Chemistry of Heterocyclic Compounds, Vol. 45, No. 7, 2009

FUSED PYRIDOTHIENOPYRIMIDINE HETEROCYCLES. 2*. A FACILE AND EFFICIENT SYNTHESIS OF THE ANNELATED PYRIDO[3',2':4,5]THIENO-[2,3-*e*]PYRIMIDO[3,2-*c*]PYRIMIDONES

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The cyclocondensation reactions of 4-aminopyridothienopyrimidine with malonates and their acetylation were studied. All structures were determined by ^{1}H NMR and mass spectra techniques.

Keywords: fused pyrimidines, pyridothienopyrimidines, pyridothienopyrimidopyrimidines.

We have previously reported the synthesis of new tetracyclic compounds containing the pyridothieno-pyrimidine moiety in order to search for new pharmacological or biologically active compounds [1]. The pyridothienopyrimidine ring system represents an important class of heterocyclic compounds owing to their medicinal interest [2, 3]. In addition, certain pyrimidines and annelated pyrimidine derivatives are known to display anticancer, antimalarial, and antifilarial activitives [4, 5]. These features prompted us to design a specific program aimed at constructing novel tetracyclic ring systems containing a pyrimidine moiety, which condensed with pyridothienopyrimidine derivatives. The cyclocondensation reaction of diethyl malonates with sufficiently reactive 1,3-dinucleophiles such as amidines and amides is a known reaction [6]. In continuation of our ongoing search for new heterocycles by the cyclocondensation reaction of enamines or amidines with malonate derivatives [7–11], we here wish to report a simple and efficient method, utilizing 4-aminopyrido-thienopyrimidine **4**, which is a typical heterocyclic amidine, for the synthesis of a new tetracyclic system, namely pyrido[3',2':4,5]thieno[2,3-*e*]pyrimido[3,2-*c*]pyrimidines. The newly synthesized tetracyclic compounds, pyridothienopyrimidopyrimidines, seem promising for biological activity evaluation studies, but to the best of our knowledge, this ring system has remained totally unexplored.

As depicted in Scheme 1, the required key intermediate **4** was obtained in three steps. Thus, the chloro compound **1** [12] reacted with sodium azide in DMF to give the corresponding azido derivative **2**. The structure of compound **2** was supported by its IR spectrum, which showed the presence of azide absorption at 2144 cm^{-1}.

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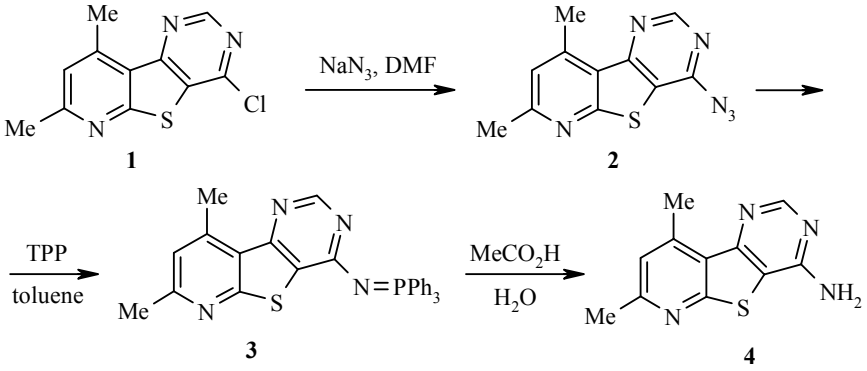
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1054-1060, June, 2009. Original article received January 7, 2009.

An elegant method for the reduction of azides to amines is offered by the Staudinger reaction [13], in which azide reacts with phosphane to yield phosphazene. Hydrolysis of phosphazene with aqueous acids or bases leads to the corresponding amine and phosphane oxide [14].

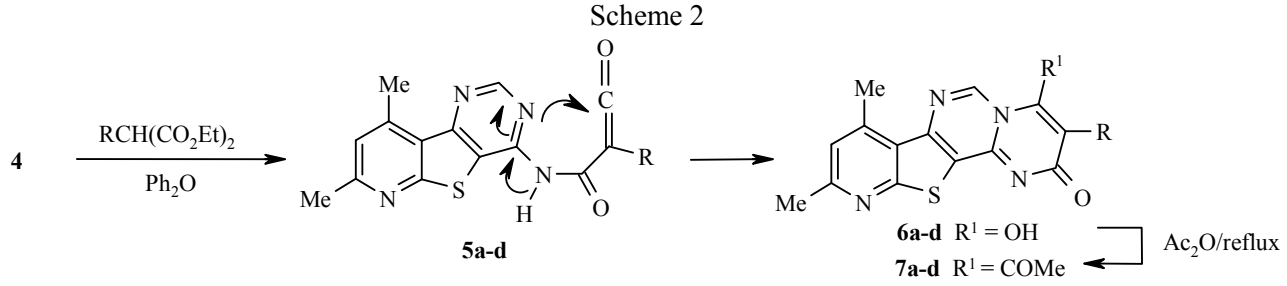
Consequently, this reaction has been applied in the present investigation to synthesize 4-amino-7,9-dimethylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine **4** by reduction of azido derivative **2** *via* the formation of phosphazene intermediate **3** in excellent yields. The structures of compounds **3** and **4** were established on the basis of elemental analysis and spectral data.

Scheme 1



A general method for the preparation of 3-substituted 4-hydroxy-7,9-dimethylpyrido[3',2':4,5]thieno-[2,3-*e*]pyrimido[3,2-*c*]pyrimidin-2-ones **6a-d** is outlined in Scheme 2 by thermal reaction of amino derivative **4** with substituted diethylmalonates at 220-250°C, the method without restrictions described in [15]. This probably formed throughout the synthesis of ketene intermediate **5a-d** as described earlier [16]. The yields range between 71 and 95%, which showed that no further activation of malonates is necessary. The only disadvantage of this reaction sequence is its high reaction temperature, which prevents its use for sensitive substrates and substituents. The structures of compounds **6a-d** were established on the basis of elemental analysis and spectral data. The existence of a 2,4-dioxo structure can be excluded because of the appearance of OH signals of the 4-hydroxy group in the ^{1}H NMR spectra at δ 11.80-12.21 ppm and the lack of aliphatic signals deriving from hydrogen at C-3. Acetylation of compounds **6a-d** with acetic anhydride gave the acetyl derivatives **7a-d**, whose combustion analysis indicated the acetylation of the OH group.

Scheme 2



5-7 a R = Me, **b** R = Et, **c** R = *n*-Bu, **d** R = Ph

Their IR spectra showed absorptions at 1781, 1764, 1765, and 1787 cm^{-1} corresponding to OAc groups. The ^{1}H NMR spectra of compounds **7a-d** confirmed the presence of OAc group as a singlet signal at δ 1.86-1.91 ppm and lack of OH signals.

In a further investigation of the cyclocondensation scope of malonates with amidines to synthesize new heterocyclic system, we studied the reaction of amino derivative **4** with ethoxymethylene malonic ester (EMME). Thus, condensation of an equimolar amount of compound **4** with EMME in refluxing ethanol yielded the corresponding pyridothienopyrimidylaminomethylene malonate **8**, which underwent intramolecular cyclization in boiling diphenyl ether to give ethyl 7,9-dimethyl-4-oxo-pyrido[3',2':4,5]thieno[2,3-*e*]pyrimido-[3,2-*c*]pyrimidine-3-carboxylate **9** (Scheme 3). Alternatively, pyridothienopyrimidopyrimidine derivative **9** could also be obtained in one step by refluxing amino derivative **4** with EMME in diphenyl ether. The structure of compound **9** was established on the basis of elemental analysis and spectral data (see Experimental). The reaction of compound **9** with either an equimolar or excess amount of hydrazine hydrate in absolute ethanol at reflux temperature led to the formation of the unexpected 4-amino-7,9-dimethylpyrido[3',2':4,5]thieno-

Scheme 3

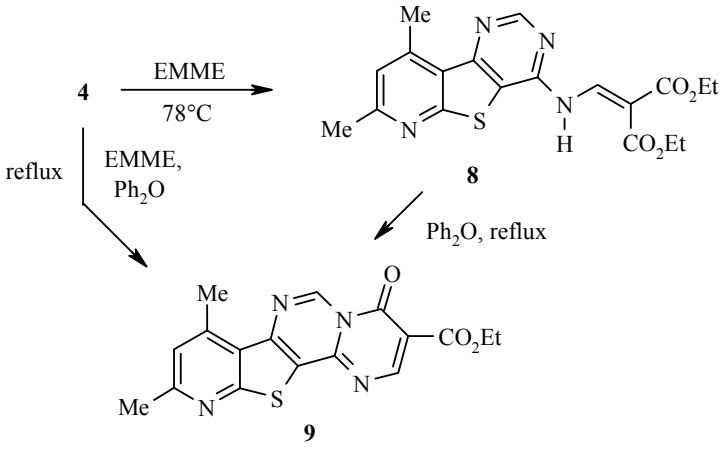


TABLE 1. Experimental Characteristics of Compounds **6a-d** and Acetylated Compounds **7a-d**

Com-pound	Empirical formula	Found, % / Calculated, %			mp, ºC*	Yield, %
		C	H	N		
6a	$C_{15}H_{12}N_4O_2S$	57.37 / 57.68	3.94 / 3.87	17.63 / 17.94	>330	95
6b	$C_{16}H_{14}N_4O_2S$	58.62 / 58.88	4.58 / 4.32	16.86 / 17.17	>330	77
6c	$C_{18}H_{18}N_4O_2S$	61.32 / 61.00	5.33 / 5.12	16.13 / 15.81	>330	86
6d	$C_{20}H_{14}N_4O_2S$	64.16 / 64.30	3.77 / 3.53	14.96 / 14.73	>330	71
7a	$C_{17}H_{14}N_4O_3S$	57.34 / 57.62	4.21 / 3.98	15.64 / 15.81	282-285	80
7b	$C_{18}H_{16}N_4O_3S$	58.92 / 58.68	4.62 / 4.38	15.42 / 15.21	272-275	72
7c	$C_{20}H_{20}N_4O_3S$	60.73 / 60.59	5.32 / 5.08	14.42 / 14.13	209-212	72
7d	$C_{22}H_{16}N_4O_3S$	63.15 / 63.45	3.96 / 3.87	13.26 / 13.45	>300	83

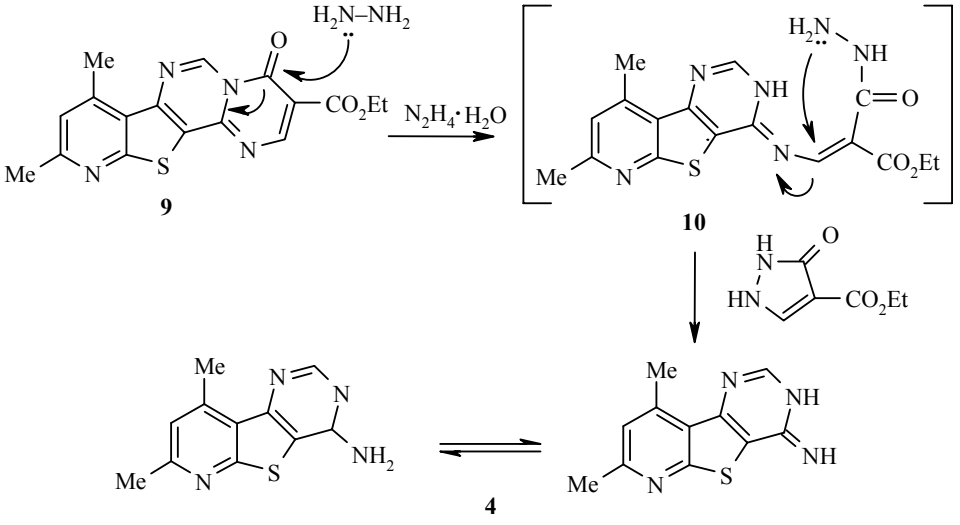
* Solvents: DMF (compounds **6a,d**) and AcOH (compounds **6b,c** and **7a-d**).

TABLE 2. Spectral Characteristics of Compounds **6a-d** and **7a-d**

Compound	IR ν, cm^{-1}	^1H NMR δ, ppm (*J*, Hz)	MS, *m/z* (*I*, %)
6a	3482 (OH); 1671 (CO); 1583 (C=N)	1.93 (3H, s, CH_3); 2.55 (3H, s, CH_3); 2.84 (3H, s, CH_3); 7.22 (1H, s, H-8); 9.34 (1H, s, H-5); 12.21 (1H, br. s, OH)	312 $[M]^+$ (10)
6b	3440 (OH); 1671 (CO); 1602 (C=N)	1.08 (3H, t, *J* = 7, CH_2-$C\underline{H}_3$); 2.5 (2H, q, *J* = 7, CH_3-$C\underline{H}_2$); 2.54 (3H, s, CH_3); 2.88 (3H, s, CH_3); 7.38 (1H, s, H-8); 9.53 (1H, s, H-5); 11.90 (1H, br. s, OH)	326 $[M]^+$ (5)
6c	3438 (OH); 1667 (CO); 1583 (C=N)	0.91 (3H, t, *J* = 7.2, -CH_3); 1.34 (2H, m, -CH_2); 1.94 (2H, m, -CH_2); 2.5 (2H, t, *J* = 6, -CH_2); 2.58 (3H, s, CH_3); 2.9 (3H, s, CH_3); 7.28 (1H, s, H-8); 9.43 (1H, s, H-5); 11.80 (1H, br. s, OH)	354 $[M]^+$ (100)
6d	3436 (OH); 1667 (CO); 1579 (C=N)	2.56 (3H, s, CH_3); 2.89 (3H, s, CH_3); 7.26-7.56 (6H, m, H-8 and C_6H_5); 9.46 (1H, s, H-5); 12.03 (1H, br. s, OH)	374 $[M]^+$ (10)
7a	1781 ($COCH_3$); 1693 (CO); 1607 (C=N)	1.90 (3H, s, $COCH_3$); 1.95 (3H, s, CH_3); 2.60 (3H, s, CH_3); 2.91 (3H, s, CH_3); 7.33 (1H, s, H-8); 9.5 (1H, s, H-5)	354 $[M]^+$ (20)
7b	1764 ($COCH_3$); 1699 (CO); 1602 (C=N)	1.10 (3H, t, *J* = 7, -CH_3); 1.91 (3H, s, $COCH_3$); 2.43 (2H, q, *J* = 7, -CH_2); 2.59 (3H, s, CH_3); 2.88 (3H, s, CH_3); 7.21 (1H, s, H-8); 9.36 (1H, s, H-5)	368 $[M]^+$ (15)
7c	1765 ($COCH_3$); 1699 (CO); 1602 (C=N)	0.91 (3H, t, *J* = 7.2, -CH_3); 1.34 (2H, m, CH_2); 1.86 (3H, s, $COCH_3$); 1.94 (2H, m, CH_2); 2.54 (2H, t, *J* = 6, CH_2); 2.62 (3H, s, CH_3); 2.91 (3H, s, CH_3); 7.48 (1H, s, H-8); 9.63 (1H, s, H-5)	396 $[M]^+$ (30)
7d	1787 ($COCH_3$); 1670 (CO); 1600 (C=N)	1.91 (3H, s, $COCH_3$); 2.59 (3H, s, CH_3); 2.92 (3H, s, CH_3); 7.28–7.58 (6H, m, H-8 and C_6H_5); 9.5 (1H, s, H-5)	416 $[M]^+$ (20)

[3,2-*d*]pyrimidine **4** in acceptable yield. The validity of this product structure was deduced from its correct elemental analysis and compatible spectral data, which was in accordance with an authentic sample prepared by hydrolysis of phosphazene **3**. A reasonable mechanism for this transformation involves the nonisolable intermediate **10**, which is formed *via* nucleophilic attack by one site of the binucleophile hydrazine hydrate on the activated carbonyl group at C-4 with concomitant ring opening to form acyclic intermediate **10**, followed by attack of the second site on C-2, forming pyrazolinone ester, which may be decomposed through the reaction mixture (Scheme 4).

Scheme 4



EXPERIMENTAL

Melting points were determined on a Buchi melting point apparatus. NMR spectra were recorded (300 and 75 MHz, respectively) on a Varian Germini-2000 apparatus and registered in DMSO-d_6, ppm to internal Me_4Si. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were measured on Kratos 50 tc spectrometers. Microanalysis was performed in the microanalysis lab at Cairo University. Common reagent-grade chemicals are either commercially available and used without further purification, or prepared by standard literature procedure. All reactions were monitored by TLC, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (254 and 360 nm) for detection.

4-Azido-7,9-dimethylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (**2**). Sodium azide (1.63 g, 25 mmol) was added to a stirred solution of chloro compound **1** (1.25 g, 5 mmol) in DMF (20 ml). Stirring was continued for a further 12 h at 50-60ºC. Then the reaction mixture was poured into ice water, and the precipitated solid product was collected by filtration, washed with water, dried, and recrystallized from MeOH to afford the corresponding azido compound **2**. (0.90 g, 70%); mp 183-184ºC. IR spectrum, ν, cm^{-1}: 2144 (N_3). ^{1}H NMR spectrum, δ, ppm: 2.61 (3H, s, CH_3); 2.94 (3H, s, CH_3); 7.38 (1H, s, H-8); 8.29 (1H, s, ArH). Mass spectrum, *m/z* (*I*, %): 256 $[M]^+$ (20); 228 (100). Found, %: C 51.25; H 3.13; N 32.56. $C_{11}H_8N_6S$. Calculated, %: C 51.55; H 3.15; N 32.79.

7,9-Dimethyl-4-(triphenylphosphoranylideneamino)pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (**3**). A solution of azidopyridothienopyrimidine **2** (1.28 g, 5 mmol) and triphenylphosphane (1.31 g, 5 mmol) in toluene (20 ml) was heated under reflux for 30 min. The solvent was then removed under reduced pressure and the resulting solid product was collected by filtration and recrystallized from ethanol to afford compound **3** as white prisms (3.0 g, 88%); mp 273–275ºC. ^{1}H NMR spectrum, δ, ppm: 2.59 (3H, s, CH_3); 2.89 (3H, s, CH_3); 7.22 (1H, s, H-8); 7.56–7.89 (15H, m, ArH); 8.36 (1H, s, ArH). Mass spectrum, *m/z* (*I*, %): 490 $[M]^+$ (100). Found, %: C 70.91; H 4.66; N 11.33. $C_{29}H_{23}N_4PS$. Calculated, %: C 71.00; H 4.73; N 11.42.

4-Amino-7,9-dimethylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (**4**). A solution of iminophosphorane **3** (1.5 g, 3 mmol) in acetic acid (80%, 20 ml)) was heated under reflux for 5 h. The solvent was then removed in vacuum, and the resulting solid product was digested with MeOH, collected by filtration, washed well with MeOH to remove Ph_3PO, dried, and recrystallized from AcOH to afford compound **4** as white prisms (0.8 g, 89%); mp 287–289ºC (reported, >360°C [17]). IR spectrum, ν, cm^{-1}: 3459, 3288 (NH_2). ^{1}H NMR spectrum, δ, ppm: 2.49 (3H, s, CH_3); 2.86 (3H, s, CH_3); 7.25 (1H, s, ArH); 7.46 (2H, bs, NH_2); 8.38 (1H, s, ArH). ^{13}C NMR spectrum, δ, ppm: 18.61 (CH_3); 23.61 (CH_3); 118.08; 122.03; 123.11; 146.01; 145.57; 154.67; 157.89; 159.13; 160.76 (C-ArH). Mass spectrum, *m/z* (*I*, %): 230 $[M]^+$ (100). Found, %: C 57.22; H 4.35; N 24.18. $C_{11}H_{10}N_4S$. Calculated, %: C 57.37; H 4.38; N 24.33.

4-Hydroxy-7,9-dimethyl-3-(methyl, ethyl, *n*-butyl, phenyl)pyrido[3',2':4,5]thieno[2,3-*e*]pyrimido-[3,2-*c*]pyrimidin-2-ones 6a-d (General Method). A mixture of 4-aminopyridothienopyrimidine **4** (0.46 g, 2 mmol) and the appropriate malonic ester (4 mmol) in diphenyl ether (5 ml) was refluxed in an oil bath for 20-40 min, using a short air condenser to remove the liberated ethanol. After cooling, the reaction mixture was triturated with diethyl ether, and the obtained precipitate was filtered off, washed with diethyl ether, dried, and recrystallized from the proper solvent (Tables 1 and 2).

4-Acetyl-7,9-dimethyl-3-(methyl, ethyl, *n*-butyl, phenyl)pyrido[3',2':4,5]thieno[2,3-*e*]pyrimido-[3,2-*c*]pyrimidin-2-ones 7a-d (General Method). A suspension of compounds **6a-d** (1.5 mmol) in acetic anhydride (10 ml) was refluxed for 24 h. After cooling, the separated crystals from the obtained clear solution were filtered off, washed with ethanol, dried, and recrystallized from acetic acid (Tables 1 and 2).

Diethyl (7,9-dimethylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-4-imino)methylene Malonate (**8**). A mixture of amino derivative **4** (0.46 g, 2 mmol), diethyl ethoxymethylenemalonate (0.43 g, 2 mmol), and 2-3 drops of piperidine in absolute ethanol (5 ml) was refluxed for 24 h. After cooling, the reaction mixture was

evaporated under reduced pressure, and the residue was triturated with diethyl ether (10 ml). The resulting solid product was collected by filtration, washed with diethyl ether, dried, and recrystallized from methanol to give compound **8** (0.3 g, 60%); mp 210-212ºC. IR spectrum, ν, cm^{-1}: 3414 (NH); 1721 (CO); 1664 (CO); 1622 (C=C). ^{1}H NMR spectrum δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.1, $C\underline{H}_3CH_2$); 1.38 (3H, t, *J* = 7.1, $C\underline{H}_3CH_2$); 2.60 (3H, s, CH_3); 2.91 (3H, s, CH_3); 4.25 (2H, q, *J* = 7.1, $CH_3C\underline{H}_2$); 7.31 (1H, s, H-8); 8.41 (1H, s, H-2); 8.94 (1H, d, *J* = 13.5, CH=C); 10.83 (1H, d, *J* = 13.5, NH). Found, %: C 56.63; H 5.21; N 13.68. $C_{19}H_{20}N_4O_4S$. Calculated, %: C 56.99; H 5.03; N 13.99.

Ethyl 7,9-dimethyl-4-oxo-pyrido[3',2':4,5]thieno[2,3-*e*]pyrimido[3,2-*c*]pyrimidine-3-carboxylate (9).

A. A suspension of compound **8** (0.4 g, 1 mmol) in diphenyl ether (4 ml) was heated under reflux for 1 h. After cooling, the reaction mixture was digested with diethyl ether, and the brown solid product was collected by filtration, washed with diethyl ether, and recrystallized from acetic acid to afford compound **9** (0.3 g, 86%).

B. A suspension of compound **4** (0.46 g, 2 mmol) and diethyl ethoxymethylenemalonate (0.43 g, 2 mmol) in diphenyl ether (5 ml) was heated under reflux for 20 min; after cooling, the reaction mixture was triturated with diethyl ether (10 ml) to give a brown solid, which was filtered off, washed with diethyl ether, dried, and recrystallized from acetic acid to yield compound **9** (0.5 g, 72%); mp 300–303ºC. IR spectrum, ν, cm^{-1}: 1731 (COOEt); 1693 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, *J* = 7.1, $C\underline{H}_3CH_2$); 2.64 (3H, s, CH_3); 2.96 (3H, s, CH_3); 4.32 (2H, q, *J* = 7.1, $CH_3C\underline{H}_2$); 7.42 (1H, s, H-8); 8.89 (1H, s, H-5); 9.73 (1H, s, H-2). Found, %: C 57.43; H 3.68; N 15.68. $C_{17}H_{14}N_4O_3S$. Calculated, %: C 57.62; H 3.98; N 15.81.

Reaction of Carboxylate 9 with Hydrazine Hydrate. A mixture of either equimolar quantities (1 mmol) or excess (5 mmol) of hydrazine hydrate (80%) and carboxylate **9** (1 mmol) in absolute ethanol (10 ml) was refluxed for 2 h. The resulting mixture was evaporated and the residue was triturated with acetone. The obtained colorless solid was filtered off, dried, and recrystallized from AcOH to yield a compound that was identical in all physical and spectroscopic data to compound **4** (0.3 g, 60%); mp and mixed mp (with a sample prepared from compound **3**) 286-288ºC.

The author thanks DANIDA for financial support of this work at the Faculty of Science, Menoufia University, through the project "Development of New Drugs against Hepatitis".

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