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DOMINO REACTIONS IN THE SYNTHESIS OF BENZOTHIENO[2,3-*c*]PYRIDINES. NEW ONE-POT METHOD OF PREPARING 2-([1]BENZOTHIENO-[2,3-*c*]PYRIDIN-1-YL)BENZOIC ACIDS AND 8,13b-DIHYDRO[1]BENZOTHIENO[2',3':3,4]PYRIDO-[2,1-*a*]ISOINDOL-5(7*H*)-ONES

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A series of previously unknown 2-([1]benzothieno[2,3-c]pyridin-1-yl)benzoic acids and 8,13b-dihydro-[1]benzothieno[2',3':3,4]pyrido[2,1-a]isoindol-5(7H)-ones has been synthesized using domino reactions, taking place at the cyclization of 2-[3-oxo-4-(phenylsulfanyl)butyl]-1,3-isoindolinediones in polyphosphoric acid.

Keywords: 2-([1]benzothieno[2,3-*c*]pyridin-1-yl)benzoic acids, 8,13b-dihydro[1]benzothieno[2',3':3,4]-pyrido[2,1-*a*]isoindol-5(7*H*)-ones, 2-[3-oxo-4-(phenylsulfanyl)butyl]-1,3-isoindolinediones, cyclization, domino reaction, polyphosphoric acid .

Benzothieno[2,3-*c*]pyridines possess a broad spectrum of biological activity [1, 2]. At the present time, several methods exist for their synthesis. The most widespread methods for obtaining them are based on the aromatization of 1,2,3,4-tetrahydrobenzothieno[2,3-*c*]pyridines and 3,4-dihydrobenzothieno[2,3-*c*]pyridines, which in turn are synthesized by the Pictet-Spengler and Bischler-Napieralski reactions starting from 2-(benzo[*b*]thien-3-yl)ethylamines [2-6]. As a rule, these are multistage processes with low final yields of the desired products. In recent time, domino processes, which involve several sequential reactions and are carried out without isolating the intermediate products, have been largely developed.

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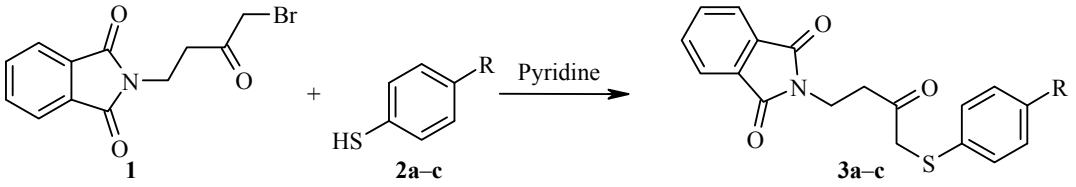
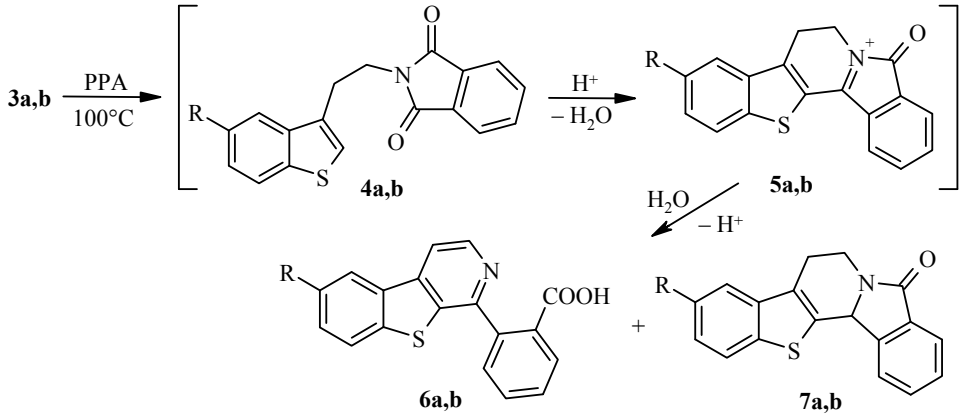
The aim of the present work was the study of one-pot processes leading to the preparation of benzothieno[2,3-*c*]pyridines.

As starting materials, we used 2-[3-oxo-4-(phenylsulfanyl)butyl]-1,3-isoindolinediones **3a-c**, obtained from thiophenols **2a-c** and 2-(4-bromo-3-oxobutyl)-1,3-isoindolinedione (**1**). Two reaction centers are present in compounds **3a-c**, enabling the construction of both the benzo[*b*]thiophene and the pyridine rings sequentially.



a R = H, **b** R = Me, **c** R = Cl

We found that on heating 2-[3-oxo-4-(phenylsulfanyl)butyl]-1,3-isoindolinediones **3a,b** in polyphosphoric acid (PPA) in a medium of chlorobenzene at 100°C for 3 h a series of sequential reactions occurs leading in the end to benzothieno[2,3-*c*]pyridine derivatives. Initially the closure of the benzothiophene ring and the intermediate formation of 2-[(2-benzo[*b*]thiophen-3-yl)ethyl]-1,3-isoindolinediones **4a,b** occur, which under the reaction conditions undergo cyclization to 5-oxo-7,8-dihydro-5*H*-[1]benzothieno[2',3':3,4]pyrido[2,1-*a*]isoindolin-6-ium derivatives **5a,b**.



a R = H, **b** R = Me

The pyridine ring formation process proceeds *via* Bischler-Napieralski type reaction. However, upon work up of the reaction mixture, in place of the expected compounds **5a,b**, a mixture of 2-([1]benzothieno[2,3-*c*]-pyridin-1-yl)benzoic acids **6a,b** and 8,13b-dihydro[1]benzothieno[2',3':3,4]pyrido[2,1-*a*]-isoindol-5(7*H*)-ones **7a,b** was obtained, which is possibly the result of disproportionation of cations **5a,b**.

Three products were isolated on cyclizing 2-[3-oxo-4-(4-chlorophenylsulfanyl)butyl]-1,3-isoindoline-dione (**3c**), namely 2-(6-chloro[1]benzothieno[2,3-*c*]pyridin-1-yl)benzoic acid (**6c**) (42%), 2-[(2-benzo[*b*]thiophen-3-yl)ethyl]-1,3-isoindolinedione (**4c**) (10%) and an unknown product with molecular mass 483, the composition of which is to be determined. The structure of compound **4c** was confirmed by an counter synthesis from 2-(5-chloro[1]benzothiophen-3-yl)ethylamine (**8**) and phthalic anhydride. 10-Chloro-8,13b-dihydro[1]benzo-thieno-[2',3':3,4]pyrido[2,1-*a*]isoindol-5(7*H*)-one (**7c**) was not detected in the reaction products.

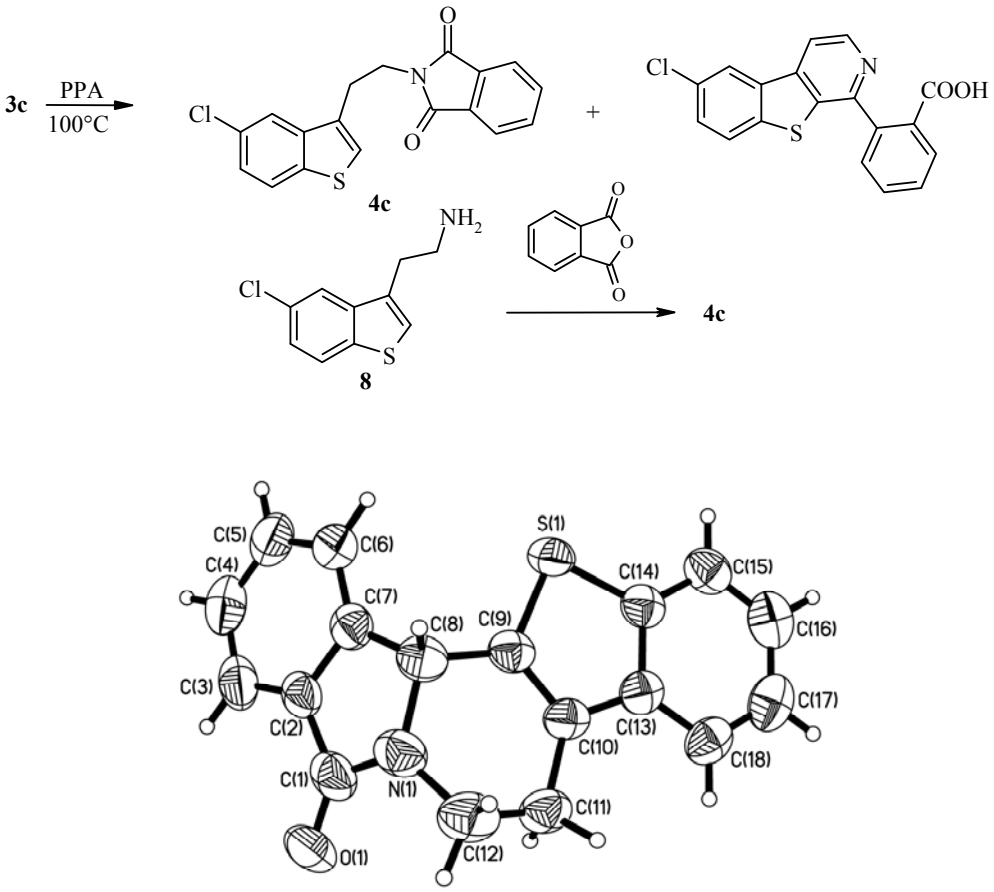


Fig. 1. Molecular structure of compound **7a** with representation of atoms by ellipsoids of thermal vibrations with 50% probability.

8,13b-Dihydro[1]benzothieno[2',3':3,4]pyrido[2,1-*a*]isoindol-5(7*H*)-one (**7a**) was identical in physicochemical properties to the compound obtained previously in [4]. The structure of compound **7a** was proved by X-ray structural analysis (Fig. 1). The tetrahydropyridine ring has a "distorted half-chair" conformation (parameters of folding, S = 0.75, Θ = 35.33, and Ψ = 26.03 [7]). The C(12) and N(1) atoms deviate from the plane of the remaining ring atoms by 0.39 and -0.26 Å respectively. The unflattening of the ring is also aided by the steric repulsion between the bicyclic fragments (shortened intramolecular contact S(1)···C(6) 3.44 Å, sum of van der Waals radii 3.55 Å [8]).

In the ^{1}H NMR spectra of 2-([1]benzothieno[2,3-*c*]pyridin-1-yl)benzoic acids **6a-c**, the signals for the methylene group, characteristic of the starting compounds **3a-c**, were missing, and only signals for the aromatic protons were observed. Signals of the pyridine ring protons were displayed as doublets in the 8.1 and 8.6 ppm region with coupling constant J = 5.2 Hz. The ^{1}H NMR spectra of 8,13-dihydro[1]benzothieno[2',3':3,4]pyrido-[2,1-*a*]isoindol-5(7*H*)-ones **7a,b** and 1-aryl-1,2,3,4-tetrahydrobenzothieno[2,3-*c*]pyridines were close in the aliphatic part [6]. Each proton of the CH_2CH_2N fragment was observed as a separately standing multiplet.

In summary, a new one-pot method has been developed for preparing substituted 2-([1]benzothieno-[2,3-*c*]pyridin-1-yl)benzoic acids and 8,13b-dihydro[1]benzothieno[2',3':3,4]pyrido[2,1-*a*]isoindol-5(7*H*)-ones, based on domino reactions proceeding on cyclization of 2-[3-oxo-4-(phenylsulfanyl)butyl]-1,3-isoindolinedione in polyphosphoric acid. 8,13b-Dihydro[1]benzothieno[2',3':3,4]pyrido[2,1-*a*]isoindol-5(7*H*)-ones are heteroanalogs of alkaloid nuevamine [9], consequently, the procedure developed by us may be used in the synthesis of substances possessing biological activity.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 and 100 MHz respectively) in DMSO-d_6, internal standard was TMS. The mass spectra were recorded on a MX1321 spectrometer using direct insertion of sample, ionization was by electron impact, ionizing voltage 70 eV, temperature of ionization chamber 220°C. Ions the intensity of which exceeded 5% are given. Data of elemental analysis were obtained on a Vario MICROcube CHN analyzer. Analysis of sulfur content was performed by titration of sulfate anion after combustion in oxygen. Melting points were determined on a Boetius hot stage apparatus.

2-[3-Oxo-4-(phenylsulfanyl)butyl]-1,3-isoindolinediones 3a-c (General Method). Pyridine (1.5 ml) was added to a solution of bromo ketone **1** (10 mmol) and thiophenol **2a-c** (11 mmol) in 2-PrOH (30 ml). The mixture was refluxed for 1 h, cooled, the precipitated crystals were filtered off, washed with water, and with cold 2-PrOH. The product was crystallized from 2-PrOH.

2-[3-Oxo-4-(phenylsulfanyl)butyl]-1,3-isoindolinedione (3a). Yield 3.19 g (98%); mp 94-95°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.02 (2H, t, *J* = 7.2, $NCH_2C\underline{H}_2$); 3.82 (2H, t, *J* = 7.2, $NC\underline{H}_2CH_2$); 3.86 (2H, s, $COCH_2S$); 7.14 (1H, t, *J* = 8.0, H-4'); 7.22-7.27 (4H, m, H-2',3',5',6'); 7.77-7.83 (4H, m, H-4,5,6,7). ^{13}C NMR spectrum, δ, ppm: 202.5; 202.5; 167.5; 134.2; 132.2; 129.1; 129.0; 126.4; 123.2; 43.3; 38.5; 33.1. Mass spectrum, *m/z* (I_{rel}, %): 326 (5), 325 $[M]^+$ (27), 202 (35), 161 (14), 160 (100), 130 (5), 123 (22), 109 (6), 104 (6), 77 (9), 76 (9), 55 (14), 51 (6), 45 (22), 41 (5). Found, %: C 66.02; H 4.83; N 4.14; S 10.00. $C_{18}H_{15}NO_3S$. Calculated, %: C 66.44; H 4.65; N 4.30; S 9.85.

2-{[4-(4-Methylphenyl)sulfanyl]-3-oxobutyl}-1,3-isoindolinedione (3b). Yield 3.26 g (96%); mp 97-98°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 2.99 (2H, t, *J* = 7.2, $NCH_2C\underline{H}_2$); 3.75 (3H, s, $COCH_2S$); 3.79 (2H, t, *J* = 7.2, $NC\underline{H}_2CH_2$); 7.02 (2H, d, *J* = 8.0, H-3',5'); 7.15 (2H, d, *J* = 8.0, H-2',6'); 7.74-7.80 (4H, m, H-4,5,6,7). ^{13}C NMR spectrum, δ, ppm: 200.2; 166.8; 135.6; 133.5; 131.5; 130.7; 129.2; 129.1; 122.5; 43.2; 37.7; 32.4; 20.4. Mass spectrum, *m/z* (I_{rel}, %): 340 (7), 339 $[M]^+$ (34), 203 (5), 202 (37), 161 (10), 160 (100), 138 (7), 137 (38), 130 (6), 123 (6), 105 (5), 91 (8), 77 (11), 76 (6), 55 (9), 45 (20). Found, %: C 67.43; H 5.19; N 4.18; S 9.28. $C_{19}H_{17}NO_3S$. Calculated, %: C 67.24; H 5.05; N 4.13; S 9.45.

2-{[4-(4-Chlorophenyl)-2-oxo-sulfanyl]butyl}-1,3-isoindolinedione (3c). Yield 3.24 g (90%); mp 96-97°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.00 (2H, t, *J* = 7.2, $NCH_2C\underline{H}_2$); 3.81 (2H, t, *J* = 7.2, $NC\underline{H}_2CH2$); 3.85 (2H, s, $COCH_2S$); 7.18-7.24 (4H, m, H-2',3',5',6'); 7.74-7.80 (4H, m, H-4,5,6,7). ^{13}C NMR spectrum, δ, ppm: 201.4; 166.8; 133.4; 131.5; 131.2; 129.7; 128.4; 122.5; 42.6; 37.8; 32.3. Mass spectrum, *m/z* (I_{rel}, %): 361 (8), 360 (6), 359 $[M]^+$ (20), 203 (7), 161 (10), 160 (100), 157 (9), 130 (7), 104 (5), 77 (9), 76 (9), 55 (11), 45 (15). Found, %: C 60.23; H 3.76; Cl 9.67; N 3.74; S 9.13. $C_{18}H_{14}ClNO_3S$. Calculated, %: C 60.08; H 3.92; Cl 9.85; N 4.89; S 8.91.

2-([1]Benzothieno[2,3-*c*]pyridin-1-yl)benzoic Acids 6a-c and 8,13b-Dihydro[1]benzothieno-[2',3':3,4]pyrido[2,1-*a*]isoindol-5(7*H*)-ones 7a,b (General Method). A solution of the corresponding isoindolinedione **3a-c** (6.15 mmol) in chlorobenzene (10 ml) was added to PPA (20 g), and the mixture was stirred for 3 h at 100°C. The still warm mixture was then poured into water (150 ml), stirred for 2 h, and left overnight. The solid acid **6a-c** was filtered off. The filtrate was extracted with CH_2Cl_2 (100 ml), washed with water (100 ml), and with 5% NaOH solution (20 ml). On acidification of the alkaline solution an additional amount of acid **6a-c** was obtained. The organic layer was evaporated in vacuum, and compounds **7a,b** were obtained. Compounds **6a-c** and **7a,b** were crystallized from MeCN.

2-([1]Benzothieno[2,3-*c*]pyridin-1-yl)benzoic Acid (6a). Yield 0.9 g (48%); mp 273-274°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.51-7.68 (5H, m, H-4,5,6,6',7'); 7.92 (1H, d, *J* = 8.0, H-3); 8.0 (1H, d, *J* = 8.0, H-8'); 8.13 (1H, d, *J* = 5.2, H-4'); 8.38 (1H, d, H-5'); 8.62 (1H, d, *J* = 5.2, H-3'); 12.36 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 167.5; 154.1; 143.3; 141.3; 140.2; 139.9; 134.1; 133.8; 131.7; 130.6; 129.9; 129.1; 128.4; 128.2; 127.4; 123.0; 122.5; 114.2. Mass spectrum, *m/z* (I_{rel}, %): 305 $[M]^+$ (10), 288 (5), 263 (5), 262 (21), 261 (100), 260 (43), 259 (15), 131 (7), 130 (24), 116 (5). Found, %: C 70.64; H 3.73; N 4.65; S 10.34. $C_{18}H_{11}NO_2S$. Calculated, %: C 70.80; H 3.63; N 4.59; S 10.50.

2-(6-Methyl[1]benzothieno[2,3-*c*]pyridin-1-yl)benzoic Acid (6b). Yield 0.9 g (46%); mp 271-272°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.53 (3H, s, 6'-CH_3); 7.39 (1H, d, *J* = 8.0, H-7'); 7.58 (1H, t, *J* = 8.0, H-4); 7.60-7.67 (2H, m, H-5,6); 7.77 (1H, d, *J* = 8.0, H-3); 8.00 (1H, d, *J* = 8.0, H-8'); 8.07 (1H, d, *J* = 5.2, H-4'); 8.16 (1H, s, H-5'); 8.60 (1H, d, *J* = 5.2, H-3'); 12.4 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 168.8; 155.3; 144.4; 142.4; 141.1; 138.5; 135.7; 135.2; 132.9; 131.8; 131.2; 131.1; 130.3; 129.4; 124.2; 123.4; 115.3; 22.1. Mass spectrum, *m/z* (I_{rel}, %): 319 $[M]^+$ (9), 302 (6), 277 (7), 276 (19), 275 (100), 274 (26), 273 (11), 272 (6), 260 (6), 259 (5), 138 (10), 137 (13). Found, %: C 71.66; H 4.19; N 4.26; S 10.21. $C_{19}H_{13}NO_2S$. Calculated, %: C 71.45; H 4.10; N 4.39; S 10.04.

2-(6-Chloro[1]benzothieno[2,3-*c*]pyridin-1-yl)benzoic Acid (6c). Yield 0.88 g (42%); mp 266-267°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.54-7.68 (4H, m, H-4,5,6,7'); 7.93 (1H, d, *J* = 8.0, H-3); 8.01 (1H, d, *J* = 8.0, H-8'); 8.20 (1H, d, *J* = 5.2, H-4'); 8.49 (1H, d, *J* = 2.0, H-5'); 8.65 (1H, d, *J* = 5.3, H-3'); 12.36 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 168.1; 155.1; 144.2; 141.0; 140.4; 139.1; 136.1; 135.6; 132.3; 131.4; 130.9; 130.6; 129.8; 129.2; 129.0; 124.6; 123.6; 115.3. Mass spectrum, *m/z* (I_{rel}, %): 339 $[M]^+$ (6), 298 (7), 297 (36), 296 (25), 295 (100), 294 (16), 261 (5), 260 (20), 259 (17), 148 (5), 147 (7), 130 (15), 129 (10), 116 (5), 44 (7). Found, %: C 63.39; H 2.73; Cl 10.28; N 4.19; S 9.61. $C_{18}H_{10}ClNO_2S$. Calculated, %: C 63.63; H 2.97; Cl 10.43; N 4.12; S 9.44.

On evaporating the organic extract remaining after the isolation of acid **6c**, a mixture of products was obtained from which **2-[2-(5-chlorobenzo[*b*]thiophen-3-yl)ethyl]-1,3-isoindolinedione (4c)** was isolated by fractional crystallization from MeCN. Yield 0.21 g (10%); mp 189-191°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.18 (2H, t, *J* = 7.6, $C\underline{H_2}CH_2N$); 3.95 (2H, t, *J* = 7.6, $CH_2C\underline{H_2}N$); 7.30 (1H, dd, *J* = 8.0, *J* = 1.6, H-6'); 7.47 (1H, s, H-2'); 7.78-7.85 (5H, m, H-4,5,6,7,7'); 7.88 (1H, d, *J* = 1.6, H-4'). Mass spectrum, *m/z* (I_{rel}, %): 343 (9), 342 (11), 341 $[M]^+$ (25), 196 (37), 195 (6), 194 (100), 183 (7), 181 (20), 161 (6), 160 (62), 159 (10), 133 (7), 115 (8), 105 (8), 104 (10), 102 (8), 77 (18), 76 (10), 51 (5), 45 (6). Found, %: C 63.44; H 3.39; Cl 10.52; N 4.26; S 9.13. $C_{18}H_{12}ClNO_2S$. Calculated, %: C 63.25; H 3.54; Cl 10.37; N 4.10; S 9.38.

Compound **4c** was also obtained by the following procedure. A solution of 2-(5-chloro[1]benzothiophen-3-yl)ethylamine (**8**) (2.12 g, 10 mmol) and phthalic anhydride (1.63 g, 11 mmol) in toluene (150 ml) was refluxed for 12 h in a flask fitted with a Dean-Stark head. The solution was evaporated and the residue crystallized from MeCN. Yield 2.5 g (73%). The product was identical with product **4c** obtained by the cyclization of compound **3c**.

8,13b-Dihydro[1]benzothieno[2',3':3,4]pyrido[2,1-*a*]isoindol-5(7*H*)-one (7a). Yield 0.48 g (27%); mp 194-195°C (mp 193-195°C [4]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.74-2.83 (1H, m,) and 2.97-3.04 (1H, m, 8-CH_2); 3.42-3.53 (1H, m,) and 4.63-4.68 (1H, m, 7-CH_2); 6.03 (1H, s, H-13b); 7.35 (2H, m, H-10,11); 7.53 (1H, t, *J* = 8.0, H-3); 7.65 (1H, d, *J* = 8.0, H-9); 7.69 (1H, t, *J* = 8.0, H-2); 7.74 (1H, d, *J* = 8.0, H-12); 7.86 (1H, d, *J* = 8.0, H-1); 7.89 (1H, d, *J* = 8.0, H-4). ^{13}C NMR spectrum, δ, ppm: 167.0; 144.3; 138.5; 138.4; 134.1; 132.3; 132.2; 129.1; 129.0; 125.2; 124.9; 123.9; 123.7; 122.9; 121.9; 58.2; 36.8; 24.4. Mass spectrum, *m/z* (I_{rel}, %): 293 (6), 292 (22), 291 $[M]^+$ (98), 290 (100), 289 (5), 288 (9), 263 (5), 262 (11), 235 (5), 234 (8), 182 (19), 145 (9), 131 (5), 130 (13), 117 (18), 104 (5), 45 (10). Found, %: C 74.38; H 4.59; N 4.74; S 11.00. $C_{18}H_{13}NOS$. Calculated, %: C 74.20; H 4.50; N 4.81; S 11.00.

10-Methyl-8,13b-dihydro[1]benzothieno[2',3':3,4]pyrido[2,1-*a*]isoindol-5(7*H*)-one (7b). Yield 0.49 g (26%); mp 160-161°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, s, 6'-CH_3); 2.75-2.84 (1H, m) and 2.93-3.00 (1H, m, 8-CH_2); 3.40-3.48 (1H, m) and 4.67-4.73 (1H, m, 7-CH_2); 5.92 (1H, s, H-13b); 7.12 (1H, d, *J* = 8.0, H-11); 7.40 (1H, s, H-9); 7.50 (1H, t, *J* = 8.0, H-2); 7.64 (1H, t, *J* = 8.0, H-3); 7.68 (1H, d, *J* = 8.0, H-12); 7.73 (1H, d, *J* = 8.0, H-1); 7.81 (1H, d, *J* = 8.0, H-4). ^{13}C NMR spectrum, δ, ppm: 168.5; 145.9; 140.2; 137.1; 135.9; 135.7; 134.1; 133.6; 130.8; 130.4; 128.4; 125.6; 125.2; 124.3; 123.5; 59.8; 38.4; 25.9; 23.0. Mass spectrum, *m/z* (I_{rel}, %): 307 (9), 306 (19), 305 $[M]^+$ (100), 304 (90), 303 (5), 302 (10), 290 (13), 277 (5), 276 (12), 234 (6), 182 (20), 153 (6), 152 (7), 137 (8), 131 (5), 130 (10), 124 (11), 123 (6), 117 (6). Found, %: C 74.86; H 4.88; N 4.67; S 10.41. $C_{19}H_{15}NOS$. Calculated, %: C 74.73; H 4.95; N 4.59; S 10.50.

X-Ray Structural Investigation of Compound 7a. Crystals were monoclinic, $C_{18}H_{13}NOS$, at 293 K: *a* = 13.735(1), *b* = 8.382(1), *c* = 12,167(1) Å, β = 98.28(1)°, *V* = 1386.2(2) Å^3, M_r = 582.71, *Z* = 4, space group

$P21/c$, d_{calc} = 1.396 g/cm^3, μ(MoKα) = 0.231 mm^{-1}, $F(000)$ = 608. The parameters of the unit cell and the intensities of 23531 reflections (3991 independent, R_{int} = 0.063) were determined on an Xcalibur 3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω scanning, $2\theta_{max} = 60^o$).

The structure was solved by the direct method and refined by the least squares method on F^2 in a full-matrix anisotropic approximation for the non-hydrogen atoms using the SHELXTL software set [10]. The positions of the hydrogen atoms were made apparent from an electron density difference synthesis and were refined isotropically. Final values of the probability factors were wR_2 = 0.079 on 3970 reflections (R_1 = 0.037 on 1974 reflections with $F > 4\sigma(F)$, S = 0.776). The atomic coordinates, geometric parameters and crystallographic data of compound **7a** have been deposited in the Cambridge Crystallographic Data Center (deposition CCDC 863589).

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