Synthesis of Novel Pyrido[3',2':5,6]thiopyrano[3,2-*b*]indol-5(6*H*)-ones and 6*H*-Pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinolines, two New Heterocyclic Ring Systems

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The synthesis of new pyrido[3',2':5,6]thiopyrano[3,2-*b*]indol-5(6*H*)-ones was accomplished by the Fischer-indole cyclization of some 2,3-dihydro-3-phenylhydrazonothiopyrano[2,3-*b*]pyridin-4(4*H*)-ones, obtained from the 2,3-dihydro-3-hydroxymethylenethiopyrano[2,3-*b*]pyridin-4(4*H*)-one, by the Japp-Klingemann reaction.

6*H*-Pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinolines were obtained by reaction of 2,3-dihydrothiopyrano-[2,3-*b*]pyridin-4(4*H*)-ones with *o*-aminobenzaldehyde or 5-substituted isatins. The preparation of some derivatives, functionalized with an alkylamino-substituted side chain, is also described.

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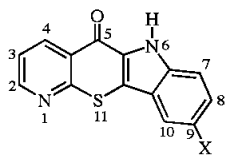
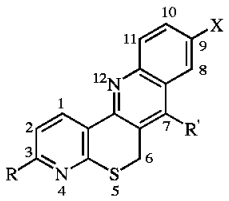
In the ongoing search for new effective antitumor agents, a wide variety of new derivatives with completely different chemical structures have been prepared and tested. Among them, polycondensed nitrogen heterocycles having a planar structure are effective moieties for drugs endowed with antineoplastic activity. Their mechanism of action is correlated with the capacity to intercalate with the macromolecule of DNA [1-4], and to interfere with the activity of Topoisomerases I and II, two enzymes capable of modifying the topological state of DNA [5-9].

On the basis of these considerations, a large part of our studies was directed towards the design and synthesis of planar heteropolycyclic derivatives, structurally related to biologically active drugs, as new potential antitumor agents. In the last few years we have reported the synthesis of several new compounds, bearing benzimidazole or purine moieties, which exhibited interesting antiproliferative activity, because of their ability to form a complex with DNA and to inhibit the Topoisomerase II [10-11].

In the present paper we wish to report the synthesis of derivatives of two new tetracyclic heteroaromatic systems of general formula **A** and **B**.

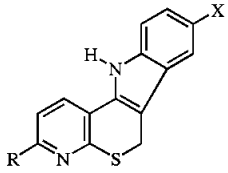


A

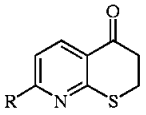


B

They were prepared starting from the 2,3-dihydrothiopyrano[2,3-*b*]pyridin-4(4*H*)-ones **2a-b** [12,13], by known reactions employed in the literature for the obtainment of analogous tetracyclic systems [14-18]. Compounds **2a-b** revealed to be versatile intermediates as, recently, they were used for the synthesis of new pyridothiopyrano[4,3-*b*]indole system **1** [12], which is structurally related to the novel heterocycle **A**.



1



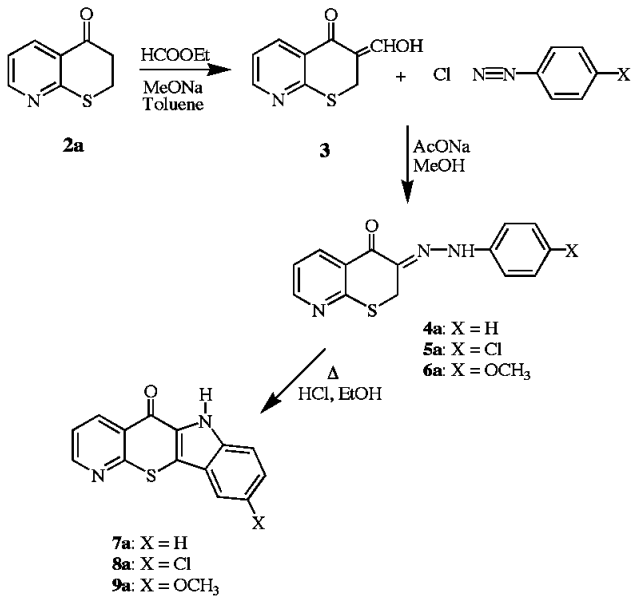
2a: R = H
2b: R = CH_3

Notwithstanding the undoubted importance of the planar aromatic ring systems, the addition of groups or side chains which project from one or both the grooves of the DNA double helix and which interact like external binder moiety, appears to be crucial for drug activity. Indeed, a large number of anti-tumor compounds have been modified by linking to a DNA intercalator a suitable basic side chain, thus modulating the biological properties and increasing solubility under physiological conditions [19-21]. More recently, in the literature, it is also reported that flexible basic side chains, linked to the chromophore moiety by a carbonyl spacer, play an important role in enhancing DNA-binding properties [22,23]. Taking it into account, we accomplished the synthesis of two derivatives of **B**, in which a carboxamidodimethylaminoalkyl side chain has been inserted in the 7 position of the heterotetracyclic system.

Results and Discussion.

Scheme 1 shows the synthetic procedure used to afford the title pyrido[3',2':5,6]thiopyrano[3,2-*b*]indol-5(6*H*)-ones of general formula **A**. The preparation of the intermediate 2,3-dihydro-3-hydroxymethylenethiopyrano[2,3-*b*]-pyridin-4(4*H*)-one **3** was accomplished from 2,3-dihydrothiopyrano[2,3-*b*]pyridin-4(4*H*)-one **2a**, by reaction

Scheme 1



with ethyl formate in anhydrous toluene in the presence of sodium methoxide. Compound **3**, containing a methine active group, was able to give the desired 3-phenylhydrazono derivatives **4a**, **5a** and **6a** in particularly good yields, by coupling with the appropriately substituted diazonium salt, by the Japp-Klingemann reaction [14-16]. Compounds **4a**, **5a** and **6a** were directly converted to the desired indole derivatives **7a**, **8a** and **9a** using Fischer cyclization, by reflux in hydrogen chloride ethanolic solution, with yields ranging from 70%-90%. The structures of all new compounds agreed with analytical, ir, ^{1}H-nmr and mass spectral data (Tables I and II). An interesting feature of the ^{1}H-nmr spectra of the derivatives **7a**, **8a** and **9a** was the low field signal (δ 12) of the indole NH group.

2,3-Dihydrothiopyrano[2,3-*b*]pyridin-4(4*H*)-one **2a** [12] and the corresponding 7-methyl derivative **2b** [13] represented the starting material for the preparation of the heterocyclic system **B**. Compounds **2a-b** and *o*-aminobenzaldehyde were allowed to react in ethanol solution, at reflux in the presence of potassium hydroxide, to yield (>60%) the desired 6*H*-pyrido[3',2':5,6]-thiopyrano[4,3-*b*]quinolines **10a-b** (Scheme 2). The proposed structures of the products were consistent with analytical, ir, ^{1}H-nmr and mass spectral data. Evidence for the structure of **10a-b** derived from an examination of their ^{1}H-nmr spectra, in which the presence was observed of a singlet at δ 4 assigned to the methylene group in the 6 position of the new ring system, instead of the two triplets, ranging from δ=2.81-3.01 and δ=3.24-3.43, due to 3-CH_2 and 2-CH_2, respectively, of compounds **2a-b**.

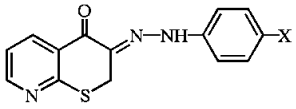
Relatively simple reaction conditions were used in the reaction between 2,3-dihydrothiopyrano[2,3-*b*]pyridin-4(4*H*)-ones **2a-b** and 5-substituted isatins, to obtain the desired 6*H*-pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinoline-7-carboxylic acids **11a-b**, **12a-b** and **13a-b** (Scheme 2). Structures of compounds **11a-b**, **12a-b** and **13a-b** were confirmed by physical, analytical and spectral data (Table III).

The synthesis of heterocyclic derivative **10a** was carried out also using the carboxylic acid **11a** as starting material. In fact, compound **11a** was subjected to heating with an excess of quinoline, at reflux temperature, in the presence of copper chromite, to give **10a**. In the ir spectrum of the thus obtained compound **10a**, is evident the absence of the absorption band at ν = 1700 cm^{-1}, typical of the carboxylic group.

As it was in our intention, carboxylic acid **11a** was then converted to the desired *N*-dialkylaminoalkyl amides **14** and **15**, as shown in Scheme 2. Treatment of **11a** with an

Table I

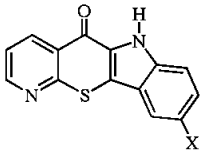
Physical and Spectral Data of Compounds **4a**, **5a** and **6a**



Compound	X	Yield (%)	M.p.°C (Recrystallization solvent)	^{1}H nmr (δ ppm)	Ms m/z	Molecular Formula	Analysis (%) Calcd./Found C	H	N
4a	H	85	176-180 (Ethanol)	4.25-4.44 (s, 2H, 2-CH_2), 6.83-6.88 (d, 2H, Ar-H), 7.45-7.53 (m, 3H, ArH), 7.64-7.74 (m, 2H, Ar-H), 8.90-8.95 (m, 1H, ArH), 12.68 (s, 1H, NH-exch.)	269	$C_{14}H_{11}N_3OS$	62.44 62.53	4.12 4.43	15.60 15.40
5a	Cl	65	126-130 (Ethanol)	4.24-4.38 (s, 2H, 2-CH_2), 7.29-7.59 (m, 5H, Ar-H), 8.27-8.31 (d, 1H, ArH), 8.58 (m, 1H, ArH), 13.41 (s, 1H, NH-exch.)	303	$C_{14}H_{10}ClN_3OS$	55.35 55.64	3.32 3.37	13.83 13.61
6a	OCH_3	81	132-135 (Ethanol)	3.75 (s, 3H, -OCH_3), 4.21-4.34 (s, 2H, 2-CH_2), 6.94-6.98 (d, 2H, Ar-H), 7.25-7.42 (m, 3H, ArH), 8.25-8.29 (d, 1H, Ar-H), 8.54-8.59 (m, 1H, ArH), 13.79 (s, 1H, NH-exch.)	299	$C_{15}H_{13}N_3O_2S$	60.19 59.88	4.38 4.06	14.04 13.94

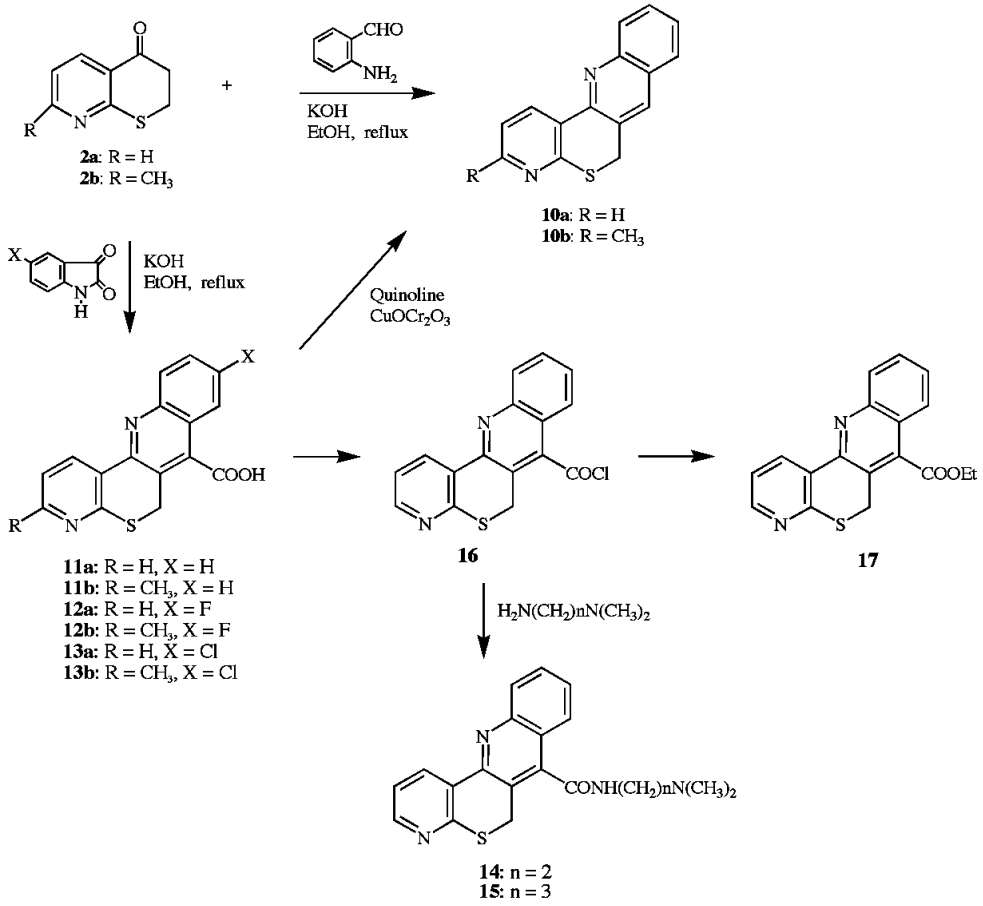
Table II

Physical and Spectral Data of Compounds **7a**, **8a** and **9a**



Compound	X	Yield (%)	M.p.°C (Recrystallization solvent)	^{1}H nmr (δ ppm)	Ms m/z	Molecular Formula	Analysis (%) Calcd./Found C	H	N
7a	H	62	>300 (Ethanol)	7.25 (t, 1H, ArH), 7.55 (t, 1H, ArH), 7.62-7.74 (m, 3H, Ar-H), 8.88-8.95 (m, 2H, ArH), 12.67 (s, 1H, NH-exch.)	252	$C_{14}H_8N_2OS$	66.65 66.53	3.19 3.43	11.10 10.90
8a	Cl	67	>300 (Ethanol)	7.32-8.96 (m, 6H, ArH), 12.86 (s, 1H, NH-exch.)	286	$C_{14}H_7ClN_2OS$	58.64 58.37	2.46 2.37	9.77 9.61
9a	OCH_3	46	247-250 (Ethanol)	3.78 (s, 3H, -OCH_3), 7.01-8.93 (m, 6H, ArH), 12.95 (s, 1H, NH-exch.)	282	$C_{15}H_{10}N_2O_2S$	63.82 63.88	3.57 3.56	9.92 9.74

Scheme 2



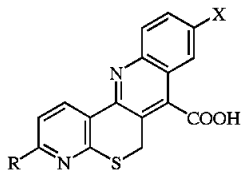
excess of thionyl chloride afforded the intermediate acyl chloride **16**, which was allowed to react with an excess of the appropriate dimethylaminoalkylamine, in anhydrous toluene, to give the target compounds **14** and **15**. The new acyl chloride **16** was characterized as ethyl ester **17**.

EXPERIMENTAL

Melting points were determined using a Reichert Köfler hot-stage apparatus and are uncorrected. Infrared spectra were obtained on a PYE/UNICAM Model PU 9561 spectrophotometer

Table III

Physical and Spectral Data of Compounds **10a-b**, **11a-b** and **12a-b**



Compound	R	X	Yield (%)	M.p.°C (Recrystallization solvent)	^{1}H nmr (δ ppm)	Ms m/z	Molecular Formula	Analysis (%) Calcd./Found C	H	N
10a	H	H	45	248-250 (Ethanol)	4.36 (s, 2H, 6-CH_2); 7.30-8.13 (m, 1H, ArH); 8.44-8.52 (m, 5H, ArH); 8.75 (d, 1H, ArH)	294	$C_{16}H_{10}N_2O_2S$	65.29 65.58	3.42 3.15	9.52 9.33
10b	CH_3	H	30	280-283 (Ethanol)	2.49 (s, 3H, 3-CH_3); 4.34 (s, 2H, 6-CH_2); 7.24 (d, 1H, ArH); 7.53-8.11 (m, 4H, ArH); 8.63 (d, 1H, ArH)	308	$C_{17}H_{12}N_2O_2S$	66.22 66.48	3.92 3.67	9.08 8.93
11a	H	F	51	248-250 (Ethanol)	4.40 (s, 2H, 6-CH_2); 7.30-8.78 (m, 6H, ArH)	312	$C_{16}H_9FN_2O_2S$	61.53 61.27	2.90 3.06	8.97 9.03
11b	CH_3	F	31	278-281 (Ethanol)	2.52 (s, 3H, 3-CH_3); 4.39 (s, 2H, 6-CH_2); 7.25 (d, 1H, ArH); 7.53-7.80 (m, 2H, ArH); 8.06-8.24 (m, 1H, ArH); 8.62 (d, 1H, ArH)	326	$C_{17}H_{11}FN_2O_2S$	62.57 62.52	3.39 3.55	8.58 8.31
12a	H	Br	33	261-264 (Ethanol)	4.40 (s, 2H, 6-CH_2); 7.31-7.97 (m, 1H, ArH); 8.00-8.11 (m, 3H, ArH); 8.45-8.79 (m, 2H, ArH)	373	$C_{16}H_9BrN_2O_2S$	51.49 51.25	2.43 2.71	7.50 7.37
12b	CH_3	Br	28	265-268 (Ethanol)	2.50 (s, 3H, 3-CH_3); 4.38 (s, 2H, 6-CH_2); 7.25 (d, 1H, ArH); 7.85-8.10 (m, 3H, ArH); 8.62 (d, 1H, ArH)	387	$C_{17}H_{11}BrN_2O_2S$	52.73 52.50	2.86 2.71	7.23 6.98

as Nujol mulls. Nuclear magnetic resonance spectra were recorded on a Varian Gemini 200 spectrometer, in dimethyl-d_6 sulfoxide solution. Mass spectra were obtained on a Hewlett-Packard 5988 A spectrometer using a direct injection probe and an electron beam energy of 70 eV. Magnesium sulfate was always used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator). Analytical tlc were carried out on Merck 0.2 mm precoated silica gel aluminium sheets (60 F-254). Elemental analyses were performed by our Analytical Laboratory.

2,3-Dihydro-3-hydroxymethylenethiopyrano[2,3-*b*]pyridin-4(4*H*)-one (**3**).

A solution of ethyl formate (0.65 ml, 8 mmoles) in anhydrous toluene (3 ml) was added dropwise to a suspension of freshly prepared sodium methoxide (0.184 g, 8 mmoles of sodium in 2 ml of absolute methanol) in the same solvent (3 ml). The ice-cooled mixture was treated dropwise with stirring, under nitrogen atmosphere, with a solution of 2,3-dihydrothiopyrano[2,3-*b*]pyridin-4(4*H*)-one **2a** (0.660 g, 4 mmoles) in anhydrous toluene (8 ml). Stirring was continued at room temperature for 24 hours. The toluene layer was separated off and the sodium salt of **3** was treated with water and acidified at 0 °C with hydrochloric acid to give **3** (0.547 g, 71% yield). An analytical sample was obtained by recrystallization from petroleum ether 40-60 °C, m.p. 188-190 °C; ^{1}H-nmr (deuteriochloroform) : δ 3.93 (s, 2H, 2-CH_2), 7.26-7.32 (m, 2H, 3-C*H*OH, Ar-H), 8.19-8.52 (m, 2H, ArH); ms: m/z = 193 (M^+).

Anal. Calcd. for $C_9H_7NO_2S$: C, 55.95; H, 3.65; N, 7.25. Found: C, 56.25; H, 3.69; N, 7.64.

2,3-Dihydro-3-phenylhydrazonothiopyrano[2,3-*b*]pyridin-4(4*H*)-ones **4a, 5a** and **6a**.

General Procedure.

A solution of 1.5 mmoles of **3** in 8 ml of methanol was added to an aqueous saturated solution of 4.6 mmoles of sodium acetate. After cooling at 0 °C, a solution of the suitable diazonium salt, obtained from the appropriately *p*-substituted aniline in diluted hydrochloric acid and sodium nitrite, was added dropwise in slight excess. An orange precipitate is immediately formed. The mixture was stirred for half an hour at 0 °C and for 3 hours at room temperature. The solid was collected and washed with water to give crude compounds **4a**, **5a** and **6a**, Table I.

Pyrido[3',2':5,6]thiopyrano[3,2-*b*]indol-5(6*H*)-ones **7a, 8a** and **9a**.

General Procedure.

A solution of 0.1 mmole of phenylhydrazono derivatives **4a**, **5a** or **6a** in 2 ml of hydrogen chloride ethanolic solution was refluxed for 20 minutes. After cooling, the orange precipitate was collected and washed with ethanol to give crude indoles **7a**, **8a** and **9a**, which were purified by recrystallization, Table II.

3-Unsubstituted- **10a** and 3-Methyl-6*H*-pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinoline **10b**.

General Procedure.

A suspension of 2,3-dihydrothiopyrano[2,3-*b*]pyridin-4(4*H*)-one **2a** or 7-methyl derivative **2b** (2 mmoles) and 0.242 g (2 mmoles) of *o*-aminobenzaldehyde in 12 ml of ethanol, in the presence of 0.10 g of potassium hydroxide, was refluxed until

disappearance of the starting reagents (20-24 hours, tlc analysis: petroleum ether 60-80 °C/ethyl acetate 7:3 as the eluting system). After cooling, the crude precipitate was collected to give compounds **10a-b**, which were purified by recrystallization from ethanol.

Compound **10a** was obtained in 69% yield, m.p.190-192 °C; ^{1}H-nmr: δ 4.40 (s, 2H, 6-CH_2), 7.28-8.80 (m, 8H, Ar-H); ms: m/z = 250 (M^+).

Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found: C, 72.28; H, 4.34; N, 11.33.

Compound **10b** was obtained in 61% yield, m.p.154-157 °C; ^{1}H-nmr: δ 2.48 (s, 3H, 3-CH_3), 4.37 (s, 2H, 6-CH_2), 7.18 (d, 1H, Ar-H, J=21 Hz), 7.45-8.24 (m, 5H, ArH), 8.61 (d, 1H, ArH, J=21 Hz); ms: m/z = 264 (M^+).

Anal. Calcd. for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.57; N, 10.59. Found: C, 71.28; H, 4.16; N, 10.24.

6*H*-Pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinoline **10a** from **11a**.

A mixture of 6*H*-Pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinoline-7-carboxylic acid **11a** (0.200 g, 0.7 mmole), copper chromite (0,060 g) in 5 ml of freshly distilled quinoline, was refluxed for 2 hours. After cooling, the precipitate obtained was collected by filtration affording the crude derivative **10a** (0.122 g, 68% yield), which was washed with water and purified by recrystallization from ethanol, m.p.191-193 °C.

3-Unsubstituted- **11a**, 3-Methyl-6*H*-pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinoline-7-carboxylic Acid **11b** and Corresponding 9-Fluoro- **12a-b** and 9-Chloro- **13a-b** Derivatives.

General Procedure.

To a suspension of 2,3-dihydrothiopyrano[2,3-*b*]pyridin-4(4*H*)-one **2a** or 7-methyl derivative **2b** (5.4 mmoles) and the appropriately 5-substituted isatin (6 mmoles) in 5 ml of ethanol were added 3 ml of 0.2% sodium hydroxide aqueous solution. The reaction mixture was refluxed until disappearance of the starting reagents (18-24 hours, tlc analysis: chloroform/methanol 7:3 as the eluting system). After cooling, the solution obtained was acidified with concentrated hydrochloric acid until pH 5, affording the crude acids **11a-b**, **12a-b** and **13a-b**, which were purified by recrystallization from ethanol (Table III).

6*H*-Pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinoline-7-carbonyl Chloride (**16**).

A suspension of 6*H*-pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinoline-7-carboxylic acid **11a** (0.40 g, 1.36 mmoles) in 1 ml of thionyl chloride and 4 ml of anhydrous toluene was refluxed (70 °C) for 16 hours. The excess thionyl chloride was distilled off, and the residue was washed with few additional amounts of anhydrous toluene to give pure **16**, which was used without further purification in the next reactions.

N-(Dimethylaminoalkyl)-6*H*-Pyrido[3',2':5,6]thiopyrano[4,3-*b*]-quinoline-7-carboxamides **14** and **15**.

General Procedure.

To a suspension of carbonyl chloride **16** (1.36 mmoles) in 20 ml of anhydrous toluene the appropriate *N*,*N*-dimethylaminoalkylamine was added. The reaction mixture was stirred at room temperature until no starting materials were detected by tlc (approximately 10 hours, chloroform/methanol 9:1 as the eluting system). The mixture obtained was evaporated to dryness to give crude amides **14** or **15** as dark viscous oils, which were purified by column chromatography (alumina grade I, 70-230 mesh, chloroform as eluent) to give solid amides **14** and **15**, which were crystallized from toluene-petroleum ether 60-80 °C.

Compound **14** was obtained in 46% yield, mp 127-130 °C; ^{1}H nmr: δ 2.31 (s, 6H, N(CH_3)$_2$); 2.58 (t, 2H, CH_2CH_2N(CH_3)$_2$); 3.48 (t, 2H, CH_2CH_2N(CH_3)$_2$); 4.33 (s, 2H, 6-CH_2); 7.29-8.80 (m, 7H, Ar-H); ms: m/z = 364 (M^+).

Anal. Calcd. for $C_{20}H_{20}N_4OS$: C, 65.91; H, 5.53; N, 15.37; Found: C, 65.74; H, 5.53; N, 15.59.

Compound **15** was obtained in 30% yield, mp 122-123 °C; ^{1}H nmr: δ 1.70-1.87 (m, 2H, $CH_2CH_2CH_2$N); 2.16 (s, 6H, N(CH_3)$_2$); 2.33 (t, 2H, $CH_2CH_2CH_2$N); 3.46 (t, 2H, $CH_2CH_2CH_2$N); 4.26 (s, 2H, 6-CH_2); 7.31-8.82 (m, 7H, Ar-H); ms: m/z = 378 (M^+).

Anal. Calcd. for $C_{21}H_{22}N_4OS$: C, 66.64; H, 5.86; N, 14.80; Found: C, 66.77; H, 6.16; N, 14.92.

6*H*-Pyrido[3',2':5,6]thiopyrano[4,3-*b*]quinoline-7-carboxylic Acid Ethyl Ester **17**.

A suspension of acyl chloride **16** (0.27 mmole) in anhydrous toluene (10 ml) and absolute ethanol (3 ml) was stirred at room temperature for 24 hours and then heated (70 °C) for 2 hours. The resulting solution was concentrated *in vacuo* to dryness to yield crude ethyl ester **17**, which was purified by recrystallization from ethanol giving pure **17**, (37 mg, 42% yield), mp 182-185 °C; ^{1}H nmr: δ 1.42 (t, 3H, CH_2CH_3), 4.36 (s, 2H, 6-CH_2), 4.57 (q, 2H, CH_2CH_3), 7.31-8.81 (m, 7H, Ar-H); ms: m/z = 322 (M^+).

Anal. Calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69; Found: C, 67.00; H, 4.64; N, 8.70.

Acknowledgments.

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* Author to whom all correspondence should be addressed.

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