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The Synthesis of Cyclopenta[*c*]pyridine (2-Pyrindene) Derivatives

Victor V. Dotsenko[1,*], **Sergey G. Krivokolysko**[1], and **Victor P. Litvinov**[2,†,‡]

[1] "ChemEx" Laboratory, Vladimir Dal' East Ukrainian National University, Lugansk, Ukraine
[2] Russian Academy of Sciences, Zelinsky Institute of Organic Chemistry, Moscow, Russian Federation

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Summary. Ethyl 2-(*N*-morpholinyl)cyclopent-1-ene-1-carboxylate reacted smoothly with cyanothioacetamide to give morpholinium 4-cyano-1-oxo-2,5,6,7-tetrahydro-1*H*-cyclopenta[*c*]pyridine-3-thiolate; the former when treated with *N*-benzyl-α-chloroacetamide gave either a *S*-alkyl derivative or cyclopenta[*d*]thieno[2,3-*b*]pyridine, depending on the reaction conditions. Under *Mannich*-type aminomethylation with primary amines and formaldehyde the above thiolate afforded derivatives of the previously unknown heterocyclic system, cyclopenta[*g*]pyrido[2,1-*b*][1,3,5]thiadiazine in 81–90% yields.

Keywords. Heterocycles; *Thorpe-Ziegler* cyclization; *Mannich* reaction; Pyridine-2-thiolates; *Guareschi-Thorpe* cyclization.

Introduction

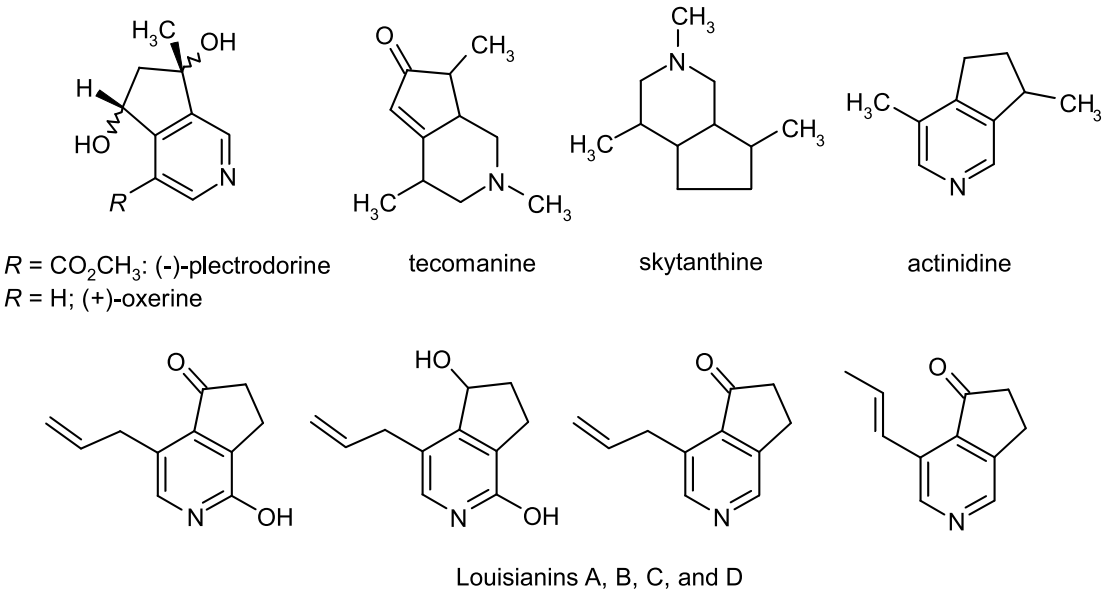
Cyclopenta[*c*]pyridine (2-pyrindine; IUPAC has recommended the name "2-pyrindene") derivatives have proven to be a class of compounds of great practical interest. Thus, the 2-pyrindene ring is the key structural unit of certain monoterpenoid alkaloids, namely, (−)-plectrodorine and (+)-oxerine [1], tecomanine [2], anti-androgenic and anti-cancer alkaloids louisianins A–D [3], skytanthine [4], and actinidine [5] (Scheme 1); the former is known as an active cat attractant derived from valerian root and a pheromone for a variety of insects. Some cyclopenta[*c*]pyridine species showed affinity for the central nicotinic receptor [6] and also were found to be effective precursors for synthesis of anti-cancer alkaloid camptothecin analogues [7].

Only a few methods are known to be useful for construction of the cyclopenta[*c*]pyridine ring system [8]. One of the most concise and handy approaches to 2-pyrindene derivatives based on the *Guareschi-Thorpe*-type reaction of cyanoacetamide with cyclic β-ketoester **1** was proposed for the first time by *Prelog* and *Metzler* [9]. In continuation of our work on the chemistry of cyanothioacetamide [10] and 3-cyanopyridine-2(1*H*)-thiones [11] we report here the synthesis of new cyclopenta[*c*]pyridine derivatives using a modified *Prelog* and *Metzler* procedure.

In the *Guareschi-Thorpe* synthesis [12], formation of a pyridine ring occurs through the reaction of ethyl cyanoacetate and ammonia (or their condensation product, cyanoacetamide) with 1,3-bielectrophilic species, usually 1,3-diketones and β-ketoesters. In most cases, however, enamines derived from 1,3-dicarbonyl compounds (β-enamino ketones and esters) should be preferred over 1,3-dicarbonyl compounds itselves due to the milder reaction conditions and higher yields [11, 13, 14].

Thus, we became interested in the synthesis of ethyl 2-(*N*-morpholinyl)cyclopent-1-ene-1-carboxylate (**2**) with cyanothioacetamide (**3**) as the method of choice to build the 2-pyrindene ring.

† Deceased
‡ This paper is dedicated to the blessed memory of our colleague, Prof. Victor Petrovich Litvinov (Dec 24, 1932–Feb 26, 2007)
* Corresponding author. E-mail: Victor_Dotsenko@bigmir.net



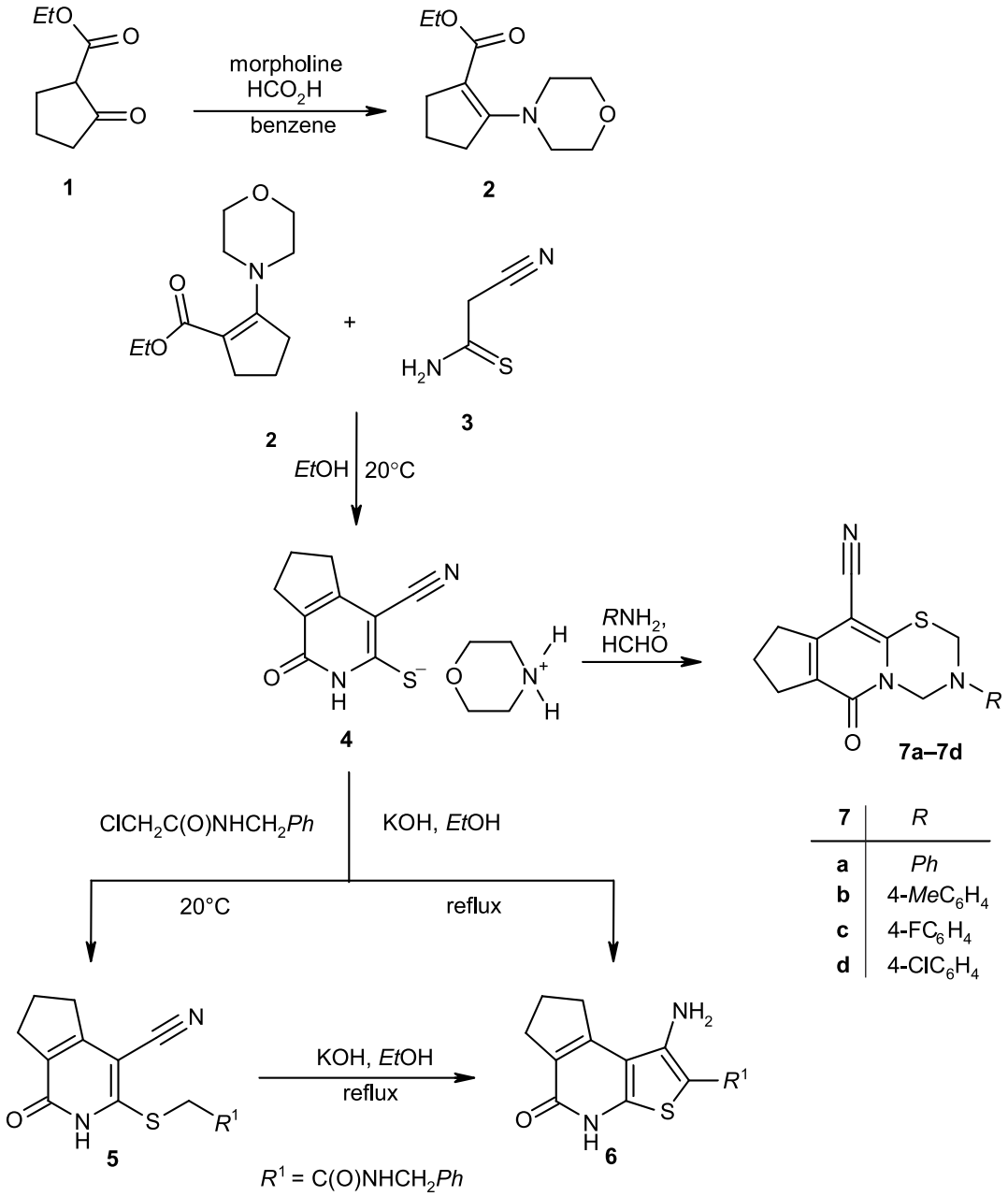
Scheme 1

Results and Discussions

Ethyl 2-(*N*-morpholinyl)cyclopent-1-ene-1-carboxylate (**2**) was obtained *via* the general protocol introduced in common practice by *Stork et al.* [15]. Enamine **2** reacted readily with cyanothioacetamide (**3**) under mild conditions to afford thiolate **4** in 57% yield (Scheme 2). The formation of **4** was found to be in a good agreement with the behavior of other β-enaminoester species which also give pyridine-2(1*H*)-one derivatives when treated with active methylene (thio)amides [13, 14]. Thiolate **4** is thought to be a promising and versatile reagent for heterocyclic synthesis and allowed a number of interesting transformations. Thus, alkylation of **4** with *N*-benzyl-α-chloroacetamide afforded the expected sulfide **5**. When treated with excessive KOH, **5** underwent a *Thorpe-Ziegler* heterocyclization to give isomeric thieno[2,3-*b*]pyridine **6** (method *A*), which also could be obtained directly from thiolate **4** under rather harsh conditions (method *B*).

Derivatives of a new heterocyclic system, cyclopenta[*g*]pyrido[2,1-*b*][1,3,5]thiadiazines **7** [16], were easily obtained in a one-pot reaction by *Mannich*-type reaction of **4** with formaldehyde and primary amines. Both aromatic and aliphatic amines reacted under these conditions; however, all efforts in extending the scope of this reaction for certain sterically hindered substrates, such as 2-ethyl-6-methylaniline, *t*-butylamine, or 2,6-dimethylaniline, remained unrewarded. It should be noted that aminomethylation of 2-thioxopyridine species or related pyridine-2-thiolates may proceed by different pathways depending on the substrate structure. Thus, 2-(aminomethyl)thiopyridines [17], pyrido[2,1-*b*][1,3,5]-thiadiazines [18], pyrido[1,2-*a*][1,3,5]triazines [19], 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene derivatives [20] or bispidines (3,7-diazabicyclo[3.3.1]-nonanes) [21] were obtained by this method.

The structures of all obtained compounds were confirmed by means of elemental analysis for C, H, and N, as well as IR- and ^{1}H NMR data. The IR-spectra of compounds (**4**, **5**, **7**) showed the characteristic conjugated bands of a C≡N group stretching at $\bar{\nu} = 2210–2200\,\text{cm}^{-1}$, such a band was absent in the IR-spectrum of thieno[2,3-*b*]pyridine **6**. In the spectra of all compounds, the intensive bands at $\bar{\nu} = 1635–1620\,\text{cm}^{-1}$ corresponding to the lactam C=O groups stretches were observed. The ^{1}H NMR spectra of all synthesized **4**–**7** revealed a multiplet and two broadened triplets (with coupling constants of $^3J = 7.0–7.6\,\text{Hz}$) at $\delta = 1.94–3.24\,\text{ppm}$ corresponding to the six protons of the three-methylene bridge. In addition to IR data, the broad peaks of NH-protons at $\delta = 10.18–12.20\,\text{ppm}$ in the spectra of **4**–**6** revealed that the latter exist both in solid state and solution in a form of lactam tautomers rather than 2-hydroxypyridine species. In the ^{1}H NMR



Scheme 2

spectra of **7a**–**7d**, the signals of $C(2)H_2NC(4)H_2$ protons appeared as two broadened singlets at $\delta = 5.43$–5.56 and 5.63–5.77 ppm.

Experimental

Melting points were measured on a *Kofler* hot stage apparatus. Elemental analyses for C, H, and N were conducted using a Perkin-Elmer C, H, and N analyzer; their results were found to be in good agreement with the calculated values (±0.2%). IR spectra were recorded on an IKS-29 spectrophotometer in Nujol mulls. The ^{1}H NMR spectra were performed on Varian Mercury VX-200 (199.97 MHz) spectrometer on *DMSO*-d_6 solutions with Me_4Si as the internal standard. The purity of all obtained compounds was checked by TLC on Silufol® UV 254 plates (sorbent – Silpearl, large-pore silica gel after *Pitra* with luminescent indicator for UV 254 on the aluminum foil, binder – starch) in the acetone:heptane (1:1) system; spots were visualized with iodine vapors and UV light. Ethyl 2-oxocyclopentanecarboxylate (**1**) (technical grade, 90%) was purchased from Acros. Cyanothioacetamide (**3**) was obtained by the known method [22].

Ethyl 2-(N-morpholinyl)cyclopent-1-ene-1-carboxylate (**2**)
To the solution of 10 cm^3 of ketoester **1** (90% purity, about 0.06 mol) and 6 cm^3 morpholine (0.069 mol) in 60 cm^3 benzene, catalytic amounts of HCO_2H (3–5 drops) were added. The mixture was refluxed in a round bottom flask equipped with a *Dean-Stark* water separator until no further separation of water was observed. The theoretical amount of water (1.1 cm^3) required approximately 0.5 h to separate. The solvent was removed by distillation *in vacuo*, the dark red oily residue (15.0 g of crude **2**, nearly quantitatively) was used in a next step without any purification.

Morpholinium 4-cyano-1-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[c]pyridine-3-thiolate (**4**, $C_{13}H_{17}N_3O_2S$)
To 15.0 g of crude enamine **2** (about 0.06 mol) dissolved in 30 cm^3 of absolute *Et*OH, 6.0 g (0.06 mol) of cyanothioacetamide **3** was added under vigorous stirring. The mixture was stirred for 5 h at 20°C and left to stand overnight. A white crystalline precipitate formed, which was filtered off and washed twice with absolute *Et*OH and acetone to afford 9.5 g (57%) of thiolate **4**. Mp 248–250°C (dec); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 1.97$ (m, C(6)H_2), 2.50 (br t, $^3J = 7.0$ Hz, C(7)H_2), 2.68 (br t, $^3J = 7.3$ Hz, C(5)H_2), 3.12 (m, N(CH_2)$_2$), 3.76 (m, O(CH_2)$_2$), 10.18 (br s, NH) ppm. Signal of NH^+-protons was not detected due to proton-deuterium exchange; IR (nujol): $\bar{\nu} = 3315$ (NH), 2200 (C≡N), 1630 (C=O) cm^{-1}.

N-Benzyl-2-[(4-cyano-1-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[c]pyridine-3-yl)thio]acetamide (**5**, $C_{18}H_{17}N_3O_2S$)
To a suspension of 0.5 g of thiolate **4** (1.79 mmol) in 10 cm^3 *Et*OH, 1 cm^3 of 10% aqueous KOH solution (1.79 mmol) was added. The solution formed was stirred for 0.5 h and filtered through a paper filter into the solution of 0.33 g (1.8 mmol) of *N*-benzyl-α-chloroacetamide in 10 cm^3 *Et*OH. The mixture was stirred for 5 h and left to stand overnight. To the resulting mixture 5 cm^3 water and 2 cm^3 *Ac*OH were added portionwise under vigorous stirring. The precipitate was filtered off and washed with cold *Et*OH and ether to afford 0.39 g of **5** (64%) as a white powder. Mp 227–229°C (dec, *Et*OH); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.14$ (m, C(6)H_2), 2.76 (br t, $^3J = 7.4$ Hz, C(7)H_2), 2.95 (br t, $^3J =$ 7.6 Hz, C(5)H_2), 3.90 (br s, SCH_2), 4.35 (d, $^3J = 5.3$ Hz, NHCH_2), 7.27 (m, *Ph*), 8.55 and 11.70 (both very br s, 2 NH) ppm; IR (nujol): $\bar{\nu} = 3315$ (N–H), 2210 (C≡N), 1660, 1620 (2 C=O) cm^{-1}.

1-Amino-N-benzyl-5-oxo-5,6,7,8-tetrahydro-4H-cyclopenta-[d]thieno[2,3-b]pyridine-2-carboxamide (**6**, $C_{18}H_{17}N_3O_2S$)

Method A
To a suspension of 0.5 g 2-pyrindene derivative **5** (1.47 mmol) in 10 cm^3 *Et*OH, an excess of 10% aqueous KOH solution (1 cm^3, 1.79 mmol) was added. The deep yellow solution formed was refluxed for 5 min under vigorous stirring and allowed to cool to ambient temperature, whereupon 2 cm^3 *Ac*OH were added. A white solid was filtered off and washed with *Et*OH to afford 0.40 g (80%) of thienopyridine **6**.

Method B
To a suspension of 0.5 g thiolate **4** (1.79 mmol) in 10 cm^3 *Et*OH, 1 cm^3 10% aqueous KOH solution (1.79 mmol) and 0.33 g *N*-benzyl-α-chloroacetamide (1.8 mmol) were added in succession. The solution formed was stirred for 0.5 h, treated with another 1 cm^3 10% KOH (1.79 mmol) whereupon the mixture was refluxed for 5 min, filtered through a paper filter and left to stand overnight. The filtrate was acidified with 2 cm^3 *Ac*OH, a white precipitate formed, which was separated by filtration and washed with *Et*OH to afford 0.56 g (71%) of thienopyridine **6**, identical to the one obtained by method A. Mp 307–310°C (dec, *Ac*OH); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.14$ (m, C(7)H_2), 2.68 (br t, $^3J = 7.3$ Hz, C(6)H_2), 3.24 (br t, $^3J = 7.0$ Hz, C(8)H_2), 4.37 (d, $^3J = 5.7$ Hz, NHCH_2), 6.45 (br s, NH_2), 7.27 (m, *Ph*), 7.85 (t, $^3J = 5.7$ Hz, N*H*CH$_2$), 12.20 (very br s, NH) ppm; IR (nujol): $\bar{\nu} = 3200$–3350 (NH, NH_2), 1640, 1630 (2C=O) cm^{-1}.

Cyclopenta[g]pyrido[2,1-b][1,3,5]thiadiazines (**7**). *General Procedure*
To 0.5 g thiolate **4** (1.79 mmol) and 1.8 mmol of the corresponding primary amine suspended in 10–12 cm^3 *Et*OH, 2 cm^3 37% aqueous HCHO (27 mmol) were added. The mixture was heated to reflux under vigorous stirring, and a crystalline solid started to precipitate from the formed solution within 1–2 min. The mixture was stirred for 5 h at 25°C and left to stand overnight. Solid product was filtered off and washed twice with *Et*OH to give the corresponding thiadiazines **7a**–**7d** as colorless crystals.

6-Oxo-3-phenyl-3,4,6,7,8,9-2H-cyclopenta[g]pyrido[2,1-b]-[1,3,5]thiadiazine-10-carbonitrile (**7a**, $C_{17}H_{15}N_3OS$)
Yield 90%; mp 209–211°C (dec, *DMF*:*Et*OH = 1:4); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 1.94$ (m, C(8)H_2), 2.65 (br t, $^3J = 7.3$ Hz, C(7)H_2), 2.78 (br t, $^3J = 7.5$ Hz, C(9)H_2), 5.56, 5.77 (both br s, C(2)H_2NC(4)H_2), 6.91–7.34 (m, *Ph*) ppm; IR (nujol): $\bar{\nu} = 2207$ (C≡N), 1630 (C=O) cm^{-1}.

3-(4-Methylphenyl)-6-oxo-3,4,6,7,8,9-2H-cyclopenta[g]-pyrido[2,1-b][1,3,5]thiadiazine-10-carbonitrile
(**7b**, $C_{18}H_{17}N_3OS$)
Yield 88%; mp 223–225°C (dec, *DMF*:acetone = 1:4); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.07$ (m, C(8)H_2), 2.27 (s, Ar–CH_3), 2.73 (br t, $^3J = 7.3$ Hz, C(7)H_2), 2.84 (br t, $^3J =$ 7.5 Hz, C(9)H_2), 5.48, 5.67 (both br s, C(2)H_2NC(4)H_2), 7.03 (dd, $^3J = 8.6$ Hz, Ar) ppm; IR (nujol): $\bar{\nu} = 2205$ (C≡N), 1620 (C=O) cm^{-1}.

3-(4-Fluorophenyl)-6-oxo-3,4,6,7,8,9-2H-cyclopenta[g]-pyrido[2,1-b][1,3,5]thiadiazine-10-carbonitrile
(**7c**, $C_{17}H_{14}FN_3OS$)
Yield 82%; mp 215–217°C (dec, *DMF*:*Et*OH = 1:3); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.02$ (m, C(8)H_2), 2.70 (br t, $^3J = 7.4$ Hz, C(7)H_2), 2.82 (br t, $^3J = 7.6$ Hz, C(9)H_2), 5.43, 5.63 (both br s, C(2)H_2NC(4)H_2), 7.00 (m, 4-FC_6H_4) ppm; IR (nujol): $\bar{\nu} = 2200$ (C≡N), 1635 (C=O) cm^{-1}.

3-(4-Chlorophenyl)-6-oxo-3,4,6,7,8,9-2H-cyclopenta[g]-pyrido[2,1-b][1,3,5]thiadiazine-10-carbonitrile
(**7d**, $C_{17}H_{14}ClN_3OS$)
Yield 81%; mp 225–227°C (dec, acetone); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 2.02$ (m, C(8)H_2), 2.70 (br t, $^3J = 7.3$ Hz, C(7)H_2), 2.81 (br t, $^3J = 7.4$ Hz, C(9)H_2), 5.47, 5.66 (both br s, C(2)H_2NC(4)H_2), 7.13 (dd, $^3J = 9.0$ Hz, *Ar*) ppm; IR (nujol): $\bar{\nu} = 2205$ (C≡N), 1635 (C=O) cm^{-1}.

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