SYNTHESIS AND REACTIONS OF 5-METHYLTHIENO[2′,3′:5,6]PYRIMIDO-[2,1-*a*]ISOINDOL-4(5*H*)-ONE

Andriy I. KYSIL[a1,*], Zoia V. VOITENKO[a2] and Jean-Gérard WOLF[b]

[a] *Taras Shevchenko National University, 64 Volodymyrska Str., 01033 Kiev, Ukraine; e-mail: [1] kysil425@mail.ru, [2] z_voitenko@mail.univ.kiev.ua*

[b] *Université Paul Sabatier, SPCMIB UMR CNRS No. 5068, 118 route de Narbonne, 31062 Toulouse cedex 9, France; e-mail: wolf@chimie.ups-tls.fr*

Received December 1, 2007
Accepted February 15, 2008
Published online March 7, 2008

The reaction of 2-(bromomethyl)benzonitrile with methyl 3-aminothiophene-2-carboxylate results in two tautomeric thienopyrimidoisoindolones. Their methylation yields 5-methylthieno[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(5*H*)-one which reacts with N-substituted maleimides and dimethyl acetylenedicarboxylate.

Keywords: Cycloadditions; Heterocycles; Thienopyrimidoisoindolone; Isoindols, Maleimides; Isoindolines tautomers; 7-Azanorbornenes.

Fused isoindoles are less investigated than simple isoindole systems[1–3] and following the literature data[4–7], they are scarcely studied. Numerous practical applications of their derivatives as antidepressants, analgesics, anti-inflammatory agents, antifungals, antipyretics, anorexigenics, antihypertensives[8,9], antimalarials[10] and herbicides[11,12] are known. From the synthetic point of view, the most interesting and challenging properties of aromatic 10π-electronic systems of simple isoindoles is their ability to react with the dienophiles[1–3,13,14] leading to the *endo*- or *exo*-Diels–Alder adducts. Moreover, competitive Michael addition products are formed under similar conditions[15,16]. The products of these reactions are either 1:1 Diels–Alder adducts or 1:2 Michael–Diels–Alder adducts, which have not been obtained so far from simple isoindole systems[7,17–20].

Herein we wish to report the synthesis of 5-methylthieno[2′,3′:5,6]-pyrimido[2,1-*a*]isoindol-4(5*H*)-one and its reactions with maleimide derivatives and dimethyl acetylenedicarboxylate.

It is known[4,21] that the common method of building the pyrimido[2,1-*a*]-isoindol-2(6*H*)-one moiety is based on the reaction of 2-(bromomethyl)-benzonitrile **1** with compounds possessing an *o*-aminoarenecarboxylate fragment. Further alkylation of pyrimido[2,1-*a*]isoindol-2(6*H*)-one with

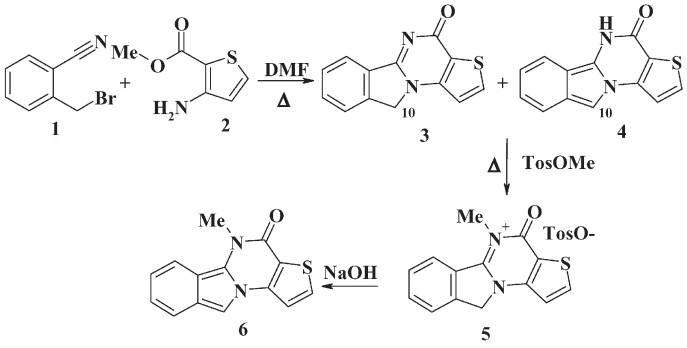
doi:10.1135/cccc20080247

alkyl tosylates leads to the formation of N-alkyl salts, which can be transformed to isoindoles by base treatment[22–24].

RESULTS AND DISCUSSION

Synthesis and Structure Determination

The reaction of **1** with methyl 3-aminothiophene-2-carboxylate (**2**) was carried out following the literature procedures described for analogous transformations[22–24] (Scheme 1). The reaction yields thieno[2′,3′:5,6]pyrimido-[2,1-*a*]isoindol-4(10*H*)-one (**3**) together with its tautomer **4**. Compounds **3** and **4** were isolated and characterized. Such type of tautomerism was not observed for the pyrimido[2,1-*a*]isoindol-2(6*H*)-one[25].



SCHEME 1

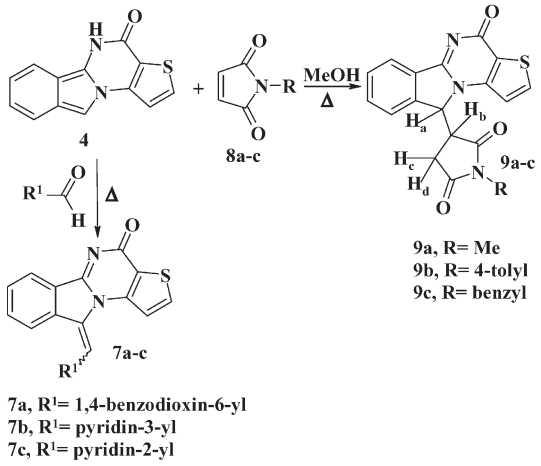
The mass spectra of compounds **3** and **4** exhibit intensive peaks at *m/z* 241 (MH^+).

The IR spectrum of **3** displays an intensive absorption band of the pyrimidine carbonyl group $\nu_{C=O}$ = 1597 cm^{-1} in addition to $\nu_{C=N}$ = 1500 cm^{-1}. In contrast, the carbonyl group of compound **4** of the pyrimidine moiety absorbs at 1691 cm^{-1}.

Complete assignment of the ^{13}C NMR signals was provided with DEPT spectra. The ^{13}C NMR-DEPT spectrum of **3** shows a characteristic methylene carbon atom (C10) at 58.63 ppm, whereas in the spectrum of **4**, the methine carbon atom (C10) is observed at 83.20 ppm and the signal at 158.39 ppm is attributed to the carbon atom of the C=O group.

Reactivity

Thieno[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(5*H*)-one (**4**) reacts with aldehydes at position 10 to give derivatives **7a**–**7c**. This reaction is similar to Ehrlich reaction of pyrroles and fused isoindoles with 4-dimethylaminobenzaldehyde[26]. Compound **4** reacts with the N-substituted maleimides **8a**–**8c** at the same position in the 1:1 ratio to form Michael adducts **9a**–**9c** (Scheme 2).



SCHEME 2

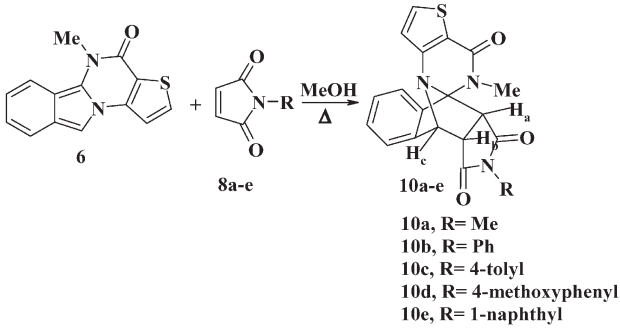
Methylation of compounds **3** and **4** or their mixture with methyl tosylate, followed by treatment of the resulting salt **5** with alkali led to the expected 5-methylthieno[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(5*H*)-one (**6**) (Scheme 1).

It is known that isoindoles are usually oxidized in air and should be kept in inert atmosphere or stored as salts. However, isoindoles **4** and **6** are stable to air for a long time.

Another interesting aspect of the reactivity of 5-methylthieno[2′,3′:5,6]-pyrimido[2,1-*a*]isoindol-4(5*H*)-one (**6**) is its reaction with N-substituted maleimides in the 1:1 or 1:2 ratio as well as with dimethyl acetylenedicarboxylate.

The reaction of 5-methylthieno[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(5*H*)-one (**6**) with 1 equivalent of maleimide derivatives **8a**–**8e** gives *endo*-Diels–Alder adducts **10a**–**10e** (Scheme 3). Their structure was confirmed by NMR and mass spectra.

Fragmentation of adducts **10** proceeds via the retro Diels–Alder reaction, which is confirmed by the intensive peaks corresponding to isoindole **6** and maleimide **8**.



SCHEME 3

IR spectra of adduct **10d** exhibit two characteristic bands of the pyrrolidine-2,5-dione moiety ($\nu_{C=O}$ = 1770–1775 and 1705–1710 cm^{-1}) and a band of the carbonyl groups of the pyrimidone ($\nu_{C=O}$ = 1620–1643 cm^{-1}).

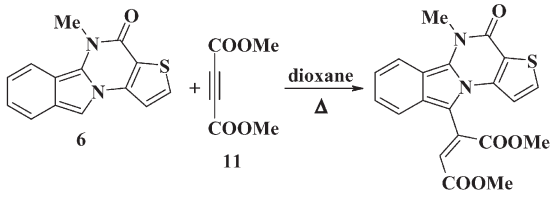
^{1}H NMR spectra of compounds **10a**–**10e** allowed to determine their spatial structure. The signal from protons of methyl groups of the quinazoline rings is observed as a three-proton singlet at 3.69–3.75 ppm. The signal of the bridgehead proton H_a appears as a one-proton doublet at 4.35–4.58 ppm with a coupling constant of 8.2–8.4 Hz. The signal of the bridge proton H_c is observed as a one-proton doublet at 6.28–6.71 ppm with a coupling constant of 5.2 Hz. The signal of the bridge proton H_b is observed as one-proton doublet of doublets at 4.05–4.20 ppm with coupling constant of J_{HbHa} = 8.2–8.8 Hz and J_{HbHc} = 5.2 Hz. These values are in accordance with the theoretically expected ones for *endo*-Diels–Alder adducts[13–15].

The reaction of isoindole **6** with 2 equivalent of maleimide **8a** under thermodynamic control yielded only the Diels–Alder adduct **10a**; the excess of the starting maleimide was recovered.

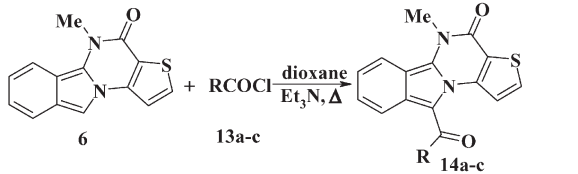
The Michael adduct **12** was obtained by heating 5-methylthieno-[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(5*H*)-one (**6**) with dimethyl acetylenedicarboxylate (**11**) in dioxane (Scheme 4).

We also tried to vary the substituent at C-10 of compound **6** in order to investigate the reaction of the compounds obtained with dienophiles. Acylation of 5-methylthieno[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(5*H*)-one (**6**) with acyl chlorides **13** led to compounds **14a**–**14c** (Scheme 5). IR spectra of compound **14b** showed an intensive characteristic band corresponding

to pyrimidine 1665 cm^{-1} and to the (4-methoxyphenyl)acetyl fragment 1593 cm^{-1}.



SCHEME 4



14a, R = 2-methyl-3-furoyl
14b, R = 4-methoxybenzoyl
14c, R = 2-phenylbutanoyl

SCHEME 5

Heating of compound **6** with trifluoroacetic anhydride in dioxane afforded compound **14d** (R = CF_3). IR spectra of compound **14d** exhibit an intensive band corresponding to pyrimidine at 1683 cm^{-1} and another one of the acyl group at 1601 cm^{-1}. Attempts to carry out the reaction of **14** with maleimide derivatives **8** failed. We recovered only the starting material.

The explanation of this fact is analogous to that for the acyl tetrasoloisoindoles[27]. The latter exhibit a strong interaction of the carbonyl group with aromatic fragment; their structure was considered to be zwitterionic, bearing no isoindole moiety.

Conclusions

The reaction of 2-(bromomethyl)benzonitrile (**1**) with methyl-3-aminothiophene-2-carboxylate (**2**) resulted in the formation of thienopyrimidoisoindolone existing in two tautomeric forms: isoindoline **3** and isoindole **4**. Methylation of compounds **3** or **4** or their mixtures with methyl tosylate, followed by further treatment of salt **5** with alkali gave 5-methylthieno-[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(5*H*)-one (**6**), which reacted with male-

imide derivatives **8** to form novel stable tricyclic 7-azanorbornenes **10**. Isoindole **6** reacted with dimethyl acetylenedicarboxylate (**11**), yielding the Michael adduct **12**. Acylation of **12** leads to acyl derivatives **14**, which do not react with dienophiles.

EXPERIMENTAL

Chemical-ionization mass spectra were recorded on a Nermag R10 instrument. NMR spectra (δ, ppm; *J*, Hz) were obtained on a Mercury 400 Varian spectrometer at 400 MHz (^{1}H NMR) or 100 MHz (^{13}C NMR) in DMSO-d_6 and CF_3COOD as the solvent. UV-VIS spectra (λ, nm) were recorded in the solid state (KBr pellets) on a Perkin–Elmer-Lambda-19 spectrophotometer equipped with a 60 mm integration sphere for solid measurements. The electrospray mass spectra were recorded on an API-365 Perkin–Elmer Sciex instrument at the Service Commun de Spectrométrie de Masse of the Paul Sabatier University, Toulouse. Elemental analyses were determined with a Carlo Erba Strumentazione apparatus at the ENSIACET Toulouse.

Preparation of Compounds **3** and **4**. General Procedure

2-(Bromomethyl)benzonitrile (0.2 g, 1 mmol) and the corresponding 3-aminothiophene-2-carboxylate (0.24 g, 1.5 mmol) were heated under reflux in dry DMF (4 ml) for 10 min. After cooling, the product was collected by filtration and recrystallized from DMF. Compound **3** is little soluble in hot DMF in contrast to compound **4**.

Thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(10H)-one (**3**). Yield 0.21 g (80%) of a light yellow powder. M.p. 85 °C. For $C_{13}H_8N_2OS$ (240.3) calculated: 64.98% C, 3.36% H, 11.66% N; found: 65.00% C, 3.42% H, 11.70% N. ^{1}H NMR (DMSO-d_6): 5.39 s, 2 H (CH_2); 7.30 d, 1 H, *J* = 5.2; 7.57 t, 1 H, *J* = 8.0; 7.66 d, 1 H, *J* = 8.0; 7.72 d, 1 H, *J* = 4.0; 7.98 d, 1 H, *J* = 8.0; 8.06 d, 1 H, *J* = 4.0. ^{13}C NMR (DMSO-d_6): 58.63, 119.31, 122.98, 126.14, 126.34, 126.53, 132.80, 139.42, 143.93, 144.37, 146.47, 157.97, 159.61. UV: λ_{max} = 340 nm. $[MH]^+$ 241.

Thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(5H)-one (**4**). Yield 24 mg (10%) of light yellow crystals. M.p. 185 °C. For $C_{13}H_8N_2OS$ (240.3) calculated: 64.98% C, 3.36% H, 11.66% N; found: 65.02% C, 3.41% H, 11.68% N. ^{1}H NMR (DMSO-d_6): 6.77 s, 1 H (CH); 7.49 d, 1 H, *J* = 8.0; 7.63–7.72 m, 3 H; 7.97 d, 1 H, *J* = 8.0; 8.23 d, 1 H, *J* = 8.0. ^{13}C NMR (DMSO-d_6): 83.20, 122.63, 122.75, 125.07, 125.65, 130.72, 131.26, 133.12, 135.76, 143.73, 155.87, 156.40, 158.39. UV: λ_{max} = 370 nm. $[MH]^+$ 241.

5-Methyl-4-oxo-4,10-dihydrothieno[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-5-ium Tosylate (**5**)

Compound **3** or **4** (2.4 g, 10 mmol) and methyl tosylate (3.4 g, 20 mmol) were heated to 100 °C for 1 h. The product was collected by filtration, and washed twice with ethanol. Yield 4.0 g (93%). M.p. 237 °C. ^{1}H NMR (DMSO-d_6): 2.31 s, 3 H (CH_3); 4.09 s, 3 H (CH_3); 6.15 s, 2 H; 6.98 s, 2 H, *J* = 7.6; 7.33 d, 2 H, *J* = 8.0; 7.62 d, 1 H, *J* = 8.4; 7.93–8.07 m, 4 H; 8.31 d, 1 H, *J* = 5.2. $[MH]^+$ 255.

5-Methylthieno[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-4(5*H*)-one (**6**)

Further treatment of the salt **5** with alkali led to the expected compound **6**. The product was collected by filtration and washed twice with water and ethanol or DMF. Yield 2.3 g (98%). M.p. 115 °C. For $C_{14}H_{10}N_2OS$ (254.3) calculated: 66.12% C, 3.96% H, 11.02% N; found: 66.30% C, 4.00% H, 11.12% N. ^{1}H NMR (DMSO-d_6): 3.88 s, 3 H (CH_3); 6.77 t, 1 H, *J* = 7.4; 6.93 t, 1 H, *J* = 7.4; 7.43 d, 1 H, *J* = 8.4; 7.85–7.95 m, 3 H; 8.26 d, 1 H, *J* = 5.2. ^{13}C NMR (DMSO-d_6): 31.06, 99.08, 107.70, 118.13, 118.42, 119.28, 119.55, 120.56, 122.80, 123.02, 124.92, 136.21, 140.40, 154.30. $[MH]^+$ 255.

Preparation of Compounds **7**. General Procedure

Compound **4** was suspended in dry DMF containing 1 equivalent of R^1CHO and heated under reflux for 10 min. After cooling, the product was recovered by filtration and crystallized from DMF.

10-[(2,3-Dihydro-1,4-benzodioxin-6-y)lmethylidene]thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(10H)-one (**7a**). From **4** (0.24 g, 1 mmol) and 2,3-dihydro-1,4-benzodioxine-6-carbaldehyde (0.25 g, 1.5 mmol). Yield 0.31 g (82%) of yellow crystals. M.p. 230 °C. ^{1}H NMR (CF_3COOD): 4.42–4.43 m, 2 H; 4.45–4.46 m, 2 H; 7.14–7.16 d, 1 H, *J* = 8.0; 7.21–7.31 m, 2 H; 7.74–7.79 d, 1 H, *J* = 20.0; 7.81–7.88 m, 3 H; 8.10–8.12 d, 1 H, *J* = 8.0; 8.33–8.39 m, 2 H. $[MH]^+$ 387.

10-(Pyridin-3-ylmethylidene)thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(10H)-one (**7b**). From **4** (0.24 g, 1 mmol) and nicotinaldehyde (0.16 g, 1.5 mmol). Yield 0.3 g (93%) of yellow crystals. M.p. 246 °C. ^{1}H NMR (CF_3COOD): 7.54 d, 1 H, *J* = 8.0; 7.98 t, 1 H, *J* = 7.2; 8.06 t, 1 H, *J* = 7.6; 8.38 d, 1 H, *J* = 4.8; 8.52 t, 1 H, *J* = 7.2; 8.62–8.68 m, 2 H; 8.71 d, 1 H; 9.15 d, 1 H, *J* = 8.0; 9.22 d, 1 H, *J* = 5.6; 9.48 s, 1 H. $[MH]^+$ 330.

10-(Pyridin-2-ylmethylidene)thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(10H)-one (**7c**). From **4** (0.24 g, 1 mmol) and pyridine-2-carbaldehyde (0.16 g, 1.5 mmol). Yield 0.28 g (87%) of yellow crystals. M.p. 253 °C. For $C_{19}H_{11}N_3OS$ (329.4) calculated: 69.28% C, 3.37% H, 12.76% N; found: 70.00% C, 3.48% H, 12.90% N. ^{1}H NMR (CF_3COOD): 7.44 d, 1 H, *J* = 8.0; 7.91 t, 1 H, *J* = 7.6; 7.99 t, 1 H, *J* = 7.6; 8.29 d, 1 H, *J* = 6.0; 8.38 t, 1 H, *J* = 6.6; 8.52–8.68 m, 4 H; 9.93 t, 1 H, *J* = 8.0; 9.19 d, 1 H, *J* = 5.2. $[MH]^+$ 330.

Preparation of Compounds **9**. General Procedure

Compound **4** was suspended in methanol containing 1 equivalent of derivatives of maleimide **8** and heated under reflux for 1 h. After cooling, the product was recovered by filtration and recrystallized from methanol.

10-(1-Methyl-2,5-dioxopyrrolidin-3-yl)thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(10H)-one (**9a**). From **4** (0.24 g, 1 mmol) and *N*-methylmaleimide (0.11 g, 1 mmol). Yield 0.29 g (83%) of a white powder. M.p. 222 °C. ^{1}H NMR (DMSO-d_6): 1.33 dd, 1 H, H_c, *J* = 17.6, 7.9; 2.23 s, 3 H (CH_3); 2.37 dd, 1 H, H_d, *J* = 18.4, 8.0; 3.96–3.99 m, 1 H, H_b; 6.17 d, 1 H, H_a, *J* = 4.0; 7.65–7.73 m, 3 H; 7.80 d, 1 H, *J* = 6.8; 8.07 d, 1 H, *J* = 7.6; 8.20 d, 1 H, *J* = 5.6. $[MH]^+$ 352.

10-[1-(4-Methylphenyl)-2,5-dioxopyrrolidin-3-yl]thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(10H)-one (**9b**). From **4** (0.24 g, 1 mmol) and *N*-(4-methylphenyl)maleimide (0.19 g, 1 mmol). Yield 0.32 g (66%) of a white powder. M.p. 231 °C. ^{1}H NMR (DMSO-d_6): 1.38 dd, 1 H, H_c, *J* = 17.6, 7.6; 2.28 s, 3 H (CH_3); 2.39 dd, 1 H, H_d, *J* = 18.4, 8.0; 4.00–4.32 m, 1 H, H_b; 6.17 d, 1 H, H_a, *J* = 4.0; 7.10 d, 2 H, *J* = 8.0; 7.30 d, 2 H, *J* = 8.0; 7.60–7.68 m, 3 H; 7.83 d, 1 H, *J* = 6.8; 8.15 d, 1 H, *J* = 7.6; 8.23 d, 1 H, *J* = 5.6. $[MH]^+$ 428.

10-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(10H)-one (**9c**). From **4** (0.24 g, 1 mmol) and *N*-benzylmaleimide (0.19 g, 1 mmol). Yield 0.31 g (73%) of a white powder. M.p. 228 °C. ^{1}H NMR (DMSO-d_6): 1.34 dd, 1 H, H_c, J = 17.6, 7.6; 2.39 dd, 1 H, H_d, J = 18.4, 8.0; 4.00 s, 2 H (CH_2); 4.09–4.32 m, 1 H, H_b; 6.15 d, 1 H, H_a, J = 4.0; 7.32–7.80 m, 9 H; 8.17 d, 1 H, J = 7.6; 8.20 d, 1 H, J = 5.6. $[MH]^+$ 428.

Preparation of Compounds **10**. General Procedure

Compound **6** was suspended in methanol containing 1 equivalent of maleimide derivative **8** and heated under reflux for 1 h. After cooling, the product was recovered by filtration, obtained product residue was separated by column chromatography (silica gel L 100/250 mesh; ethyl acetate–toluene 8:2).

2,19-Dimethyl-5-thia-2,9,19-triazahexacyclo[8.6.5.0^{1,9}.0^{4,8}.0^{11,16}.0^{17,21}]henicosa-4(8),6,11,13,15-pentaene-3,18,20-trione (**10a**). From **6** (0.25 g, 1 mmol) and *N*-methylmaleimide (0.11 g, 1 mmol or 0.22 g, 2 mmol). Yield 0.12 g (35%) of a white powder. M.p. 217 °C. ^{1}H NMR (DMSO-d_6): 2.27 s, 3 H (CH_3); 3.70 s, 3 H (CH_3-N); 4.21 dd, 1 H, H_b, J_{HbHa} = 8.2, J_{HbHc} = 5.2; 4.35 d, 1 H, J = 8.2, H_a; 6.28 d, 1 H, J = 5.2, H_c; 7.25 d, 1 H, J = 5.2; 7.60 t, 1 H, J = 8.0; 7.64 d, 1 H, J = 8.0; 7.75 d, 1 H, J = 4.0; 7.93 d, 1 H, J = 8.0; 8.00 d, 1 H, J = 4.0. $[MH]^+$ 366.

2-Methyl-19-phenyl-5-thia-2,9,19-triazahexacyclo[8.6.5.0^{1,9}.0^{4,8}.0^{11,16}.0^{17,21}]henicosa-4(8),6,11,13,15-pentaene-3,18,20-trione (**10b**). From **6** (0.25 g, 1 mmol) and *N*-phenylmaleimide (0.17 g, 1 mmol or 0.34 g, 2 mmol). Yield 0.24 g (57%) of a white powder. M.p. 205 °C. ^{1}H NMR (DMSO-d_6): 3.72 s, 3 H (CH_3-N); 4.26 dd, 1 H, H_b, J_{HbHa} = 8.8, J_{HbHc} = 5.2; 4.55 d, 1 H, J = 8.8, H_a; 6.61 d, 1 H, J = 5.2, H_c; 7.42–7.88 m, 10 H; 7.95 d, 1 H, J = 4.0. $[MH]^+$ 428.

2-Methyl-19-(4-methylphenyl)-5-thia-2,9,19-triazahexacyclo[8.6.5.0^{1,9}.0^{4,8}.0^{11,16}.0^{17,21}]henicosa-4(8),6,11,13,15-pentaene-3,18,20-trione (**10c**). From **6** (0.25 g, 1 mmol) and *N*-(4-methylphenyl)maleimide (0.19 g, 1 mmol or 0.38 g, 2 mmol). Yield 0.26 g (60%) of a light yellow powder. M.p. 213 °C. ^{1}H NMR (DMSO-d_6): 2.96 s, 3 H (CH_3); 3.75 s, 3 H (CH_3-N); 4.29 dd, 1 H, H_b, J_{HbHa} = 8.8, J_{HbHc} = 5.2; 4.41 d, 1 H, J = 8.8, H_a; 6.26 d, 2 H, J = 8.4; 6.71 d, 1 H, J = 5.2, H_c; 7.00 d, 2 H, J = 8.4; 7.30–7.71 m, 4 H; 7.90 d, 1 H, J = 8.0; 7.98 d, 1 H, J = 4.0. ^{13}C NMR (DMSO-d_6): 25.67, 38.10, 51.88, 55.11, 66.82, 91.31, 119.38, 120.30, 127.26, 128.01, 128.05, 133.69, 135.04, 135.19, 135.73, 135.84, 135.78, 143.08, 143.77, 145.81, 146.58, 147.90, 160.12, 178.28, 178.24. $[MH]^+$ 442.

2-Methyl-19-(4-methoxyphenyl)-5-thia-2,9,19-triazahexacyclo[8.6.5.0^{1,9}.0^{4,8}.0^{11,16}.0^{17,21}]henicosa-4(8),6,11,13,15-pentaene-3,18,20-trione (**10d**). From **6** (0.25 g, 1 mmol) and *N*-(4-methoxyphenyl)maleimide (0.2 g, 1 mmol or 0.4 g, 2 mmol). Yield 0.2 g (44%) of a white powder. M.p. 209 °C. ^{1}H NMR (DMSO-d_6): 3.70 s, 3 H (CH_3); 3.73 s, 3 H (CH_3-N); 4.22 dd, 1 H, H_b, J_{HbHa} = 8.4, J_{HbHc} = 5.3; 4.55 d, 1 H, J = 8.4, H_a; 6.38 d, 2 H, J = 8.9; 6.70 d, 1 H, J = 5.2, H_c; 6.80 d, 2 H, J = 8.9; 7.44–7.75 m, 4 H; 7.88 d, 1 H, J = 8.0; 7.95 d, 1 H, J = 4.0. IR (KBr): 1706 (CO), 1774 (CO), 1655 (CO). $[MH]^+$ 458.

2-Methyl-19-(1-naphthyl)-5-thia-2,9,19-triazahexacyclo[8.6.5.0^{1,9}.0^{4,8}.0^{11,16}.0^{17,21}]henicosa-4(8),6,11,13,15-pentaene-3,18,20-trione (**10e**). From **6** (0.25 g, 1 mmol) and *N*-(1-naphthyl)-maleimide (0.22 g, 1 mmol or 0.44 g, 2 mmol). Yield 0.24 g (51%) of a light yellow powder. M.p. 216 °C. ^{1}H NMR (DMSO-d_6): 3.74 s, 3 H (CH_3-N); 4.29 dd, 1 H, H_b, J_{HbHa} = 8.4, J_{HbHc} = 5.2; 4.58 d, 1 H, J = 8.4, H_a; 6.68 d, 1 H, J = 5.2, H_c; 7.42–7.79 m, 12 H; 7.99 d, 1 H, J = 4.1. $[MH]^+$ 478.

Dimethyl (2*E*)-2-(5-Methyl-4-oxo-4,5-dihydrothieno[2′,3′:5,6]pyrimido-[2,1-*a*]isoindol-10-yl)but-2-enedioate (**12**)

Compound **6** (0.5 g 2 mmol) and dimethyl acetylenedicarboxylate (**11**; 0.35 g, 2.5 mmol) in a dioxane were heated under reflux for 30 min. The solution was evaporated under reduced pressure and the residue was separated by chromatography (silica gel L 100/250 mesh; dichloromethane–acetone 3:1). Yield 0.72 g (92%) of a red powder. M.p. 211 °C. ^{1}H NMR (DMSO-d_6): 3.54 s, 3 H (CH_3); 3.61 s, 3 H (CH_3); 4.09 s, 3 H (CH_3); 6.93 t, 1 H, *J* = 7.6; 7.03 s, 1 H; 7.07–7.11 m, 2 H, *J* = 7.8; 7.36 d, 1 H, *J* = 5.2; 8.07 d, 1 H, *J* = 8.8; 8.18 d, 1 H, *J* = 5.2. $[MH]^+$ 397.

Preparation of Acyl Derivatives **14a**–**14c**. General Procedure

One equivalent of an acyl chloride and 1.5 equivalent of triethylamine were added to a solution of **6** in 15 ml of dioxane. The mixture was heated at 100 °C for 1 h. After cooling, the product was recovered by filtration and recrystallized from ethanol.

5-Methyl-10-(2-methyl-3-furoyl)thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(5H)-one (**14a**). From **6** (0.25 g, 1 mmol), 2-methyl-3-furoyl chloride (0.17 g, 1.2 mmol) and triethylamine (0.15 g, 1.5 mmol). Yield 0.34 g (95%) of yellow crystals. M.p. 251 °C. For $C_{20}H_{14}N_2O_3S$ (362.4) calculated: 66.28% C, 3.89% H, 7.73% N; found: 66.31% C, 3.94% H, 7.75% N. ^{1}H NMR (DMSO-d_6): 2.46 s, 3 H (CH_3); 4.12 s, 3 H (CH_3); 6.65 s, 1 H; 7.00–7.04 t, 1 H, *J* = 7.6; 7.17–7.21 t, 1 H, *J* = 7.8; 7.26–7.28 d, 1 H, *J* = 8.4; 7.56–7.59 m, 2 H; 8.10–8.11 d, 1 H, *J* = 3.6; 8.18–8.20 d, 1 H, *J* = 8.8. $[MH]^+$ 363.

10-(4-Methoxybenzoyl)-5-methylthieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(5H)-one (**14b**). From **6** (0.25 g, 1 mmol), 4-methoxybenzoyl chloride (0.2 g, 1.2 mmol) and triethylamine (0.15 g, 1.5 mmol). Yield 0.37 g (97%) of yellow crystals. M.p. 234 °C. ^{1}H NMR (DMSO-d_6): 3.92 s, 3 H (OCH_3); 4.11 s, 3 H (CH_3); 6.90–7.01 m, 5 H; 7.53–7.55 d, 1 H, *J* = 8.0; 7.83–7.86 m, 2 H; 8.08–8.10 m, 1 H; 8.15–8.17 d, 1 H, *J* = 8.0. ^{13}C NMR (CF_3COOD): 17.21, 36.02, 112.44, 122.55, 121.24, 124.50, 128.10, 129.55, 132.08, 135.63, 141.06, 144.06, 144.61, 146.60, 147.24, 160.33, 163.29, 163.55, 171.46, 188.18. $[MH]^+$ 389.

5-Methyl-10-(2-phenylbutanoyl)thieno[2′,3′:5,6]pyrimido[2,1-a]isoindol-4(5H)-one (**14c**). From **6** (0.25 g, 1 mmol), 2-phenylbutanoyl chloride (0.21 g, 1.2 mmol) and triethylamine (0.15 g, 1.5 mmol). Yield 0.39 g (98%) of yellow crystals. M.p. 222 °C. ^{1}H NMR (DMSO-d_6): 0.99 t, 3 H, *J* = 7.2 ($CH_2C\mathbf{H}_3$); 1.91–1.94 m, 1 H; 2.24–2.30 m, 1 H; 4.04 s, 3 H (CH_3); 4.61 t, 1 H, *J* = 7.2; 7.03 t, 1 H, *J* = 7.6; 7.16–7.23 m, 2 H; 7.27–7.23 m, 2 H; 7.37 t, 1 H, *J* = 7.6; 7.44–7.46 m, 2 H; 8.01 d, 1 H, *J* = 5.2; 8.04 d, 1 H, *J* = 9.2; 8.16 d, 1 H, *J* = 8.8. $[MH]^+$ 401.

5-Methyl-10-(trifluoroacetyl)thieno[2′,3′:5,6]pyrimido[2,1-*a*]isoindol-4-(5*H*)-one (**14d**)

Trifluoroacetic anhydride (0.31 g, 1.5 mmol) and triethylamine (0.15 g, 1.5 mmol) were added to a solution of **6** (0.25 g, 1 mmol) in 15 ml of dioxane. The mixture was heated to 60 °C for 1 h. After cooling, the product was recovered by filtration and recrystallized from ethanol. Yield 0.33 g (96%) of yellow crystals. M.p. 236 °C. For $C_{16}H_9F_3N_2O_2S$ (350.3) calculated: 54.86% C, 2.59% H, 8.00% N; found: 54.90% C, 2.61% H, 7.97% N. ^{1}H NMR (DMSO-d_6): 4.12 s, 3 H (CH_3); 7.25 t, 1 H, *J* = 7.8; 7.59 d, 1 H, *J* = 5.6; 7.57 t, 1 H, *J* = 7.6; 7.88 d, 1 H, *J* = 8.8; 8.19 d, 1 H, *J* = 5.2; 8.36 d, 1 H, *J* = 8.8. $[MH]^+$ 351.

REFERENCES

1. Bonnett R., North S.: *Adv. Heterocycl. Chem.* **1981**, *29*, 341
2. Bonnett R., Brown R. F. C., Smith R. G.: *J. Chem. Soc., Perkin Trans. 1* **1973**, 1432.
3. Kovtunenko V. A., Voitenko Z. V.: *Usp. Khim.* **1994**, *63*, 997; *Chem. Abstr.* **1994**, *124*, 86716.
4. Babichev F. S., Kovtunenko V. A.: *The Chemistry of Isoindoles*. Naukova Dumka Press, Kiev 1983.
5. a) Voitenko Z. V., Yegorova T. V., Kovtunenko V. A.: *Khim. Geterotsikl. Soedin.* **2002**, *9*, 1171; b) Voitenko Z. V., Yegorova T. V., Kovtunenko V. A.: *Chem. Heterocycl. Comp.* **2002**, *38*, 1019.
6. Voitenko Z. V., Pocholenko O. A.: *Russ. Chem. Rev.* **2004**, *73*, 833; *Chem. Abstr.* **2004**, *142*, 74477.
7. Voitenko Z. V.: *Ph.D. Thesis*. Taras Shevchenko National University, Kiev 2005.
8. Metlesics W., Sternbach L.: U.S. 3 905 994; *Chem. Abstr.* **1976**, *84*, 17346.
9. Graf W.: CH 480 350; *Chem. Abstr.* **1970**, *73*, 56082.
10. Gomes P., Araujo M. J., Rodrigues M., Vale N., Azevedo Z., Iley J., Chambel P.: *Tetrahedron* **2004**, *60*, 5551.
11. Los M.: U.S. 4 041 045; *Chem. Abstr.* **1977**, *87*, 168034.
12. Los M.: Neth. 7 700 387; *Chem. Abstr.* **1979**, *90*, 34991.
13. Kovtunenko V. A., Voitenko Z. V., Tyltin A. K., Turov A. V., Babichev F. S.: *Ukr. Khim. Zh.* **1983**, *49*, 1287; *Chem. Abstr.* **1984**, *100*, 173943.
14. Kovtunenko V. A., Voitenko Z. V., Tyltin A. K., Kornilov M. Yu., Babichev F. S.: *Ukr. Khim. Zh.* **1988**, *54*, 1186; *Chem. Abstr.* **1989**, *111*, 23418.
15. a) Kovtunenko V. A., Voitenko Z. V., Kucherenko T. T., Turov A. V., Tyltin A. K., Babichev F. S.: *Khim. Geterotsikl. Soedin.* **1990**, *2*, 190; b) Kovtunenko V. A., Voitenko Z. V., Kucherenko T. T., Turov A. V., Tyltin A. K., Babichev F. S.: *Chem. Heterocycl. Comp.* **1990**, *26*, 161.
16. Kovtunenko V. A., Voitenko Z. V., Kucherenko T. T.: *Ukr. Khim. Zh.* **1992**, *58*, 1035; *Chem. Abstr.* **1993**, *119*, 27957.
17. a) Voitenko Z. V., Samoylenko V. P., Kovtunenko V. A., Gurkevich V. Yu., Tyltin A. K., Shcherbakov M. V., Shishkin O. V.: *Khim. Geterotsikl. Soedin.* **1999**, *5*, 669; b) Voitenko Z. V., Samoylenko V. P., Kovtunenko V. A., Gurkevich V. Yu., Tyltin A. K., Shcherbakov M. V., Shishkin O. V.: *Chem. Heterocycl. Comp.* **1999**, *35*, 600.
18. Voitenko Z. V., Samoylenko V. P., Donnadieu B., Bonnet J.-J.: *Tetrahedron* **2002**, *58*, 6103.
19. a) Voitenko Z. V., Samoylenko V. P.: *Khim. Geterotsikl. Soedin.* **2002**, *2*, 219; b) Voitenko Z. V., Samoylenko V. P.: *Chem. Heterocycl. Comp.* **2002**, *38*, 197.
20. Voitenko Z. V., Pocholenko O. A., Chkarov O. O., Shishkin O. V., Wolf J. G.: *Eur. J. Org. Chem.* **2001**, *7*, 1401.
21. Babichev F. S., Tyltin A. K., Kovtunenko V. A.: *Ukr. Khim. Zh.* **1970**, *36*, 175; *Chem. Abstr.* **1970**, *73*, 3877.
22. Babichev F. S., Melnichenko A. V., Tyltin A. K., Kovtunenko V. A.: *Ukr. Khim. Zh.* **1986**, *52*, 296; *Chem. Abstr.* **1987**, *106*, 84540.
23. a) Tyltin A. K., Kovtunenko V. A., Rytova N. N., Babichev F. S.: *Khim. Geterotsikl. Soedin.* **1977**, *8*, 1129; b) Tyltin A. K., Kovtunenko V. A., Rytova N. N., Babichev F. S.: *Chem. Heterocycl. Comp.* **1977**, 912.

24. Kovtunenko V. A., Ishchenko V. V., Tyltin A. K., Babichev F. S.: *Dokl. Akad. Nauk SSSR* **1988**, *299*, 373.
25. Voitenko Z. V., Kysil A. I., Wolf J. G.: *C. R. Chim.* **2007**, *10*, 813.
26. Barton D., Ollis W. D.: *Comprehensive Organic Chemistry*, Vol. 4. Pergamon, London 1979.
27. Voitenko Z. V., Boisdon M. T., Egorova T. V., Kysil A. I., Favrot J., Wolf J. G.: *J. Mol. Struct.* **2003**, *658*, 171.