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CONDENSED ISOQUINOLINES 32*. SYNTHESIS OF 4H-THIENO-[3',2':5,6]- AND -[2',3':5,6]PYRIMIDO-[1,2-b]ISOQUINOLINES AND 6,12-DIHYDRO-5H-ISOQUINO-[2,3-a]QUINAZOLINE-5,12-DIONE DERIVATIVES

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Treatment of 2-(4-oxo-3,4-dihydrothieno[2,3-d]- and -[3,2-d]pyrimidin-2-ylmethyl)benzoic acids and 2-(4-oxo-3,4-dihydro-2-quinazolinylmethyl)benzoic acid with acetic anhydride gave thieno[3',2':5,6]- and -[2',3':5,6]pyrimido[1,2-b]isoquinoline-4,11-diones and isoquino[2,3-a]quinazoline-5,12-dione respectively. NMR spectroscopy showed that an intramolecular acylation of the above acids occurs at the atom N-1 of the pyrimidinone part of the bicycle.

Keywords: isoquinoquinazoline-5,12-dione, 4-oxopyrimidinones, thienopyrimidinones, thieno-pyrimidoisoquinoline-4,11-diones, quinazolines.

We have previously reported 2-(4-oxo-3,4-dihydrothieno[2,3-*d*]- and -[3,2-*d*]pyrimidin-2-ylmethyl)-benzoic acids **1** and **2** [2] and 2-(4-oxo-3,4-dihydro-2-quinazolinylmethyl)benzoic acid **3** [3]. This work continues our investigation of thienopyrimidines and quinazolones.

The attempted esterification of acids **1-3** by a classical method [4] (heating an alcohol suspension in the presence of concentrated sulfuric acid) gave yellow crystalline materials whose properties differed from the starting materials although not being the esters. Hence like the starting acid they dissolve in a 2N solution of base but, in contrast, are completely insoluble in 2N hydrochloric acid. According to TLC data their chromatographic mobility is markedly greater than the starting acids and esters. The elemental analytical data and chromato-mass spectra of the products obtained point to the loss of a molecule of water from the starting acids, i.e. that an intramolecular acylation had occurred under these reaction conditions. It was found that the sulfuric acid dehydrating agent originally used by us was not a totally suitable reagent since cyclization is accompanied by a vigorous tarring of the reaction product and this significantly lowers the yields. A smoother dehydration occurs upon refluxing a suspension of the acids **1-3** in acetic anhydride.

* For Communication 31 see [1].

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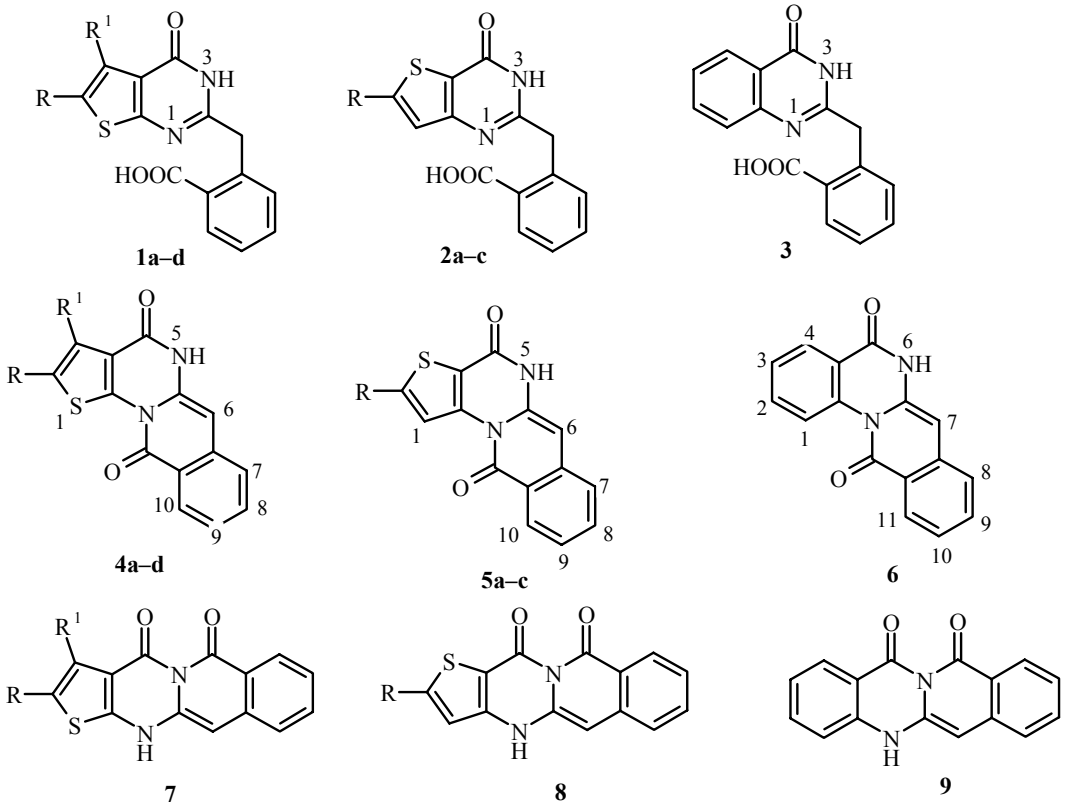

1a–d **2a–c** **3**

4a–d **5a–c** **6**

7 **8** **9**

4 a R = R[1] = Me; **b** R+R[1] = $(CH_2)_3$; **c** R+R[1] = $(CH_2)_4$; **d** R = H, R[1] = Ph;
5 a R = H; **b** R = 4'-ClC_6H_4; **c** R = 4'-FC_6H_4

The series of 4-oxothieno[2,3-*d*]- and -[3,2-*d*]pyrimidine acids (**1** and **2**) and also the 4-oxoquinazoline acid (**3**) have two nucleophilic centers of attack, *viz*. the N-1 and N-3 atoms. An intramolecular cyclization involving these centers can lead to angular (**4-6**) or linear (**7-9**) tetracyclic systems. However, both our study of the alkylation of the esters of the acids **1-3** [3, 4] and also from literature data for the alkylation [5] and acylation [6] of 2-benzyl derivatives of the thienopyrimidine and quinazoline systems would infer that this reaction occurs with the involvement of the N-3 atom exclusively. On this basis it would follow that the systems obtained have the linear structures **7-9**.

At the same time, quantum-chemical calculations of the energies of the isomeric angular and linear systems **4** and **7**, **5** and **8**, and also the corresponding isoquinoquinazolinediones **6** and **9** using the computer program [7] within the scope of the 3-21G** *ab initio* method (taking into account *d*-orbitals) and with full optimization of the geometry showed these to be -792188.67 for the **4a** molecule and -792170.65 kcal/mol for **7**. For the positional isomer **5a** this is -743454.73 and its linear isomer **8** -743437.23 kcal/mol. For the molecule **6** this is -543176.13 and its linear isomer **9** -543165.97 kcal/mol. Hence, against literature data, the calculations predict an intramolecular cyclization at the N-1 atom of the acid (**1**, **2**, and **3**) as the thermodynamically favored process. The markedly lower difference in full energies of the linear and angular isomers in molecules **6**/**9** when compared with the thiophene pairs **4**/**7** and **5**/**8** deserves mention.

Similar conclusions about the direction of cyclization at atom N-1 of the acids **1**, **2**, and **3** can be made from the NMR data for compounds **4** (or **7**), **5** (or **8**) and also **6** (or **9**). The linear or angular isomers formed upon cyclization contain identical structural fragments and hence a direct determination of their structures based on the spectra of their ^{1}H or ^{13}C nuclei was not possible. Hence we have carried out a 2D NMR spectroscopic study using homonuclear (COSY, NOESY) and ^{1}H–^{13}C heteronuclear correlation through one (HMQC) and through 2-3 bonds (HMBC).

In the first place an assignment of the signals in the ^{1}H NMR spectra of the compounds was needed. The spatial proximity of the NH proton to an aromatic proton and the long range correlations of the NH proton signal with the carbon atoms of the molecular skeleton are the basis for the determination of the structure of compound **4** (or **7**). We depict in Fig. 1 the results of the analysis for compound **4c** only since all of the remaining compounds of the **4** series are similar. Consideration of the formulae **4** and **7** shows that the only structurally significant difference is the positioning of the NH proton relative to the carbonyl carbon atoms. Whereas there are 2 chemical bonds between the NH proton and one of the carbonyl carbon atoms in the structure **4**, in the structure **7** they are separated by 4 bonds. Since the carbonyl group carbon atoms have quite a characteristic positioning in the ^{13}C NMR spectrum the presence of a spin-spin interaction between the NH proton signals and carbon atom of one of the carbonyl groups unambiguously supports structure **4**. Table 1 gives the correlations for the signals of the protons in compound **4c**. The correlations found (see Fig. 1) allowed us to assign the signals securely and to choose between the alternative structures in favour of structure **4**. The presence of a correlation for the aromatic proton doublet with a chemical shift of 8.14 ppm with the signal of one of the carbonyl carbon atoms found at 158.6 ppm makes possible its assignment as shown in the figure. The NH signal correlates with that of the second carbonyl signal in the molecule which occurs at 156.8 ppm. The presence of this correlation safely confirms the compound structure. The arrows in Fig. 1 show the HMBC correlations. The signals for the carbon atoms bound to hydrogen atoms are assigned on the basis of the correlation in the HMQC spectrum. The only carbon signal for which an HMBC correlation was not observed has a chemical shift of 141.5 ppm. We assign it to the carbon atom bridging between the heterocyclic nitrogen atoms and the sulfur. For assignment of the signals of the cyclohexene fragment it was assumed that the methylene protons closest in space to the carbonyl group absorb at somewhat lower field than the remaining aliphatic proton signals.

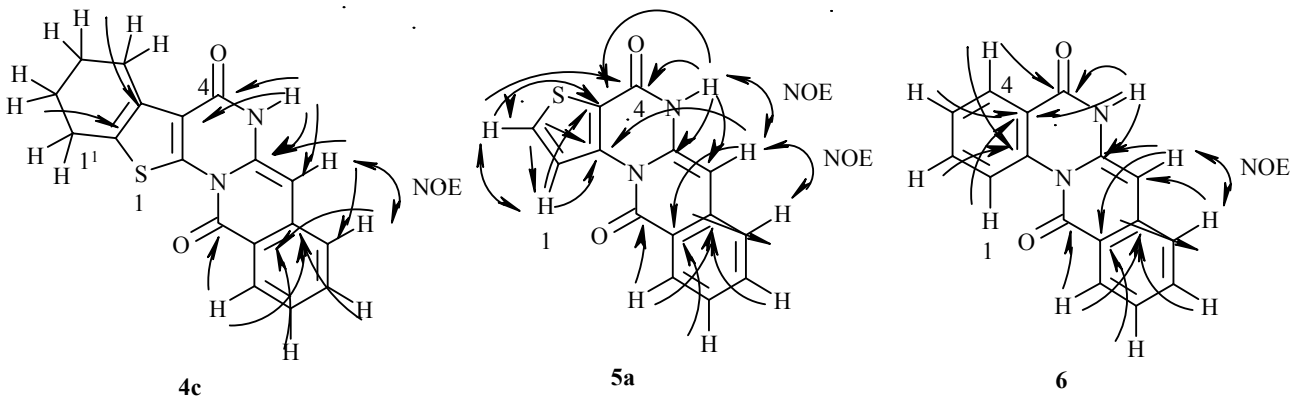

Fig. 1. Model of the HMQC and HMBC correlations for compounds **4c**, **5a**, and **6.**

Conclusions regarding the structure of compounds of series **5** (or **8**) are based on the occurrence of a steric proximity of the NH proton to the aromatic protons on the one hand and of long range correlations of the NH signal with the skeletal carbon atoms in the molecule. Correlations are only analyzed in this publication for compound **5a** because they are the same for all of the remaining compounds in the series (Table 2). Inspection of the formulae of the isomers shows that a steric proximity of the NH proton to two aromatic protons would be expected in the case of the linear isomer **8** but there would only be one in the example of the angular isomer **5a**. The experimental data shows that there is a cross peak in the NOESY spectrum between the NH proton signal and that at 6.27 ppm. Other cross peaks were not seen for this signal and this supports the angular structure for the compound, i.e. **5a**. Further confirmation comes from the heteronuclear correlation data (see Fig. 1).

TABLE 1. Results of the Heteronuclear Correlation Experiments (HMBC and HMQC) for Compound **4c**

Atom position	δ, ppm	HMQC	HMBC
5	11.71	—	156.8; 137.6; 118.2; 86.5
10	8.14	128.1	158.6; 137.3; 134.0
8	7.63	134.0	137.3; 128.1
7	7.51	125.6	137.3; 124.7; 118.8; 86.5
9	7.31	124.7	125.6; 118.8
6	6.26	86.5	137.6; 141.5; 125.6; 118.8
3(4')	2.82	25.4	132.9; 130.6; 23.0; 22.5
2(1')	2.65	24.0	132.9; 130.6; 23.0; 22.5
2', 3'	1.73	23.0; 22.5	132.9; 130.6; 25.4; 24.0; 23.0; 22.5

TABLE 2. Results of the Homonuclear (NOESY Spectrum) and Heteronuclear (HMBC and HMQC) Correlation Experiments for Compound **5a**

Atom position	δ, ppm	HMQC	HMBC	NOESY
5	12.03	—	138.8; 120.6; 155.6; 82.7	6.27
1	8.68	123.9	141.7; 133.8; 120.6	8.17
10	8.21	128.3	137.1; 133.8; 159.9	—
2	8.17	133.8	141.7; 123.9; 120.6; 155.6	8.68
8	7.65	133.9	137.1; 128.3	7.54; 7.33
7	7.53	125.3	124.7; 120.6; 87.2	7.65
9	7.33	124.7	125.2; 120.6	7.65; 8.21
6	6.27	87.2	141.7; 138.8; 125.3; 120.6	12.03; 7.54

TABLE 3. Results of the Heteronuclear Correlation Experiments (HMBC and HMQC) for Compound **6**

Atom position	δ, ppm.	HMQC	HMBC
6	11.86	—	119.9; 137.8; 158.4
1	9.22	121.6	158.4; 138.7; 126.8; 119.9
11	8.17	128.7	162.7; 136.9; 134.1
4	8.09	127.5	158.4; 138.7; 134.2
2	7.75	134.2	138.7; 127.5; 121.6
9	7.61	134.1	136.9; 128.7
3	7.46	126.8	121.6; 119.9
8	7.45	125.1	136.9; 125.0; 122.2; 87.7
10	7.30	125.0	125.1; 122.2; 136.9; 134.1; 128.7
7	6.18	87.7	137.8; 125.1; 122.2

Assignments of the chemical shifts of the carbon atoms bound to the hydrogen atoms are made based on HMQC correlations and those of the quaternary carbon atoms on those showing in the HMBC. From the viewpoint of establishing the structure of the compound the absence of a correlation between the NH proton signal and the carbon atom signal with a shift of 123.9 ppm corresponding to the C-4 atom of the thiophene ring is most important. In the alternative linear structure this correlation would have to be rather strong.

For determining the structure of compound **6** (or **9**) difficulties arise because the spin systems for the two benzene rings occurring in the composition of the molecules are identical. The assignment can be made

TABLE 4. ^{1}H NMR Spectra of the Compounds **4-6**

Compound	Chemical shifts, δ, ppm (*J*, Hz)									
	Position of resonating group (atom)									
	1	2	3	4	5	6	7	8	9	10
4a	—	2.41 (3H, s)	2.36 (3H, s)	—	11.71 (1H, s)	6.30 (1H, s)	7.50 (1H, d, ^3J = 8.0)	7.62 (1H, t, ^3J = 7.6)	7.32 (1H, t, ^3J = 7.6)	8.22 (1H, d, ^3J = 8.4)
4b	—	2.99-2.93 (6H, m)		—	11.83 (1H, s)	6.34 (1H, s)	7.53 (1H, d, ^3J = 8.0)	7.65 (1H, t, ^3J = 7.6)	7.35 (1H, t, ^3J = 7.6)	8.24 (1H, d, ^3J = 8.0)
4c	—	1.90-1.80 (4H, m); 2.77-2.75 (2H, m); 2.93-2.91 (2H, m)		—	11.71 (1H, s)	6.26 (1H, s)	7.51 (1H, d, ^3J = 7.6)	7.63 (1H, t, ^3J = 7.6)	7.31 (1H, t, ^3J = 7.6)	8.14 (1H, d, ^3J = 8.0)
4d	—	9.00 (1H, s)	7.78 (2H-2', d, *J* = 8.0); 7.51 (3H-3',4', m)	—	12.00 (1H, s)	6.28 (1H, s)	7.51 (1H, m)	7.64 (1H, t, ^3J = 7.6)	7.33 (1H, t, *J* = 7.6)	8.24 (1H, d, ^3J = 8.0)
5a	8.68 (1H, d, ^3J = 5.2)	8.17 (1H, d, ^3J = 5.2)	—	—	12.03 (1H, s)	6.27 (1H, s)	7.47 (1H, d, ^3J = 7.6)	7.65 (1H, t, ^3J = 8.0)	7.33 (1H, t, ^3J = 8.0)	8.21 (1H, d, ^3J = 8.0)
5b	8.97 (1H, s)	7.77 (2H-3', s) 7.51 (2H-2', s)	—	—	12.04 (1H, s)	6.26 (1H, s)	7.51 (1H, m)	7.63 (1H, s)	7.32 (1H, s)	8.19 (1H, s)
5c	8.92 (1H, s)	7.80 (2H-3', m); 7.33-7.29 (2H-2', m)	—	—	12.03 (1H, s)	6.26 (1H, s)	7.49 (1H, d, ^3J = 6.4)	7.63 (1H, t, ^3J = 6.0)	7.33-7.29 (1H, m)	8.19 (1H, d, ^3J = 6.4)
6*	9.24 (1H, d, ^3J = 7.2)	7.74 (1H, t, ^3J = 6.8)	7.48 (2H, m)	8.10 (1H, d, ^3J = 6.0)	11.87 (1H, s) {6}	6.20 (1H, s) {7}	7.48 (2H, m) {8}	7.63 (1H, t, ^3J = 5.6) {9}	7.32 (1H, t, ^3J = 5.6) {10}	8.19 (1H, d, ^3J = 6.4) {11}

* The numbering sequence of the atoms of the molecule according to the established nomenclature given in { }

using a comparison of the correlations existing in the COSY and NOESY spectra. The key in the assignment of signals is the presence of an NOE between the H-7 proton singlet absorbing at 6.18 ppm and the doublet at 7.45 ppm. Since the assignment of the singlet is not in doubt the NOE can only be observed for the H-8 proton signal near to it. All of the remaining signals for this spin system can be assigned on the basis of their COSY correlation. The signals of the protons of the second benzene ring can be assigned if one assumes that the proton near to the carbonyl carbon atom has the chemical shift of 9.22 ppm. The assignments of the remaining signals of the spin system then follow from their COSY correlation. This data supports the existence of the studied molecule as having the structure **6**. This follows from the occurrence of the H-1 proton signal at anomalously low field due to steric proximity to the unshared electron pair of the carbonyl oxygen atom (in the alternative structure **9** such a situation does not arise). In addition the NH proton signal only has a COSY correlation with one aromatic proton signal. For structure **9** there would be two such correlations. Additional confirmation of structure **6** was obtained from the heteronuclear correlations. The HMQC and HMBC correlations found for the proton signals in the heterocycle synthesized are given in Table 3. Most important in establishing the structure as **6** for this product is the correlation of the NH proton signal absorbing at 11.86 ppm with one of the carbonyl group carbons (found at 158.4 ppm). Such a correlation would not have been possible in the case of the alterative structure **9** since the carbonyl carbon atoms in it are separated from the NH by more than 3 chemical bonds. Figure 1 shows the carbon signal assignments indicated by the arrows for the important HMBC correlations which served as a basis for the structure. The assignment of the bridging carbon atoms was based on the presence of correlations with the proton signals found in a *meta* position relative to it. The signal of the bridging carbon atom placed between the heterocyclic nitrogen atoms was assigned on the basis of the correlation with the singlet at 6.18 ppm and with the NH protons signal. The signals of the carbon atoms bonded to hydrogen atoms are assigned from the presence of their correlation with the bonded protons in the HMQC spectrum.

Table 4 shows the ^{1}H NMR spectroscopic data for all of the synthesized compounds **4-6**.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra of compounds **4-6**, the NOE and 2D COSY ^{1}H NMR experiments, and the HMQC and HMBC heteronuclear correlation spectra were recorded on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively). All of the 2D experiments were carried out with gradient selection of useful signals. The mixing times in the pulse sequences were respectively $^{1}J_{CH}$ = 140 and $^{2\text{-}3}J_{CH}$ = 8 Hz. The numbers of increments in the COSY and HMQC spectra were 128 and in the HMBC spectra 400. In all cases the solvent was DMSO-d_6 and the internal standard TMS.

Mass spectra were measured on an Agilent 1100 series mass spectrometer with an Agilent LC/MSD SL detector, the sample was introduced in a trifluoroacetic matrix, EI ionization was used and the *m/z* values (I_{rel}, %) are given. [M^{+}+1] was the molecular ion peak. Melting points for the synthesized materials were measured in a Pyrex capillary using a Thiele apparatus and are not corrected. TLC was performed on Merck 60 F254 plates with benzene–methanol (9:1) as eluent. The products **4-6** have R_f 0.90-0.92. The esters have R_f 0.65-0.68 and the starting acids **1-3** have R_f 0.25-0.28.

2,3-Dimethyl-4H-thieno[3',2':5,6]pyrimido[1,2-b]isoquinoline-4,11(5H)-dione (4a). Acetic anhydride (10 ml, 106 mmol) was added to 2-(5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-yl)benzoic acid (**1a)** (0.31 g, 10 mmol) and refluxed with stirring for 4 h using a reflux condenser. The precipitate was filtered off and washed with ether. Yield 90%; mp 325ºC (DMF). Mass spectrum, *m/z*: 297 [M^{+}+1]. Found, %: C 64.80; H 4.00; N 9.39; S 10.78. $C_{16}H_{12}N_2O_2S$. Calculated, %: C 64.85; H 4.08; N 9.45; S 10.82.

2,3-Dihydro-1H,4H-cyclopenta[4',5']thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinoline-4,11(5H)-dione (4b) was obtained similarly from 2-(4-oxo-3,5,6,7-tetrahydro-4H-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-2-ylmethyl)-

benzoic acid (**1b)** (0.33 g, 10 mmol). Yield 92%; mp 305ºC (DMF). Mass spectrum, *m/z*: 309 [M^++1]. Found, %: C 66.12; H 3.86; N 8.96; S 10.35. $C_{17}H_{12}N_2O_2S$. Calculated, %: C 66.22; H 3.92; N 9.08; S 10.40.

8,9,10,11-Tetrahydro-7H-benzo[1]thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinoline-4,14(6H)-dione (4c) was prepared similarly from 2-(4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-2-ylmethyl)-benzoic acid (**1c)** (0.34 g, 10 mmol). Yield 93%; mp 325ºC (DMF). Mass spectrum, *m/z*: 323 [M^++1]. Found, %: C 66.95; H 4.31; N 8.57; S 9.86. $C_{18}H_{14}N_2O_2S$. Calculated, %: C 67.06; H 4.38; N 8.69; S 9.95.

3-Phenyl-4H-thieno[3',2':5,6]pyrimido[1,2-*b*]isoquinoline-4,11(5H)-dione (4d) was prepared similarly from 2-(4-oxo-5-phenyl-3,4-dihydrothioeno[2,3-*d*]pyrimidin-2-ylmethyl)benzoic acid (**1d**) (0.36 g, 10 mmol). Yield 90%; mp 300ºC (DMF). Mass spectrum, *m/z*: 345 [M^++1]. Found, %: C 69.72; H 3.46; N 8.05; S 9.52. $C_{20}H_{12}N_2O_2S$. Calculated, %: C 69.75; H 3.51; N 8.13; S 9.31.

4H-Thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinoline-4,11(5H)-dione (5a) was prepared similarly from 2-(4-oxo-3,4-dihydrothieno[3,2-*b*]pyrimidin-2-ylmethyl)benzoic acid (**2a)** (0.29 g, 10 mmol) in acetic anhydride (10 ml, 106 mmol). Yield 92%; mp 290ºC (HOAc). Mass spectrum, *m/z*: 269 [M^++1]. Found, %: C 62.72; H 3.09; N 10.52; S 11.84. $C_{14}H_8N_2O_2S$. Calculated, %: C 62.68; H 3.01; N 10.44; S 11.95.

2-(4-Chlorophenyl)-4H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinoline-4,11(5H)-dione (5b) was prepared similarly from 2-[6-(4-chlorophenyl)-4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-ylmethyl]benzoic acid (**2b)** (0.40 g, 10 mmol). Yield 90%; mp 320ºC (DMF). Found, %: C 63.32; H 2.90; N 7.43; S 8.38. $C_{20}H_{11}ClN_2O_2S$. Calculated, %: C 63.41; H 2.93; N 7.39; S 8.46.

2-(4-Fluorophenyl)-4H-thieno[2',3':5,6]pyrimido[1,2-*b*]isoquinoline-4,11(5H)-dione (5c) was prepared similarly from 2-[6-(4-fluorophenyl)-4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-ylmethyl]benzoic acid (**2c)** (0.38 g, 10 mmol). Yield 93%; mp 300ºC (DMF). Mass spectrum, *m/z*: 363 [M^++1]. Found, %: C 66.11; H 3.11; N 7.65; S 8.93. $C_{20}H_{11}FN_2O_2S$. Calculated, %: C 66.29; H 3.06; N 7.73; S 8.85.

5H-Isoquino[2,3-*a*]quinazoline-5,12(6H)-dione (6) was prepared similarly from 2-[(4-oxo-3,4-dihydro-2-quinazolinyl)methyl]benzoic acid (**3)** (0.28 g, 10 mmol) in acetic anhydride (10 ml, 106 mmol). Yield 90%; mp 305ºC (HOAc). Mass spectrum, *m/z*: 263 [M^++1]. Found, %: C 73.16; H 3.76; N 10.60. $C_{16}H_{10}N_2O_2$. Calculated, %: C 73.27; H 3.84; N 10.68.

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