Preparation of Phthalamic Acid Derivatives and Ring Closure to Phthalimidobarbituric Acids
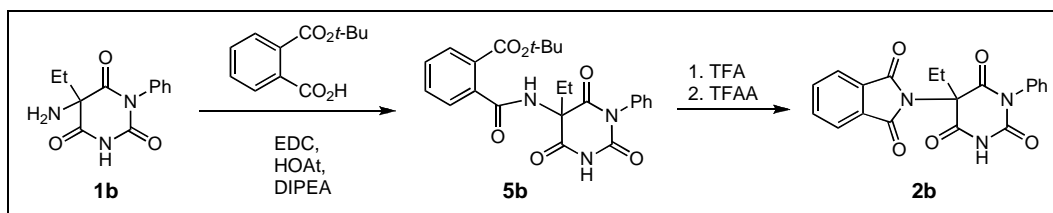
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Phthalamic acid derivatives with a barbiturate moiety were prepared from 5-amino-5-ethylbarbituric acids. To circumvent an undesired acetylation in glacial acetic acid during the preparation of phthalimidobarbituric acids, two routes were proven exemplarily. On the one hand, a phthalamic acid (**6a**) was isolated and subsequently cyclized with acetic anhydride to the corresponding phthalimide **2a**. On the other hand, a phthalamic acid *tert*-butyl ester (**5b**) was successively treated with trifluoroacetic acid and trifluoroacetic anhydride to achieve heterocyclization to the phthalimide **2b**. These routes might be useful for the preparation of other phthalimides derived from sterically hindered primary amines.

The common method to prepare phthalimides is to heat primary amines with phthalic anhydride in acetic acid [1]. We have observed an undesired acetylation of the amino group when reacting 5-amino-5-ethylbarbituric acids **1** with phthalic anhydride in glacial acetic acid to give mixtures of phthalimides **2** and acetamides **3** (Scheme 1). The isolation of **2** is possible [2], but reproducibility was limited and acetamides **3** predominated in certain experiments. The impaired phthalimide formation might be attributed to the sterically hindered amines used.

Our interest in the chemistry of aminobarbituric acids is based on their utilization as substrates of the aminobarbituric acid-hydantoin rearrangement [3,4] as well as on their conversion to biologically active phthalimide derivatives. The latter compounds, mainly tetrafluoro analogues, inhibited the TNF-α production in human monocytes [2] and also angiogenesis [5].

Herein we report on an investigation to explain the mechanism of the acetylation and a new route to phthalimidobarbituric acids that prevents the undesired acetamide formation. Exemplarily, barbituric acids **1a** and **1b** were chosen as sterically hindered substrates.

The reaction of primary amines with phthalic anhydride includes ring opening to intermediate phthalamic acids [6] followed by ring closure to the phthalimide [7]. Recently, a detailed kinetic study on the cyclization of *N*-phenylphthalamic acids has been reported. Several derivatives substituted at the *N*-phenyl moiety underwent cyclization on heating in glacial acetic acid [8].

5-Acetylamino-1-cyclohexyl-5-ethylbarbituric acid (**3a**), needed as a reference substance, was prepared by condensation of diethyl 2-acetylamino-2-ethylmalonate with cyclo-

Scheme 1
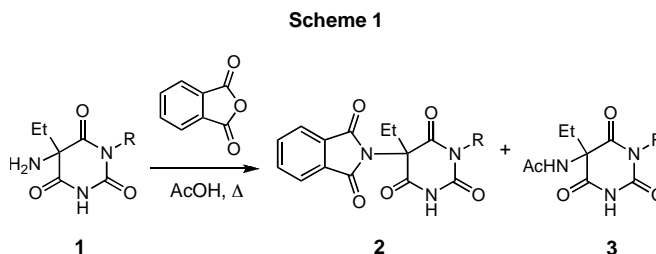
hexylurea in sodium ethoxide solution. The phthalamic acid **6a** was expected to be the intermediate in the formation of the corresponding phthalimide **2a**. The isolation of **6a** was accomplished when **1a** and phthalic anhydride were refluxed in dimethylformamide. This reaction gave the phthalimide **2a** as by-product (Scheme 2). Next, phthalamic acid **6a** was treated with acetic anhydride to achieve ring closure to **2a**, which was obtained in 59 % yield.

To study the acetylation reaction, **6a** was heated in glacial acetic acid for four hours, and the product distribution was analyzed by means of NMR. With the spectra of the authentic samples of **3a**, **2a**, phthalic anhydride and **6a** in hands, we were able to detect the three products and unreacted substrate **6a** to be the components of the resulting mixture. Thus, the formation of phthalic anhydride indicates the release of **1a** from **6a** and the simultaneous ring closure to phthalic anhydride. We considered the formation of **3a** to result from an acetylation of **1a**. Therefore, **1a** was treated under the same conditions with boiling acetic acid to exclusively produce **3a**. These two experiments let us conclude that the release of **1a** is *prior* to its acetylation to give **3a**.
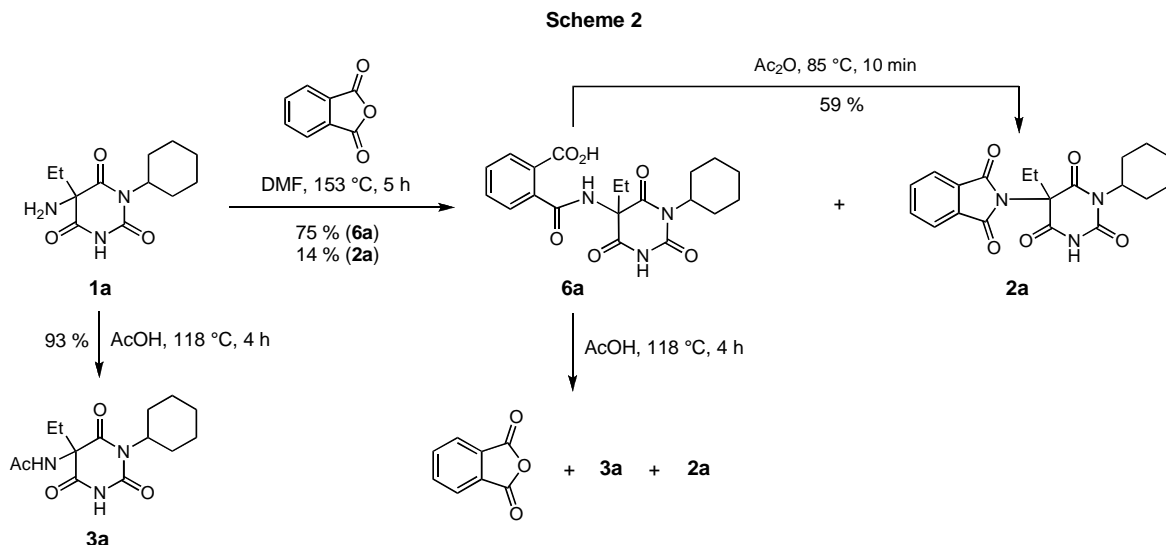
Scheme 2

An alternative route to the phthalamic acid **6a** was envisaged [9] and is outlined in Scheme 3. Phthalic acid mono-*tert*-butyl ester was coupled to **1a** in a reaction promoted by *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC) and 1-hydroxy-7-azabenzotriazole (HOAt) [10] in the presence *N*-ethyldiisopropylamine (DIPEA). Whereas **5a** was obtained in only 30 % yield, cleavage of the *tert*-butyl ester with trifluoroacetic acid (TFA) occurred easily to produce the phthalamic acid **6a**. This compound can be used for the preparation of the phthalimide **2a** upon

treatment with acetic anhydride (see above). The reaction of **6a** with trifluoroacetic anhydride (TFAA), however, gave an unidentified by-product besides **2a**.

Our attempts to prepare the phenyl-substituted phthalimidobarbituric acid **2b** are shown in Scheme 4. Conditions are required to prevent acetylation of **1b** as observed in acetic acid, but also to avoid the undesired ring contraction [3] of **1b** to the corresponding hydantoin, as observed in DMF (data not shown). Thus, the alternative route *via* a phthalamic ester was chosen.

Scheme 3

Scheme 4
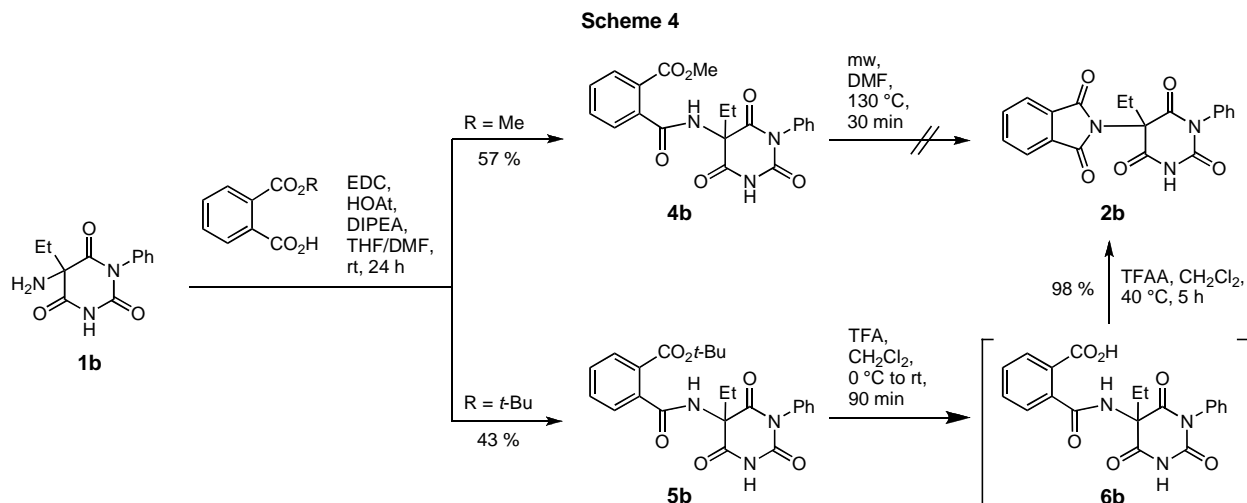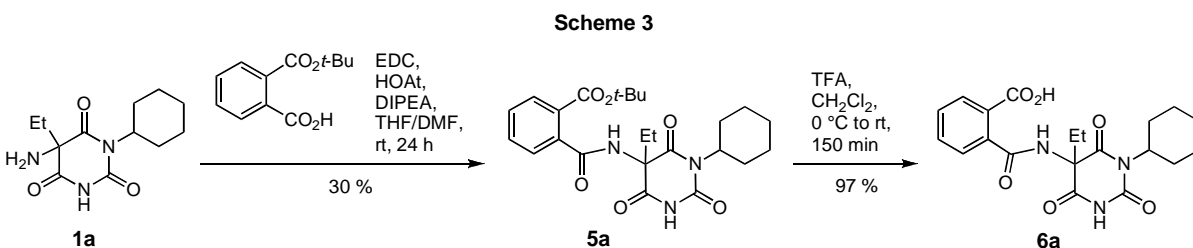
The methyl ester **4b** was prepared from phthalic acid mono-methyl ester in a EDC/HOAt-mediated condensation reaction. An attempt to cyclize **4b** upon microwave-assisted treatment at 130 °C for 30 minutes was not successful. It gave unreacted starting material. To prove the stability of **4b** in trifluoroacetic acid, the compound was treated for 90 minutes in a TFA/CH_2Cl_2 1:1 mixture at room temperature and remained unchanged. Thus, in a further approach, the *tert*-butyl ester **5b** was prepared from **1b** and was directly subjected to the final conversions, *i.e.* the acid-catalyzed cleavage of the *tert*-butyl ester and ring closure. The desired compound **2b** was obtained in excellent yield.

Thus, this protecting group strategy provided the desired phthalimidobarbituric acids **2a** and **2b** and should be applicable for the preparation of other phthalimides from sterically demanding primary amines. Phthalamic acid *tert*-butyl esters have also been utilized for other purposes, such as preparation of amino acid derivatives [11], protection of the guanidino group during peptide synthesis [12], and polycondensation reactions [13].

EXPERIMENTAL

Melting points were obtained on a Rapido Boetius apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FT-IR instrument. [1]H nmr spectra were recorded on a Bruker Avance spectrometer at 500 MHz. [13]C nmr spectra were recorded on a Bruker Avance spectrometer at 125 MHz. Mass spectra (EI, 70 eV) were measured on a MS-50 A.E.I. spectrometer. Thin-layer chromatography was carried out using aluminum sheets coated with silica gel 60 F_{254} (Merck). Diethyl 2-acetylamino-2-ethylmalonate [14] and aminobarbituric acids **1a** and **1b** were prepared as reported [3].

5-Acetylamino-1-cyclohexyl-5-ethylbarbituric acid (3a). Diethyl 2-acetylamino-2-ethylmalonate (9.81 g, 40 mmoles) and cyclohexylurea (5.69 g, 40 mmoles) were added to a solution of sodium ethoxide in ethanol (200 ml, 0.24 *M*), stirred under reflux for 3 hours, and the solvent was evaporated under reduced pressure. The oily residue was dissolved in water (95 ml), acidified to pH 2-3 by dropwise addition of 2 *M* hydrochloric acid and kept overnight at 5 °C. The precipitate was filtered off, dried and recrystallized from ethanol to give 2.84 g (24 %) of **3a** as white crystals; mp 282-288 °C; ir (potassium bromide): ν 3344, 3019 (NH), 1739, 1687, 1637 cm^{-1} (C=O); ^{1}H nmr (DMSO–d_6): δ 0.82 (t, 3H, J = 7.7 Hz, CH$_2$C*H$_3$*), 1.03-2.18 (m, 10H, CH_2-cyclohexyl), 1.82 (s, 3H, COC*H$_3$*), 1.86 (q, 2H, J = 7.7 Hz, C*H$_2$*CH$_3$), 4.42 (tt, 1H, J = 12.2, 3.7 Hz, CH-cyclohexyl), 8.94 (s, 1H, NH), 11.49 (s, 1H, N(3)-H); ^{13}C nmr (DMSO–d_6): δ 7.60 (CH$_2$*C*H$_3$), 21.26 (CO*C*H$_3$), 25.08, 25.89, 25.97, 28.38, 29.18 (CH$_2$-cyclohexyl), 29.97 (*C*H$_2$CH$_3$), 54.09 (CH-cyclohexyl), 63.10 (C-5), 150.01 (C-2), 169.37, 169.97, 170.45 (CO). Anal. Calcd. for $C_{14}H_{21}N_3O_4$: C, 56.94; H, 7.17; N, 14.23. Found: C, 56.71; H, 7.21; N, 14.10.

N-(1-Cyclohexyl-5-ethyl-hexahydro-2,4,6-trioxo-pyrimidin-5-yl)phthalamic acid (6a). 5-Amino-1-cyclohexyl-5-ethyl-barbituric acid **1a** (0.38 g, 1.50 mmoles) and phthalic anhydride (0.22 g, 1.50 mmoles) were stirred in dimethylformamide (11 ml) under reflux for 5 hours. After cooling to room temperature,

the mixture was poured into water (50 ml) and the precipitate was collected by filtration. The crude product was recrystallized from ethanol to give 81 mg (14 %) of 1-cyclohexyl-5-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-5-ethylbarbituric acid (**2a**). After removal of the crude **2a**, *N*-(1-cyclohexyl-5-ethyl-hexahydro-2,4,6-trioxo-pyrimidin-5-yl)-phthalamic acid (**6a**) precipitated in pure form from the dimethylformamide-water filtrate after standing at room temperature for three days. The isolated material was dried to give 0.45 g (75 %) of **6a** as colorless crystals; mp 198-203 °C; ir (potassium bromide): ν 3490, 3312 (NH), 1754, 1722, 1609, 1658 cm^{-1} (C=O); ^{1}H nmr (DMSO–d_6): δ 0.86 (t, 3H, J = 7.5 Hz, CH$_3$), 1.05-2.24 (m, 10H, CH$_2$-cyclohexyl), 2.13-2.24 (m, 2H, C*H$_2$*CH$_3$), 4.47 (tt, 1H, J = 12.1, 3.7 Hz, CH-cyclohexyl), 7.50-7.68 (m, 4H, arom. H), 9.50 (s, 1H, NH), 11.53 (s, 1H, N(3')-H), 12.79 (s, 1H, CO_2H); ^{13}C nmr (DMSO–d_6): δ 7.65 (CH$_3$), 25.11, 25.96, 26.01, 28.42, 29.06 (CH$_2$-cyclohexyl), 30.25 (*C*H$_2$CH$_3$), 54.14 (CH-cyclohexyl), 63.31 (C-5'), 128.59 (C-3), 128.94 (C-6), 130.35 (*C*-CO$_2$H), 130.71 (C-4), 132.48 (C-5), 134.83 (C-2), 150.18 (C-2'), 168.27, 168.33, 168.96, 170.04 (CO); ms: m/z 401 (5 %, M$^+$), 320 (11 %, M$^+$ – C_6H_9), 253 (100 %, M$^+$ – $C_8H_4O_3$), 171 (53 %, M$^+$ – C_6H_9 – $C_8H_5O_3$), 142 (42 %, M$^+$ – C_6H_9 – $C_8H_5O_3$ – C_2H_5,), 104 (80 %, $C_7H_4O^+$), 76 (38 %, $C_6H_4^+$). Anal. Calcd. for $C_{20}H_{23}N_3O_6$ × H_2O: C, 57.27; H, 6.01; N, 10.02. Found: C, 57.01; H, 5.92; N, 9.85.

1-Cyclohexyl-5-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-5-ethylbarbituric acid (2a). *N*-(1-Cyclohexyl-5-ethyl-hexahydro-2,4,6-trioxo-pyrimidin-5-yl)phthalamic acid **6a** (450 mg, 1.12 mmoles) was heated in acetic anhydride (7 ml) at 85 °C for 10 minutes. After cooling, the precipitated material was collected and washed with a mixture of hexane/diethyl ether (1:1) to give 0.34 g (59 %) of **2a** as a colorless solid; mp 245-250 °C, ref 248-253 °C [2]; ir (potassium bromide): ν 3271 (NH), 1701 cm^{-1} (br, C=O); ^{1}H nmr (DMSO–d_6): δ 0.98 (t, 3H, J = 7.4 Hz, CH$_3$), 1.02-2.17 (m, 10H; CH$_2$-cyclohexyl), 2.67 (q, 2H, J = 7.4 Hz, C*H$_2$*CH$_3$), 4.45 (tt, 1H, J = 12.1, 3.7 Hz, CH-cyclohexyl), 7.93 (s, 4H, arom. H), 12.07 (s, 1H, NH); ^{13}C nmr (DMSO–d_6): δ 9.24 (CH$_3$), 24.99, 25.78, 25.87, 27.40, 28.08 (CH$_2$-cyclohexyl), 29.21 (*C*H$_2$CH$_3$), 54.83 (CH-cyclohexyl), 67.99 (C-5), 123.90 (C-4', C-7'), 130.50 (C-3a', C-7a'), 135.72 (C-5', C-6'), 149.40 (C-2), 167.35, 167.96, 168.44 (CO).

Reaction of *N*-(1-Cyclohexyl-5-ethyl-hexahydro-2,4,6-trioxo-pyrimidin-5-yl)phthalamic acid (6a) with acetic acid. Glacial acetic acid (25 ml) was added to *N*-(1-cyclohexyl-5-ethyl-hexahydro-2,4,6-trioxo-pyrimidin-5-yl)phthalamic acid **6a** (401 mg, 1.00 mmol), and the mixture was refluxed for 4 hours. It was evaporated to dryness and the residue was washed with hexane/diethyl ether (1:1). The resulting mixture as analyzed by nmr. [1]H nmr (DMSO–d_6), signals of **3a**: δ 0.83 (t, 3H, J = 7.7 Hz, CH$_2$C*H$_3$*), 1.03-2.24 (m, CH$_2$-cyclohexyl), 1.82 (s, 3H, COC*H$_3$*), 1.86 (q, 2H, J = 7.6 Hz, C*H$_2$*CH$_3$), 4.38-4.50 (m, CH-cyclohexyl), 8.94 (s, 1H, NH), 11.49 (s, 1H, N(3)-H), signals of **2a**: δ 0.98 (t, 3H, J = 7.4 Hz, CH$_3$), 1.03-2.24 (m, CH$_2$-cyclohexyl), 2.67 (q, 2H, J = 7.4 Hz, C*H$_2$*CH$_3$), 4.38-4.50 (m, CH-cyclohexyl), 7.93 (s, 4H, arom. H), 12.07 (s, 1H, NH), signals of phthalic anhydride: δ 7.99-8.01 (m, 2H, 4-H, 5-H), 8.07-8.09 (m, 2H, 3-H, 6-H), signals of **6a**: δ 0.86 (t, 3H, J = 7.6 Hz, CH$_3$), 1.03-2.24 (m, CH$_2$-cyclohexyl, C*H$_2$*CH$_3$), 4.38-4.50 (m, CH-cyclohexyl), 7.50-7.69 (m, 4H, arom. H), 9.49 (s, 1H, NH), 11.53 (s, 1H, N(3')-H), 12.77 (s, 1H, CO_2H). The compounds **3a**, **2a**, phthalic anhydride and **6a** were present in a ratio of 4.5 : 1 : 1.5 : 2. [13]C nmr (DMSO–d_6), signals of **3a**: δ 7.64 (CH$_2$*C*H$_3$), 21.27 (CO*C*H$_3$), 25.08, 25.89, 25.97, 28.38, 29.18

(CH_2-cyclohexyl), 29.97 (CH_2CH_3), 54.09 (CH-cyclohexyl), 63.10 (C-5), 150.01 (C-2), 169.36, 169.96, 170.45 (CO), signals of **2a**: δ 9.25 (CH_3), 25.00, 25.79, 27.40, 28.09 (CH_2-cyclohexyl), 54.84 (CH-cyclohexyl), 67.99 (C-5), 123.91 (C-4', C-7'), 130.50 (C-3a', C-7a'), 135.73 (C-5', C-6'), 149.40 (C-2), 167.35, 167.96, 168.44 (CO). One signal for CH_2-cyclohexyl and the signal for CH_2CH_3 are missing. Signals of phthalic anhydride: δ 125.49 (C-3, C-6), 131.39 (C-1, C-2), 136.32 (C-4, C-5), 163.40 (C=O), signals of **6a**: δ 7.64 (CH_3), 29.06 (CH_2-cyclohexyl), 30.24 (CH_2CH_3), 54.13 (CH-cyclohexyl), 63.29 (C-5'), 128.59 (C-3), 128.93 (C-6), 130.33 (C-CO_2H), 130.70 (C-4), 132.45 (C-5), 134.83 (C-2), 150.17 (C-2'), 168.26, 168.32, 168.95, 170.03 (CO). Four signals for CH_2-cyclohexyl are missing.

N-(1-Cyclohexyl-5-ethyl-hexahydro-2,4,6-trioxo-5-pyrimidinyl)phthalamic acid *tert*-butyl ester (5a). To a suspension of phthalic acid mono-*tert*-butyl ester (1.22 g, 5.5 mmoles, 1.1 equiv) in dry tetrahydrofuran (16 ml), a solution of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.44 g, 7.5 mmoles, 1.5 equiv) in dry tetrahydrofuran (16 ml), a suspension of 1-hydroxy-7-azabenzotriazole (0.75 g, 5.5 mmoles, 1.1 equiv) in dry terahydrofuran (20 ml) and N-ethyldiisopropylamine (0.95 ml, 0.71 g, 5.5 mmoles, 1.1 equiv) were added successively. The resulting mixture was stirred for 20 min at room temperature. Afterwards, the suspension of 5-amino-5-ethyl-1-phenylbarbituric acid **1a** (1.26 g, 4.07 mmoles) in dry DMF (30 ml) was added, and the stirring was continued for 24 h at room temperature. After this time, the resulting solution was poured into water (300 ml) and the basic mixture was adjusted to pH 2 by dropwise addition of HCl (4 *M*). After extraction with ethyl acetate (5 × 100 ml), the combined organic layers were washed with saturated $NaHCO_3$ solution (2 × 220 ml) and with brine (220 ml). The organic layer was dried over sodium sulfate, filtrated and evaporated *in vacuo* to give a crude product which was recrystallized from methanol to give 0.68 g (30 %) of **5a** as white crystals; mp 230-233 °C; ir (potassium bromide): ν 3297, 3179 (NH), 1735, 1672, 1643 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 0.89 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.08-2.23 (m, 10H, CH_2-cyclohexyl), 1.43 (s, 9H, $(CH_3)_3$), 2.02 (q, 2H, J = 7.6 Hz, CH_2CH_3), 4.48 (tt, 1H, J = 12.3, 3.6 Hz, CH-cyclohexyl), 7.49-7.65 (m, 4H, arom. H), 9.56 (s, 1H, NH), 11.61 (s, 1H, N(3')-H); ^{13}C nmr (DMSO-d_6): δ 7.70 (CH_2CH_3), 25.08, 25.91, 27.47, 28.44, 29.35 (CH_2-cyclohexyl), 25.99 ($C(CH_3)_3$), 30.31 (CH_2CH_3), 54.13 (CH-cyclohexyl), 63.54 (C-5'), 81.43 ($C(CH_3)_3$), 128.32, 128.93, 129.98, 130.99, 133.07, 134.63 (arom. C), 150.02 (C-2'), 167.20, 167.54, 169.04, 170.23 (CO). Anal. Calcd. for $C_{24}H_{31}N_3O_6$: C, 63.01; H, 6.83; N, 9.18. Found: C, 62.53; H, 7.14; N, 9.12.

Reaction of N-(1-cyclohexyl-5-ethyl-hexahydro-2,4,6-trioxo-5-pyrimidinyl)phthalamic acid *tert*-butyl ester (5a) with trifluoroacetic acid. A mixture of trifluoroacetic acid (26 ml) and anhydrous dichloromethane (5.5 ml) was added in portions at 0 °C to the phthalamic acid mono-*tert*-butyl ester **5a** (0.46 g, 1.00 mmol). When a clear solution was obtained, the mixture was allowed to warm to room temperature and stirred for additional 150 minutes. The solution was evaporated to give 0.39 g (97 %) of N-(1-cyclohexyl-5-ethyl-hexahydro-2,4,6-trioxo-pyrimidin-5-yl)phthalamic acid (**6a**) as a white solid. The material was pure and identical (mp, nmr) to that obtained from **1a**.

N-(5-Ethyl-hexahydro-2,4,6-trioxo-1-phenyl-5-pyrimidinyl)phthalamic acid methyl ester (4b). To a suspension of phthalic acid mono-methyl ester (0.5 g, 2.75 mmoles) in dry tetrahydrofuran (5 ml), a solution of N-(3-dimethylamino-

propyl)-N'-ethylcarbodiimide hydrochloride (0.72 g, 3.75 mmoles) in dry tetrahydrofuran (5 ml), a suspension of 1-hydroxy-7-azabenzotriazole (0.37 g, 2.75 mmoles) in dry tetrahydrofuran (6 ml) and N-ethyldiisopropylamine (0.48 ml, 0.36 g, 2.75 mmoles) were added successively. The resulting mixture was stirred for 20 minutes at room temperature. Afterwards, the suspension of 5-amino-5-ethyl-1-phenylbarbituric acid **1b** (0.62 g, 2.5 mmoles) in dry dimethylformamide (12 ml) was added and the stirring was continued for 24 hours at room temperature. The solution was poured into water (120 ml) and adjusted to pH 2 by dropwise addition of 4 *M* hydrochloric acid. After extraction with ethyl acetate (5 × 40 ml), the combined organic layers were washed with saturated sodium hydrogen carbonate solution (2 × 100 ml) and with brine (100 ml). The organic layer was dried over sodium sulfate, filtrated and evaporated *in vacuo*. The crude product was recrystallized from methanol to give 0.58 g (57 %) of **4b** as white crystals; mp 250-256 °C; ir (potassium bromide): ν 3327, 33210 (NH), 1705, 1667 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 1.03 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.15 (q, 2H, J = 7.5 Hz, CH_2), 3.66 (s, 3H, OCH_3), 7.21-7.74 (m, 9H, arom. H), 9.78 (s, 1H, NH), 11.94 (s, 1H, N(3')-H); ^{13}C nmr (DMSO-d_6): δ 7.89 (CH_2CH_3), 29.86 (CH_2CH_3), 52.40 (OCH_3), 63.46 (C-5'), 128.47, 128.79, 129.24, 130.63, 130.79, 131.50, 134.96, 135.15 (arom. C, two signals are missing), 149.94 (C-2'), 167.52, 168.85, 169.27, 169.98 (CO); ms: 409 (6 %, M$^+$), 317 (34 %, M$^+$ – C_6H_5 – CH_3), 163 (100 %, M$^+$ – C_6H_5 – CH_3 – $C_6H_6N_2O_3$), 77 (6 %, $C_6H_5^+$). Anal. Calcd. for $C_{21}H_{19}N_3O_6$: C, 61.61; H, 4.68; N, 10.26. Found: C, 61.73; H, 4.98; N, 10.22.

N-(5-Ethyl-hexahydro-2,4,6-trioxo-1-phenyl-5-pyrimidinyl)phthalamic acid *tert*-butyl ester (5b). Compound **1b** (0.62 g, 2.5 mmoles) was reacted with phthalic acid mono-*tert*-butyl ester (0.61 g, 2.75 mmoles), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 1-hydroxy-7-azabenzotriazole and N-ethyldiisopropylamine in tetrahydrofuran/dimethylformamide according to the aforementioned procedure. Recrystallization from methanol gave 0.49 g (43 %) of **5b** as colorless crystals; mp 212-217 °C; ir (potassium bromide): ν 3303, 3113 (NH), 1738 (br), 1694 (C=O); ^{1}H nmr (DMSO-d_6): δ 1.04 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.44 (s, 9H, $(CH_3)_3$), 2.18 (q, 2H, J = 7.6 Hz, CH_2CH_3), 7.20-7.65 (m, 9H, arom. H), 9.72 (s, 1H, NH), 11.95 (s, 1H, N(3')-H); ^{13}C nmr (DMSO-d_6): δ 7.93 (CH_2CH_3), 27.57 (($CH_3)_3$), 30.05 (CH_2CH_3), 63.53 (C-5'), 81.52 ($C(CH_3)_3$), 128.41, 128.77, 128.82, 128.91, 129.13, 130.09, 131.07, 132.99, 134.56, 134.88 (arom. C), 149.91 (C-2'), 167.11, 167.98, 169.33, 169.99 (CO). Anal. Calcd. for $C_{24}H_{25}N_3O_6$: C, 63.85; H, 5.58; N, 9.31. Found: C, 63.24; H, 5.90; N, 9.24.

5-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-5-ethyl-1-phenylbarbituric acid (2b). A mixture of trifluoroacetic acid (10 ml) and anhydrous dichloromethane (6 ml) was added in portions at 0 °C to the phthalamic acid mono-*tert*-butyl ester **5b** (0.17 g, 0.38 mmoles). When a clear solution was obtained, the mixture was allowed to warm to room temperature and stirred for additional 90 minutes. The solution was evaporated to give a white solid to which anhydrous dichloromethane (5 ml) and trifluoroacetic acid anhydride (13 ml) were added. The resulting solution was stirred at 40 °C for 5 hours until no starting material was detectable by thin-layer chromatography. The mixture was evaporated to dryness to give 0.14 g (98 %) of **2b** as a white solid; mp 236-239 °C, ref 212-214 °C [2]; ir (potassium bromide): ν 3243 (NH), 1707 cm^{-1} (br, C=O); ^{1}H nmr (DMSO–d_6): δ 1.10 (t, 3H, J = 7.3 Hz, CH_3), 2.87 (q, 2H, J

= 7.3 Hz, CH$_2$), 7.26-7.28 (m, 2H, 2"-H, 6"-H), 7.44-7.52 (m, 3H, 3"-H, 4"-H, 5"-H), 7.92-7.97 (m, 4H, 4'-H, 5'-H, 6'-H, 7'-H), 12.40 (s, 1H, NH); ^{13}C nmr (DMSO-d$_6$): δ 9.55 (CH$_3$), 27.18 (CH$_2$), 67.82 (C-5), 124.00 (C-4', C-7'), 128.72 (C-2", C-6"), 129.15 (C-4"), 129.41 (C-3", C-5"), 130.48 (C-3a', C-7a'), 134.21 (C-1"), 135.81 (C-5', C-6'), 149.22 (C-2), 167.67, 168.00, 168.05 (CO).

REFERENCES

[1a]   Muller, G. W.; Chen, R.; Huang, S. Y.; Corral, L. G.; Wong, L. M.; Patterson, R. T.; Chen, Y.; Kaplan, G.; Stirling, D. I. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1625; [b] Collin, X.; Robert, J.; Wielgosz, G.; Le Baut, G.; Bobin-Dubigeon, C.; Grimaud, N.; Petit, J. *Eur. J. Med. Chem.* **2001**, *36*, 639; [c] Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Org. Lett.* **2003**, *5*, 2865; [d] Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Bioorg. Med. Chem.* **2004**, *12*, 327.

[2]   Gütschow, M.; Hecker, T.; Thiele, A.; Hauschildt, S.; Eger, K. *Bioorg. Med. Chem.* **2001**, *9*, 1059.

[3]   Gütschow, M.; Hecker, T.; Eger, K. *Synthesis* **1999**, 410.

[4a]   Meusel, M.; Ambrożak, A.; Hecker, T. K.; Gütschow, M. *J. Org. Chem.* **2003**, *68*, 4684; [b] Ambrożak, A.; Gütschow, M. *J. Heterocycl. Chem.* **2006**, *43*, 807.

[5a]   Ng, S. S.; Gütschow, M.; Weiss, M.; Hauschildt, S.; Teubert, U.; Hecker, T. K.; Luzzio, F. A.; Kruger, E. A.; Eger, K.; Figg, W. D. *Cancer Res.* **2003**, *63*, 3189; [b] Ng, S. S.; MacPherson, G. R.; Gütschow, M.; Eger, K.; Figg, W. D. *Clin. Cancer Res.* **2004**, *10*, 4192; [c] Lepper, E. R.; Ng, S. S.; Gütschow, M.; Weiss, M.; Hauschildt, S.; Hecker, T. K.; Luzzio, F. A.; Eger, K.; Figg, W. D. *J. Med. Chem.* **2004**, *47*, 2219.

[6]   Kluger, R.; Hunt, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 3325.

[7a]   Brown, J.; Su, S. C.; Shafer, J. A. *J. Am. Chem. Soc.* **1966**, *88*, 4468; [b] Onofrio, A. B.; Gesser, J. C.; Joussef, A. C.; Nome, F. *J. Chem. Soc. Perkin Trans II* **2001**, 1863.

[8]   Perry, C. J.; Parveen, Z. *J. Chem. Soc. Perkin Trans II*, **2001**, 512.

[9a]   Aguilar, N.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **1998**, 313; [b] de Saint Laumer, J. Y.; Frérot, E.; Herrmann, A. Helv. Chim. Acta **2003**, *86*, 2871; [c] Frérot, E.; Herbal, K.; Herrmann, A. *Eur. J. Org. Chem.* **2003**, 967.

[10a]   Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397; [b] Carpino, L. A.; El-Faham, A.; Albericio, F. *J. Org. Chem.* **1995**, *60*, 3561.

[11a]   Suzuki, M.; Kumar, S. D.; Stammer, C. H. *J. Org. Chem.* **1983**, *45*, 4769; [b] Suzuki, M.; Orr, G. F.; Stammer, C. H. *Biorg. Chem.* **1987**, *15*, 43.

[12]   Johnson, T.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1990**, 1605.

[13]   Ueda, M.; Mori, H. *Makromol. Chem.* **1993**, *194*, 511.

[14a]   Albertson, N. F. *J. Am. Chem. Soc.* **1946**, *68*, 450; [b] Singh, P.; Berlinguet, L. *Can. J. Chem.* **1964**, *42*, 605.