid Methyl Ester Semicarbazone **11**.

To the mother liquor of the precipitate from methanol/water was added a solution of semicarbazide hydrochloride (4.5 g, 0.04 mole) and of sodium acetate trihydrate (6.8 g, 0.05 mole) in water (40 ml) and the mixture was stirred overnight at room temperature. The white precipitate was recrystallized from water and dried *in vacuo* yielding **11** (0.35 g, 13%), mp 214°, (mp 206° [4]); ^1H nmr (DMSO-d_6): δ = 3.74 (s, 3H, OCH_3), 6.58 (br s, 2H, NH_2), 7.27 (s, 1H, CH=N), 10.95 (s, 1H, NH).

Anal. Calcd. for $C_4H_7N_3O_3$ (145.12): C, 33.11; H, 4.86; N, 28.96. Found: C, 32.91; H, 4.89; N, 28.74.

Acidic Hydrolysis of **6**.

1-Benzyl-4-methyl-1,2-dihydropyrimidin-2-one **13**.

A suspension of ester **6** (1.91 g, 7.35 mmoles) in 18% aqueous hydrochloric acid (11 ml) was heated at reflux for 1 hour. The mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was suspended and stirred in water (40 ml), the *p*H adjusted to 7 by addition of 0.1 *N* Sodium Hydroxide and the mixture was extractively worked up with dichloromethane and water. The dichloromethane extracts were combined, dried (sodium sulfate) and evaporated. The residue (1.45 g) was purified by medium pressure chromatography on silica gel with dichloromethane/ethanol (95/5) as eluent, by sublimation (80° bath temperature, 0.07 mbar) and by recrystallization from dichloromethane/diethyl ether and dried *in vacuo* to give **13** (260 mg, 17%), mp 159-160°; ^1H nmr (deuteriochloroform): δ = 2.43 (s, 3H, 4-CH_3), 5.08 (s, 2H, N-$CH_2C_6H_5$), 6.15 (d, 1H, 5-H, J = 6 Hz), 7.33 (m, 5H, C_6H_5), 7.47 (d, 1H, 6-H, J = 6 Hz); ms: (DI) m/z 200 (M^+). The ir and uv spectra were in agreement with those of **13** synthesized from **14**.

Anal. Calcd. for $C_{12}H_{12}N_2O$ (200.24) with 0.25 H_2O: C, 70.39; H, 6.15; N, 13.68. Found: C, 70.57; H, 5.92; N, 13.61.

1-Benzyl-4-methyl-1,2-dihydropyrimidin-2-one **13** from **14**.

A mixture of 97% 2-hydroxy-4-methylpyrimidine hydrochloride (15.1 g, 0.1 mole), potassium carbonate (27.6 g, 0.2 mole) and benzyl chloride (13.2 g, 0.103 mole) in dimethylformamide (300 ml) was heated at 65° for 16 hours. The mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane and water. The organic phase was dried (sodium sulfate), filtered and concentrated *in vacuo*. The residue was purified by medium pressure chromatography on silica gel using dichloromethane/methanol (30/1). The pure fractions (tlc) were combined and dried *in vacuo* to give **13** (10.9 g, 54%) as a white solid. A small sample was sublimed at 0.05 mbar and 110° bath temperature, mp 156-157°; ir (potassium bromide): ν = 3080, 3025, 1655, 1640, 1620, 1520, 1500, 1470, 1460, 1425, 1375, 1360, 1325, 1170, 790, 730, 700 cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.4 (s, 3H, 4-CH_3), 5.1 (s, 2H, N-$CH_2C_6H_5$), 6.17 (d, 1H, 5-H, J = 6 Hz), 7.38 (m, 5H, C_6H_5), 7.48 (d, 1H, 6-H, J = 6 Hz); ^{13}C nmr (deuteriochloroform): δ = 25.2, 53.2, 104.9, 128.34, 128.38, 128.9 (128.34-128.9 aromatic *C*H), 135.1 (aromatic *C*), 145.8, 156.1, 176.3; ms: (EI) m/z 200 (M^+); uv (methanol): λ_{max} 304 nm (ε = 5,700).

Anal. Calcd. for $C_{12}H_{12}N_2O$ (200.24): C, 71.98; H, 6.04; N, 13.99. Found: C, 71.81; H, 5.93; N, 13.78.

Methylation of **6**.

(*E*)-(1-Benzyl-3-methyl-2-oxotetrahydropyrimidin-4-ylidene)-acetic Acid Methyl Ester **7**.

To a solution of **6** (3 g, 11.5 mmoles) in dimethylformamide (75 ml) was added 80% sodium hydride (363 mg, 12.1 mmoles). The suspension was heated in 10 minutes to 50° and methyl iodide (1.72 g, 12.1 mmoles) was added over 10 minutes. After stirring at 50° for 5 hours the mixture was evaporated *in vacuo*. The residue was repeatedly partitioned between dichloromethane and water and the combined organic extracts were dried (sodium sulfate) and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel using *tert*-butyl methyl ether/hexane (1/3) and by recrystallization from dichloromethane/hexane to give **7** (1.42 g, 45%) as a white powder, mp 106-107°; ^1H nmr (deuteriochloroform): δ = 3.19 (m, 2H, 6-H), 3.21 (s, 3H, N-CH_3), 3.33 (m, 2H, 5-H), 3.66 (s, 3H, OCH_3), 4.61 (s, 2H, N-$CH_2C_6H_5$), 5.09 (s, 1H, =CH), 7.3 (m, 5H, C_6H_5);

The ^{13}C nmr and ir spectra were in agreement with those of **7** obtained from **1** and **4b**.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$ (274.32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.67; H, 6.69; N, 10.20.

3-Methyl-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]pyrimidine-2,4-dione **15**.

A solution of **2** (96 g, 0.35 mole) in glacial acetic acid (1.5 ℓ) was treated with hydrogen at 25° and 3.5 bar by shaking in a Parr apparatus in the presence of 10% palladium-on-charcoal (14.6 g) for 6 hours. The mixture was filtered and the filtrate was evaporated *in vacuo*. This procedure was repeated and the residues were combined and suspended in water. To the stirred mixture was added 33% aqueous sodium hydroxide until a *p*H = 6.9 was reached. The precipitate was washed with water and dried *in vacuo* at 60° to give **15** (115.3 g, 90%). This was dissolved in ethanol and treated with ethereal hydrogen chloride. The precipitate was dried *in vacuo* and recrystallized from methanol/diethyl ether to give a colorless powder of **15** hydrochloride (106.3 g, 77%), mp 303-304° dec; ir (potassium bromide): ν = 3080 (sh), 2930, 2780, 1725, 1660, 1645, 1600, 1520, 1450, 1400, 1385, 1370, 1280, 1175, 1060, 1025, 980, 910, 865, 840, 785, 760, 745, 730, 680 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.71 (t, 2H, 8-H), 3.15 (s, 3H, N-CH_3), 3.30 (t, 2H, 7-H), 3.73 (s, 2H, 5-H), 9.8 (br m, 2H, NH), 11.4 (br m, 1H, NH).

Anal. Calcd. for $C_8H_{12}ClN_3O_2$ (217.66): C, 44.15; H, 5.56; Cl, 16.29; N, 19.31. Found: C, 44.21; H, 5.68; Cl, 16.11; N, 19.21.

3-Methyl-6-(2-methylallyl)-5,6,7,8-tetrahydro-1*H*-pyrido[4,3-*d*]-pyrimidine-2,4-dione Hydrochloride **16**.

A mixture of **15** (18.1 g, 0.1 mole), ethyldiisopropylamine (17.7 ml, 0.1 mole) and 95% 2-methylallyl chloride (9.5 g, 0.1 mole) in dimethylformamide (350 ml) was stirred at room temperature for 19 hours. After addition of more ethyldiisopropylamine (17.7 ml, 0.1 mole) and 95% 2-methylallyl chloride (9.5 g, 0.1 mole) stirring was continued for 3 hours. The mixture was evaporated *in vacuo* and the residue was repeatedly partitioned between dichloromethane and water. The organic phases were combined, dried over sodium sulfate and concentrated *in vacuo*. The residue (17.7 g) was recrystallized from 2-propanol and the precipitate dried *in vacuo* yielding the base of **16** (15.8 g). This was dissolved in dichloromethane (300 ml) and treated with ethereal hydrogen chloride. The precipitate was recrystallized from 2-propanol and dried *in vacuo* to give **16** (11.8 g, 43%), mp 238° dec; ir (potassium bromide): ν = 3085, 2930, 2790, 2680, 2590, 1720, 1680, 1665, 1650, 1520, 1440, 1390, 1280, 1015, 940, 880, 750, 680 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.94 (s, 3H, =C-CH_3), 2.7 (m, 1H, 8-$CH_{2/2}$), 3.05 (m, 1H, 8-$CH_{2/2}$), 3.15 (s, 3H, N-CH_3), 3.23 (m, 1H, 7-$CH_{2/2}$), 3.57 (m, 1H, 7-$CH_{2/2}$), 3.83 (m, 2H, N-CH_2-C=), 3.65-4.0 (m, 2H, 5-CH_2), 5.28 (m, 2H, =CH_2), 11.6 (s, 2H, 2 NH).

Anal. Calcd. for $C_{12}H_{18}ClN_3O_2$ (271.75): C, 53.04; H, 6.68; Cl, 13.05; N, 15.46. Found: C, 52.83; H, 6.75; Cl, 12.96; N, 15.35.

Acknowledgements.

We wish to express our gratitude to S. G. Davies for helpful discussions. The pharmacological evaluation of the compounds by J. Grome, I. Okyayuz-Baklouti and D. Seiffge is gratefully acknowledged. H. F. thanks O. Schwalbach for experimental assistance.

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