A CONVENIENT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED 2', 2' - BIS(ETHOXYCARBONYL)METHYLENE - 5'-METHOXYCARBONYL-(CYANO)SPIRO[DIHYDROACRIDINE-9(10H), 4'-THIAZOLIDINES]

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Abstract - 2-(Acridin-9-ylthiocarbamoyl)malonic acid diethyl esters **(2a-c)** obtained *via* reaction of isothiocyanatoacridines **(1a-c)** *with sodium diethyl malonate afforded* with methyl bromoacetate (bromoacetonitrile) non-isolable *S*-alkylated intermediates **(3a-f)**, which cyclized in alkaline medium to 2',2'-bis(ethoxycarbonyl)methylene-5'-methoxycarbonyl(cyano)spiro[dihydroacridine-9(10H), 4'-thiazolidines] **(4a-f)**.

In spite of a great variety of spirocyclic heterocycles only a few of them contain an acridine skeleton so far.[1,2] Taking into account a marked biological activity of acridines we focused on the synthesis of new spiroacridine compounds based on novel synthons prepared in our laboratory. This resulted in new syntheses of spirodihydroacridinethiazolines **(A)** employing acridinylthiocarbonimidates **(B)**,[3] acridinyl-dithiocarbamates **(C)** [4] and acridinylthioureas **(D)** [5] as precursors (Figure 1).

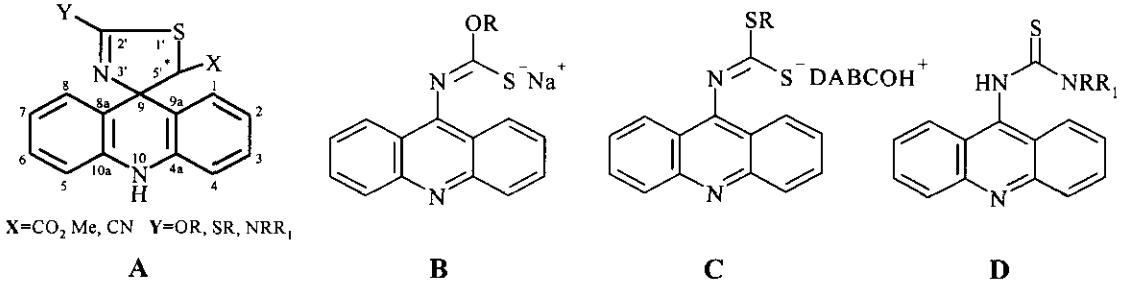
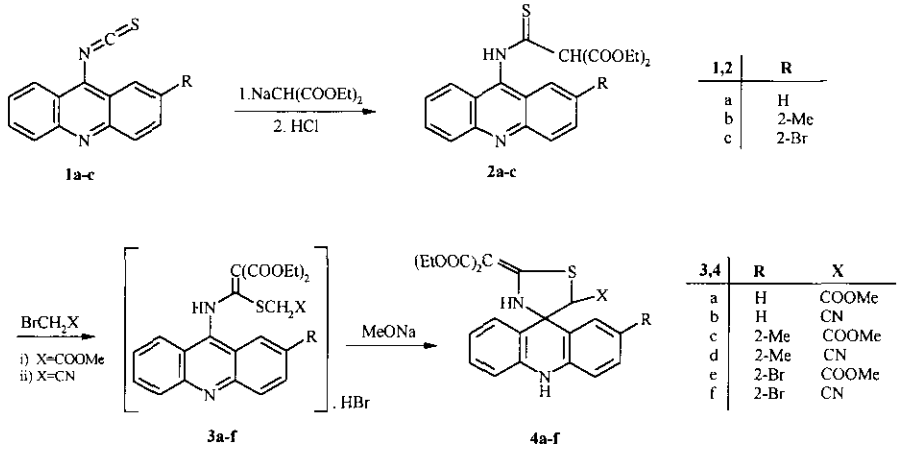


Figure 1

As shown in Figure 1 the spiro compounds prepared contain OR, SR and NRR_1 substituents in position 2′. In this work we attempted to extend the variety of the acridine spiro compounds by the synthesis of spiro[dihydroacridinethiazolidines] which possess a reactive exocyclic C=C bond in position 2′. As suitable precursors diethyl esters of 2-(acridin-9-ylthiocarbamoyl)malonic acid **(2a-c)** obtained by addition of sodium salt of diethyl malonate to corresponding 9-isothioacridines **(1a-c)** [6,7] were used. In the reaction with methyl bromoacetate (bromoacetonitrile) in dichloromethane they afforded intermediate diethyl 2-[(acridin-9-ylamino)methoxycarbonyl(cyano)methylsulfanylmethylene]malonate hydrobromides **(3a-f)**, which were not isolated. The subsequent cyclization with sodium methoxide in methanol gave final 2′,2′-bis(ethoxycarbonyl)methylene-5′-methoxycarbonyl(cyano)spiro[dihydroacridine-9(10H), 4′-thiazolidines] **(4a-f)** (Scheme 1).

Compounds **(4a-f)** may exist, in principle, in two tautomeric forms, a thiazolidine type with 2′-exocyclic C=C bond shown in the Scheme 1 and a thiazoline type with endocyclic C=N bond (not shown). According to DEPT spectra, both carbons of the C=C bond are quarternary. This fact confirms **4a-f** to be thiazolidines. Nevertheless, a strong polarization of exocyclic C=C bond expressed in ^{13}C chemical shift difference greater than 85 ppm is observed for **4a, b** as a result of "push-pull" effect of substituents.



Scheme 1

The basic compounds **(4a, b)** contain one chiral center (C-5′) what causes two lateral rings of dihydroacridine to be chemically unequivalent. In 2-substituted derivatives **(4c-f)** two chiral centers are present in the molecule (C-9 as next) and so two diastereoisomers in 1:1 ratio (determined from NMR) were obtained from the reaction mixture in all cases. We did not attempt their separation yet. The NMR spectra of diastereoisomeric mixture, described in EXPERIMENTAL, involve chemical shifts of both diastereoisomers provided they were different.

EXPERIMENTAL

Elemental analyses were performed on a Perkin-Elmer CHN 2400 analyzer. IR spectra were recorded using a Specord 75 IR instrument (Zeiss, Jena) in chloroform. ^1H NMR spectra (80 MHz, δ, ppm) were measured on a Tesla BS 587 FT NMR spectrometer in deuterochloroform. ^{13}C NMR spectra (100 MHz) of **4a, b** were taken (δ, ppm) on a Jeol 400 Lambda spectrometer in deuterochloroform at room temperature. MS spectra were recorded on VG MM 7070E instrument equipped with an OPUS system.

Preparation of 2-(Acridin-9-ylthiocarbamoyl)malonic acid diethyl esters (2a-c). General Procedure. 9-Isothiocyanatoacridine **(1a-c)** (1 mmol) was stirred with sodium diethyl malonate (0.2 g , 1.1 mmol) in dry ether (25 mL) for 2 h. The end of the reaction was followed by TLC on silica plates, eluent benzene-acetone (5:2). Water (30 mL) was then added to the reaction mixture and a solid was filtered off after shaking. Water layer containing dissolved sodium salt of **(2a-c)** was separated and acidified with 12 % hydrochloric acid. A precipitate was filtered off, dried and crystallized from the mixture chloroform-ether. **Diethyl 2-(Acridin-9-ylthiocarbamoyl)malonate (2a)**: mp 156-158 °C; yield 95%. Anal. Calcd for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.08; N, 7.06. Found: C, 63.37; H, 5.02; N, 4.99. IR: 1716, 1160 cm^{-1}.

^{1}H NMR : 11.87 (br s, 1H, NH), 8.55-7.12 (m, 8H, AcrH), 5.28 (s, 1H, CH), 4.42 (q, J=7.2 Hz, 4H, OCH_2), 1.41 (t, J=7.2 Hz, 6H, CH_3).

Diethyl 2-(2-Methylacridin-9-ylthiocarbamoyl)malonate (2b): mp 159-161 °C; yield 94%. Anal. Calcd for $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.07; H, 5.32; N, 6.73. IR : 1716, 1155 cm^{-1}. ^{1}H NMR: 11.89 (br s, 1H, NH), 8.60-7.20 (m, 7H, AcrH), 5.32 (s, 1H, CH), 4.43 (q, J=7.1 Hz, 4H, OCH_2), 2.52 (s, 3H, CH_3), 1.42 (t, J=7.1 Hz, 6H, CH_3).

Diethyl 2-(2-Bromoacridin-9-ylthiocarbamoyl)malonate (2c): mp 158-162 °C; yield 90%. Anal. Calcd for $C_{21}H_{19}N_2O_4BrS$: C, 53.06; H, 4.03; N, 5.89. Found: C, 52.77; H, 4.00; N, 5.81. IR : 1716, 1155 cm^{-1}. ^{1}H NMR: 11.88 (br s, 1H, NH), 8.63-7.15 (m, 7H, AcrH), 5.30 (s, 1H, CH), 4.41 (q, J=7.2 Hz, 4H, OCH_2), 1.40 (t, J=7.2 Hz, 6H, CH_3).

Preparation of 2',2'-bis(ethoxycarbonyl)methylene-5'-methoxycarbonyl(cyano)spiro[dihydroacridine-9(10H), 4'-thiazolidines] (4a-f). General Procedure.

To solution of **2a-c** (1 mmol) in dichlormethane or chloroform (15 mL) methyl bromoacetate (0.17 g, 1.11 mmol) or bromoacetonitrile (0.13 g, 1.11 mmol), was added dropwise with stirring. The reaction course was followed by TLC [eluent benzene-acetone (5:2)], whereby hydrobromides formed **(3a-f)** did not move from the start. When the reaction was finished sodium methoxide (0.13 g, 1.31 mmol) in methanol (20 mL) was added and stirring continued for 30 min. The reaction mixture was then poured into water (50 mL), a precipitate formed was filtered off, dried and crystallized from the mixture dichloromethane-cyclohexane.

2', 2'-Bis(ethoxycarbonyl)methylene-5'-methoxycarbonylspiro[dihydroacridine-9(10H), 4'-thiazolidine] (4a): mp 214-217 °C; yield 90%. Anal. Calcd for $C_{24}H_{24}N_2O_6S$: C, 61.52; H, 5.16; N, 5.98. Found: C, 61.37; H, 5.11; N, 5.87. IR : 3433, 1730 cm^{-1}. ^{1}H NMR : 10.66 (br s, 1H, NH), 7.57-6.75 (m, 9H, AcrH+NH), 4.34, 4.29 (q, J=7.1 Hz, 4H, OCH_2), 4.11 (s, 1H, CH), 3.24 (s, 3H, OCH_3), 1.37, 1.36 (t, J=7.1 Hz, 6H, CH_3). ^{13}C NMR: 14.3, 14.4 (CH_3), 52.5 (OCH_3), 60.4, 60.5 (OCH_2), 60.6 (5'-CH), 70.6 (C-9), 87.5 (exocyclic C=), 114.0, 114.4, 120.9, 121.6, 125.6, 126.5, 129.2, 129.6 (aromatic CH), 117.3, 121.3, 137.3, 138.6 (aromatic C), 167.9, 168.4, 169.0 (COO), 174.7 (2'-C=). MS, *m/z (%)*: 468 (78, M^+).

2', 2'-Bis(ethoxycarbonyl)methylene-5'-cyanospiro[dihydroacridine-9(10H), 4'-thiazolidine] (4b): mp 211-214 °C; yield 85%. Anal. Calcd for $C_{23}H_{21}N_3O_4S$: C, 63.43; H, 4.86; N, 9.65. Found: C, 62.99; H, 4.81; N, 9.55. IR : 3430, 2240 cm^{-1}. ^{1}H NMR: 10.64 (br s, 1H, NH), 7.58-6.71 (m, 9H, AcrH+NH), 4.32, 4.28 (q, J=7.1 Hz, 4H, OCH_2), 4.09 (s, 1H, CH), 1.37, 1.36 (t, J=7.1 Hz, 6H, CH_3). ^{13}C NMR spectrum ($CDCl_3$): 14.2, 14.3 (CH_3), 46.1 (5'-CH), 60.8, 61.0 (OCH_2), 70.3 (C-9), 88.4 (exocyclic C=), 115.4 (CN), 114.6, 114.7, 118.9, 121.7, 125.2, 126.0, 129.8, 130.3 (aromatic CH), 116.8, 121.6, 137.6, 138.1 (aromatic C), 168.0, 168.6 (COO), 173.2 (2'-C=). MS, *m/z (%)*: 435 (78, M^+).

2', 2'-Bis(ethoxycarbonyl)methylene-5'-methoxycarbonylspiro[2-methyldihydroacridine-9(10H), 4'-thiazolidine] (4c): mp 201-204 °C; yield 80%. Anal. Calcd for $C_{25}H_{26}N_2O_6S$: C, 62.22; H, 5.43; N, 5.81. Found: C, 61.97; H, 5.40; N, 5.75. IR : 3435, 1730 cm^{-1}. ^{1}H NMR: 10.66 (br s, 1H, NH), 7.50-6.70 (m, 7H, AcrH), 6.62 (br s, 1H, NH), 4.34 (m, 4H, OCH_2), 4.13 and 4.04 (s, 1H, CH), 3.27 and 3.26 (s, 3H, OCH_3), 2.38 and 2.32 (s, 3H, 2-CH_3), 1.40 (t, J=7.2 Hz, 6H, CH_3). MS, *m/z (%)*: 482 (100, M^+).

2', 2'-Bis(ethoxycarbonyl)methylene-5'-cyanospiro[2-methyldihydroacridine-9(10H), 4'-thiazolidine] (4d): mp 206-209 °C; yield 82%. Anal. Calcd for $C_{24}H_{23}N_3O_4S$: C, 64.13; H, 5.16; N, 9.35. Found: C, 63.97; H, 5.10; N, 9.25. IR : 3430, 2242 cm^{-1}. ^1H NMR: 10.76 (br s, 1H, NH), 7.65-6.73 (m, 7H, AcrH), 6.58 (br s, 1H, NH), 4.33, 4.30 (q, J=7.2 Hz, 4H, OCH_2), 4.14 and 4.05 (s, 1H, CH), 2.37 and 2.32 (s, 3H, 2-CH_3), 1.40 (t, J=7.2 Hz, 6H, CH_3). MS, *m/z (%)*: 449 (78, M^+).

2', 2'-Bis(ethoxycarbonyl)methylene-5'-methoxycarbonylspiro[2-bromodihydroacridine-9(10H), 4'-thiazolidine] (4e): mp 210-219 °C (decomp); yield 55%. Anal. Calcd for $C_{24}H_{23}N_2O_6BrS$: C, 52.66; H, 4.23; N 5.12. Found: C, 52.09; H, 4.19; N, 5.17. IR : 3435, 1730 cm^{-1}. ^1H NMR: 10.67 (br s, 1H, NH), 7.58-6.73 (m, 7H, AcrH), 6.85 and 6.82 (br s, 1H, NH), 4.31, 4.27 (q, J=7.2 Hz, 4H, OCH_2), 4.15 and 3.97 (s, 1H, CH), 3.34 and 3.23 (s, 3H, OCH_3), 1.38, 1.37 (t, J=7.2 Hz, 6H, CH_3). MS, *m/z (%)*: 546 (65, M^+).

2', 2'-Bis(ethoxycarbonyl)methylene-5'-cyanospiro[2-bromodihydroacridine-9(10H), 4'-thiazolidine] (4f): mp 208-212 °C (decomp); yield 60%. Anal. Calcd for $C_{23}H_{23}N_3O_4BrS$:C, 53.70; H, 3.92; N 8.17. Found: C, 53.12; H, 3.89; N, 8.11. IR: 3430, 2240 cm^{-1}. ^1H NMR: 10.74 (br s, 1H, NH), 7.70-6.80 (m, 7H, AcrH), 6.73 (br s, 1H, NH), 4.32 (m, 4H, OCH_2), 4.11 and 4.05 (s, 1H, CH), 1.38 (t, J=7.1 Hz, 6H, CH_3). MS, *m/z (%)*: 515 (37, M^+).

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