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# 4-(10-METHYL-10H-PHENOTHIAZIN-3-YL)-1,4-DIHYDROPYRIDINES, 4,5-DIHYDROINDENO[1,2-*b*]- AND 5,5-DIOXO-4,5-DIHYDROBENZO-THIENO[3,2-*b*]PYRIDINES

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*Different modifications of the Hantzsch synthesis using 10-methyl-10H-phenothiazine-3-carbaldehyde gave 4-(10-methyl-10H-phenothiazin-3-yl)-substituted 1,4-dihydropyridine-3,5-di-, 5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridine-, and 5,5-dioxo-4,5-dihydro-1H-5$\lambda^6$-benzo[4,5]thieno[3,2-b]pyridine-3-carboxylic esters.*

**Keywords:** 10-methyl-10H-phenothiazin-3-carbaldehyde, 1,4-dihydropyridine, Hantzsch synthesis, 4-(10-methyl-10H-phenothiazin-3-yl)-5-oxo-1H-4,5-dihydroindeno[1,2-*b*]pyridine.

Highly effective coronary dilators [1, 2] and hypotensive agents [3] have already been discovered amongst 4-aryl- and 4-hetaryl-1,4-dihydropyridines (1,4-DHP) but this has not diminished the synthesis of novel 1,4-DHP's with the aim of finding compounds having an altered profile of pharmacological properties. It is known that the 1,4-DHP structure can be regarded as a pharmacophoric group or "special structure" and the variation of the substituent in the DHP ring might be expected to give a selective action of the 1,4-DHP on various cell membrane receptors [4].

The antioxidant activity of 1,4-DHP has been investigated [5, 6] and its correlation with pharmacological properties discussed [7, 8]. It was found that the exchange of an *o*-nitrophenyl group at position 4 of the 1,4-DHP for a polycyclic heterocyclic substituents (xanthone, azaxanthen-9-one, thioxanthen-9-one) had a marked effect on inotropic and vasodilator activity [9, 10]. 1,4-DHP and 4,5-dihydro-indenopyridines containing lipophilic and bulky substituents show inhibitory activity on glutathione-S-transferase [11].

At the same time, phenothiazine derivatives can possess high antioxidant, antiradical, neuroprotective, and antitumor activity [12, 13]. In recent years phenothiazine derivatives have been investigated as neuroprotectors of nerve cells in Alzheimer [14] and Creutzfeld-Jakob deseases [15]. In combination this encouraged us to synthesize 1,4-DHP derivatives having the two pharmacotropic groups (1,4-DHP and phenothiazine) in the same molecule.

To prepare the novel series of monocyclic 1,4-DHP **2**, 5-oxo-4H-dihydroindeno[1,2-*b*]pyridines **5**, and also 5,5-dioxo-4,5-dihydrobenzothieno[3,2-*b*]pyridines **8** we have employed different modifications of the Hantzsch synthesis using 10-methyl-10H-phenothiazine-3-carbaldehide **1** as the aldehyde component. Hence the 1,4-DHP **2b** was prepared in 42% yield by refluxing the aldehyde **1** with acetoacetic ester and ammonia in ethanol (Scheme 1, method A). The corresponding dimethyl ester of the 1,4-DHP-3,4-dicarboxylic acid **2a** was

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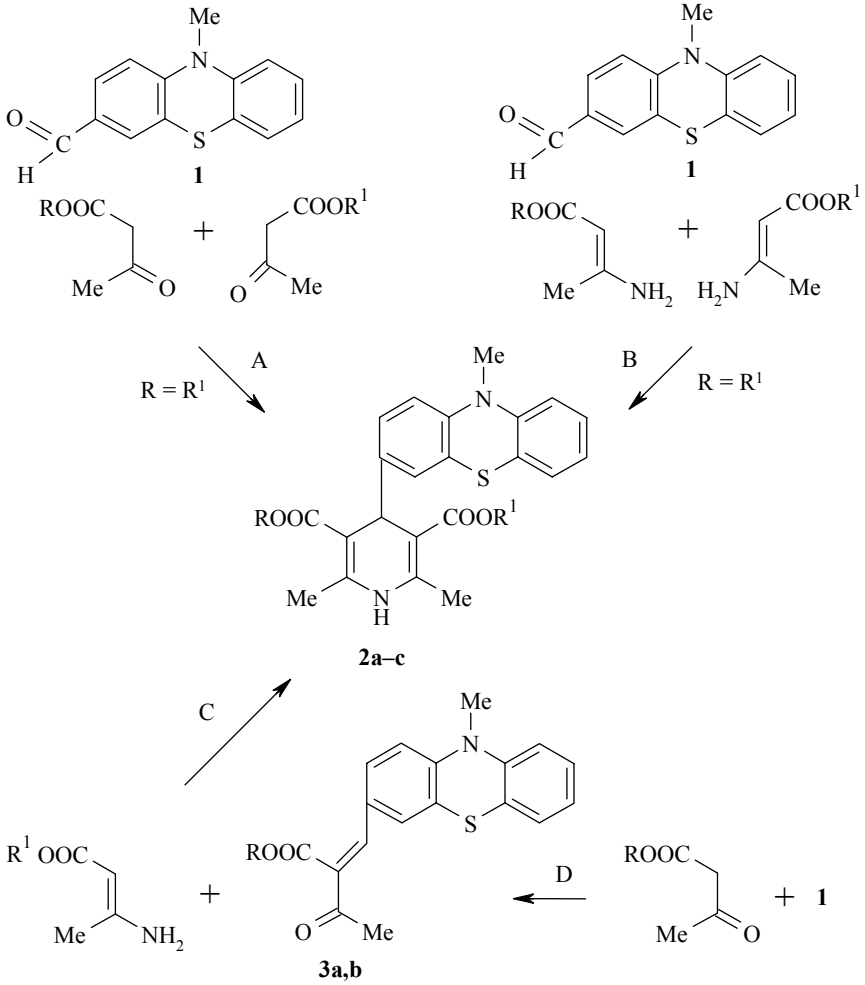
obtained under the above conditions but in 37% yield. With the aim of increasing the yield of the dimethyl ester **2a** we carried out the condensation of phenothiazine **1** with methyl β-aminocrotonate by refluxing in ethanol in the presence of glacial acetic acid (Scheme 1, method B). The best method for preparing **2a** and also the unsymmetrically 3,5-disubstituted 1,4-DHP **2c** proved to be a two stage synthesis (Scheme 1, method C) by initial synthesis of the 2-(10-methyl-10H-phenothiazin-3-ylmethylene)acetoacetic acid esters **3a,b** and subsequent cyclization with methyl β-aminocrotonate.

Sheme 1




A: $NH_4OH$, EtOH, t°; B: EtOH/AcOH, t°; C: EtOH/AcOH, t°; D: $C_6H_6$, piperidine /AcOH, t°;
**2a** R = $R^1$ = Me; **b** R = $R^1$ = Et; **c** R = Me, $R^1$ = Et; **3 a** R = Me, **b** R = Et

The corresponding ylidene derivatives **3a,b** were prepared by refluxing acetoacetic acid esters with the 10-methyl-10H-phenothiazine-3-carbaldehyde **1** in benzene in the presence of piperidine acetate with azeotropic distillation of water [16].

We have previously shown that 5-oxo-4,5-dihydroindeno[1,2-*b*]pyridines [17] and 1,4-dihydro-benzothieno[3,2-*b*]pyridine 5,5-dioxides [18] which contain aryl substituents at position 4 have high coronary dilator and antioxidant activity [19-21]. 5-Oxo-4,5-dihydroindeno[1,2-*b*]pyridines with heterocyclic substituents [3-pyridyl-, 4-(3-phenylpyrazolyl)-] at position 4 shown marked antitumor activity [22].

TABLE 1. Physicochemical Characteristics of Compounds **2-8**

| Compound | Empirical formula | Found, % / Calculated, % | | | | mp, °C* | Yield, % |
|---|---|---|---|---|---|---|---|
| | | C | H | N | S | | |
| **2a** | $C_{24}H_{24}N_2O_4S$ | 65.6 / 66.0 | 5.6 / 5.5 | 6.3 / 6.4 | 7.0 / 7.4 | 175-177 | 37 (A), 45 (B), 70 (C) |
| **2b** | $C_{26}H_{28}N_2O_4S$ | 67.0 / 67.2 | 6.1 / 6.1 | 6.0 / 6.0 | 6.6 / 6.9 | 164 | 42 (A) |
| **2c** | $C_{25}H_{26}N_2O_4S$ | 66.3 / 66.6 | 5.8 / 5.8 | 6.2 / 6.2 | 6.9 / 7.1 | 169 | 65 (C) |
| **3a** | $C_{19}H_{17}NO_3S$ | 67.5 / 67.2 | 5.0 / 5.1 | 4.1 / 4.1 | 9.0 / 9.5 | 125-127 | 81 |
| **3b** | $C_{20}H_{19}NO_3S$ | 67.7 / 68.0 | 5.5 / 5.4 | 4.1 / 4.0 | 8.7 / 9.1 | 92-97 | 73 |
| **4** | $C_{23}H_{15}NO_2S$ | 74.8 / 74.8 | 3.9 / 4.1 | 3.6 / 3.8 | 8.7 / 8.7 | 226 | 81 |
| **5a** | $C_{28}H_{22}N_2O_3S$ | 71.8 / 72.1 | 4.7 / 4.8 | 5.8 / 6.0 | 6.9 / 6.9 | 255 | 69 |
| **5b** | $C_{29}H_{24}N_2O_2S_2$ | 70.4 / 70.1 | 4.5 / 4.9 | 5.2 / 5.6 | 12.4 / 12.9 | 180-183 | 70 |
| **6a** | $C_{28}H_{20}N_2O_3S$ | 71.4 / 72.4 | 4.2 / 4.3 | 6.2 / 6.0 | 6.5 / 6.9 | 282 | 75 |
| **6b** | $C_{29}H_{22}N_2O_2S_2$ | 69.9 / 70.4 | 4.6 / 4.5 | 5.6 / 5.7 | 12.7 / 13.0 | 173-175 | 66 |
| **7** | $C_{22}H_{15}NO_3S_2$ | 65.2 / 65.2 | 3.5 / 3.7 | 3.5 / 3.5 | 15.5 / 15.8 | 252-254 | 84 |
| **8a** | $C_{27}H_{22}N_2O_4S_2$ | 63.7 / 64.5 | 4.5 / 4.4 | 5.1 / 5.6 | 12.1 / 12.8 | 200-204 | 56 |
| **8b** | $C_{28}H_{24}N_2O_4S_2$ | 64.7 / 65.1 | 4.6 / 4.7 | 5.2 / 5.4 | 12.3 / 12.4 | 172-175 | 69 |

* Solvents for crystallization: methanol (compound **2a**), aqueous methanol (**2b** and **2c**), ethanol (**3a,b**), acetic acid (**4, 5a,b**), mixture of ethanol and acetic acid (5 : 1) (**6a**).

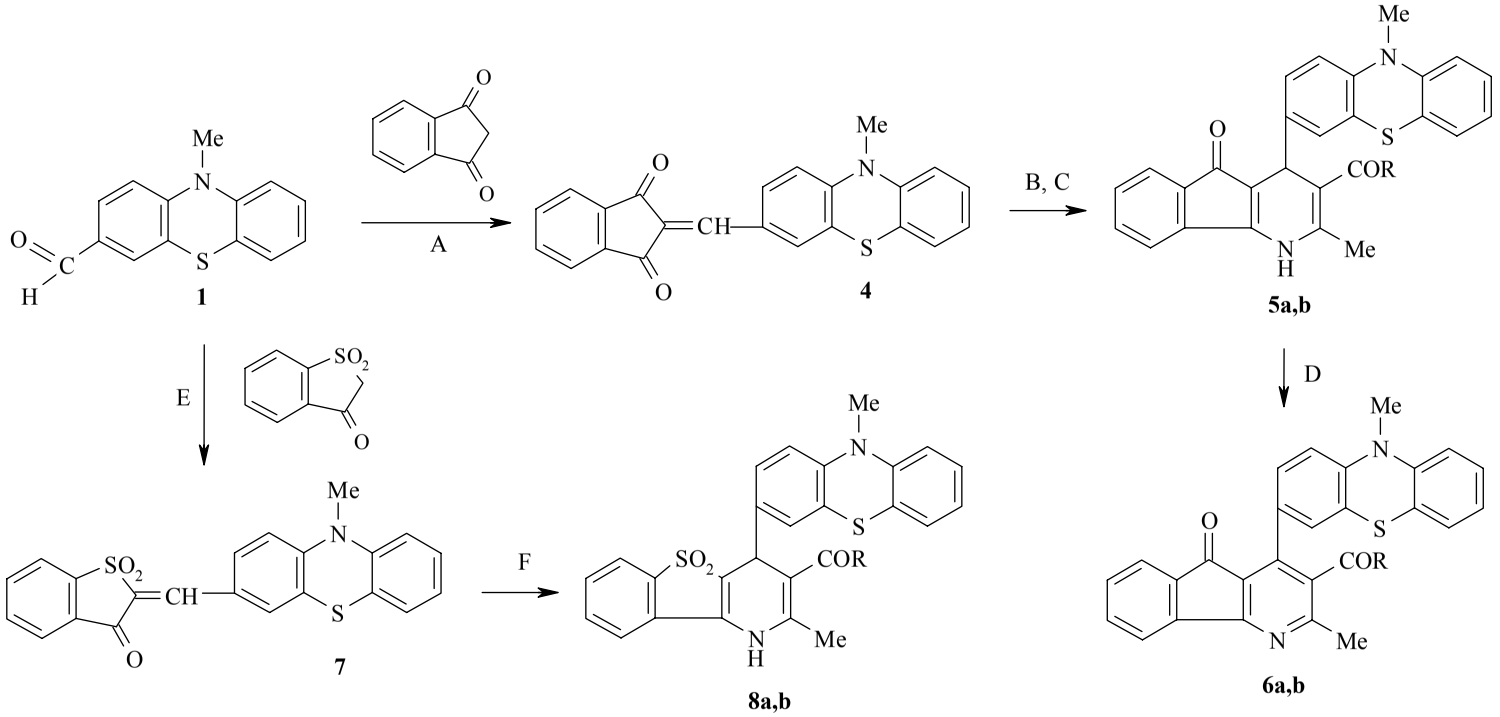
The esters of 5-oxo-1H-4,5-dihydroindeno[1,2-*b*]pyridine-3-carboxylic and thiocarboxylic acids **5a,b** were prepared by condensation of 2-(10-methyl-10H-phenothiazin-3-ylmethylene)indane-1,3-dione (**4**) with methyl β-aminocrotonate and the S-ethyl ester of acetothioacetic acid in the presence of ammonium acetate by analogy with a previously reported method [23] (Scheme 2). In turn, the ylidene derivative of 1,3-indanedione **4** was synthesized by refluxing 10-methyl-10H-phenothiazine-3-carbaldehyde with 1,3-indanedione in acetic acid using piperidine acetate as catalyst.

The 5-oxo-4H-1,4-dihydroindeno[1,2-*b*]pyridines were oxidized to the corresponding pyridines **6a,b** using sodium nitrite in acetic acid.

The 2-methyl-4-(10-methyl-10H-phenothiazin-3-yl)-5,5-dioxo-4,5-dihydro-1H-5$\lambda^6$-benzo[4,5]thieno[3,2-*b*]-pyridine-3-carboxylic acid esters **8a,b** were synthesized by cyclocondensation of the 2-(10-methyl-10H-phenothiazin-3-ylmethylene) derivative of benzo[*b*]thiophen-3(2H)-one 1,1-dioxide **7** with β-aminocrotonates in glacial acetic acid. In turn, the ylidene derivative of the 1,1-dioxide **7** was prepared in high yield by condensation of the 10-methyl-10H-phenothiazine-3-carbaldehyde **1** with dioxide **7** in glacial acetic acid in the presence of piperidine acetate as catalyst.

The structure of the synthesized 10-methyl-10H-phenothiazin-3-yl derivatives of the monocyclic and polycyclic 1,4-DHP **2, 5** and **8** were established from their spectroscopic characteristics (Tables 2 and 3).

Sheme 2




A: AcOH, t°, piperidine; B: $MeC(NH_2)=CHCOOMe$, AcOH, t°; C: $MeCOCH_2COSEt$, AcOH, $NH_4OAc$, t°; D: $NaNO_2$, AcOH, 60°C;
E: AcOH, t°, piperidine; F: $MeC(NH_2)=CHCOR$ (R = OMe, OEt); AcOH; **5,6 a** R = OMe, **b** R = SEt; **8 a** R = OMe, **b** R = SEt

TABLE 2. Spectroscopic Characteristics of Compounds **2-8**

| Compound | IR spectrum, ν, $cm^{-1}$ | UV spectrum, $\lambda_{max}$, nm (log ε) |
|---|---|---|
| **2a** | 1600, 1630, 1665, 1710, 3365 | 207 (4.58), 233 sh. (4.47), 255 (4.55), 339 (3.94) |
| **2b** | 1600, 1630, 1650, 1690, 3340 | 207 (4.58), 233 sh. (4.48), 255 (4.57), 339 (3.96) |
| **2c** | 1610, 1650, 1695, 3340 | 207 (4.60), 233 sh. (4.51), 255 (4.57), 339 (3.97) |
| **3a** | 1600, 1620, 1650, 1680, 1720 | 245 (4.33), 306 (4.36), 413 (4.11) |
| **3b** | 1600, 1620, 1645, 1680, 1720 | 246 (4.33), 305 (4.34), 412 (4.09) |
| **4** | 1620, 1650, 1680, 1720 | 250 (4.45), 267 sh. (4.25), 331 (4.18), 371 (4.08), 505 (4.29) |
| **5a** | 1610, 1640, 1670, 1710, 3180, 3260 | 233 (4.54), 256 (4.73), 303 (4.11), 473 (3. 48) |
| **5b** | 1600, 1630, 1645, 1670, 3160, 3240 | 233 sh. (4.53), 256 (4.79), 305 (4.24), 490 (3.70) |
| **6a** | 1610, 1710, 1730 | — |
| **6b** | 1610, 1640, 1675, 1710 | — |
| **7** | — | 210 (4.52), 255 sh. (4.11), 328 (3.61), 375 sh. (3.48), 520 (4.25) |
| **8a** | — | 234 sh. (4.25), 258 (4.81), 290 sh. (3.10), 380 sh. (3.50) |
| **8b** | — | 230 sh. (4.20), 259 (4.75), 288 sh. (3.20), 380 sh. (3.62) |

TABLE 3. $^1$H NMR Spectra of Compounds **2-8**

| Compound | Chemical shifts, δ, ppm (SSCS, *J*, Hz) (DMSO-$d_6$) |
|---|---|
| **2a** | 2.18 (6H, s, 2,6-$CH_3$), 3.18 (3H, s, $NCH_3$), 3.47 (6H, s, 3,5-$CH_3$), 4,71 (1H, s, 4-CH), 6.7-7.2 (7H, m, arom.), 8.76 (1H, s, NH) |
| **2b** | 1.11 (6H, t, *J* = 7.5, 3,5-$CH_3$), 2.22 (6H, s, 2,6-$CH_3$), 3.29 (3H, s, $NCH_3$), 3.96 (4H, q, *J* = 7.5, 3,5-$OCH_2$), 4.37 (1H, s, 4-CH), 6.7-7.2 (7H, m, arom.), 8.73 (1H, s, NH) |
| **2c** | 1.11 (3H, t, *J* = 7.5, 3-$CH_3$), 2.20 (6H, s, 2,6-$CH_3$), 3.20 (3H, s, $NCH_3$), 3.47 (3H, s, 5-$OCH_3$), 3.96 (2H, q, *J* = 7.5, 3-$OCH_2$), 4.71 (1H, s, 4-CH), 6.7-7.6 (7H, m, arom.), 8.76 (1H, s, NH) |
| **3a** | 2.40 (3H, s, $COCH_3$), 3.36 (3H, s, $NCH_3$), 3.87 (3H, s, $COOCH_3$), 6.9-7.4 (7H, m, arom.), 7.64 (1H, s, CH=) |
| **3b** | 1.20 (3H, t, *J* = 7.5, $OCH_2C\underline{H}_3$), 2.33 (3H, s, $CH_3$), 3.24 (3H, s, $NCH_3$), 4.20 (2H, q, *J* = 7.5, $OCH_2$), 6.9-7.4 (7H, m, arom.), 7.56 (1H, s, CH=) |
| **4** | 3.33 (3H, s, $NCH_3$), 6.9-8.5 (12H, m, arom. + CH=) |
| **5a** | 2.45 (3H, s, 2-$CH_3$), 3.27 (3H, s, $NCH_3$), 3.44 (3H, s, $COOCH_3$), 4.62 (1H, s, 4-CH), 6.7-7.5 (11H, m, arom.), 10.04 (1H, s, NH) |
| **5b** | 1.09 (3H, t, *J* = 7.8, $SCH_2C\underline{H}_3$), 2.44 (3H, s, 2-$CH_3$), 2.73 (2H, q, *J* = 7.8, $SCH_2$), 3.29 (3H, s, $NCH_3$), 4.86 (1H, s, 4-CH), 6.7-7.6 (11H, m, arom.), 10.24 (1H, s, NH) |
| **6a** | 2.60 (3H, s, 2-$CH_3$), 3.60 (3H, s, $OCH_3$), 3.84 (3H, s, $NCH_3$), 7.27-8.0 (11H, m, arom.) |
| **6b** | 0.87 (3H, t, *J* = 7.8, $SCH_2C\underline{H}_3$), 2.60 (3H, s, 2-$CH_3$), 2.76 (2H, q, *J* = 7.8, $SCH_2$), 3.82 (3H, s, $NCH_3$), 7.2-8.0 (11H, m, arom.) |
| **7** | 3.45 (3H, s, $NCH_3$), 7.06-7.27 (5H, m, arom. + CH=), 8.02-8.30 (7H, m, phenothiazine protons) |
| **8a** | 2.11 (3H, s, 2-$CH_3$), 3.16 (3H, s, $OCH_3$), 3.22 (3H, s, $NCH_3$), 4.61 (1H, s, 4-CH), 6.67-7.89 (11H, m, arom. protons + phenothiazine protons), 9.93 (1H, s, NH) |
| **8b** | 1.08 (3H, t, *J* = 7.0, $CH_3$), 2.34 (3H, s, 2-$CH_3$), 3.21 (3H, s, $OCH_3$), 3.28 (3H, s, $NCH_3$), 3.96 (2H, q, *J* = 7.0, $OCH_2$), 6.90-8.27 (11H, m, arom. protons + phenothiazine protons), 9.88 (1H, s, NH) |

Using the method given in [11] the ability of the series of compounds synthesized to inhibit the *in vitro* activity of glutathione-S-transferase was tested. It was found that the polycyclic indeno-1,4-DHPs **5** showed the clearest inhibitory activity when compared with the monocyclic 1,4-DHPs **2**. At a concentration of $5\times10^{-5}$ M compound **5a** inhibits this activity by 56% and the corresponding sulfur compound **5b** by 98% at this concentration (at a concentration an order lower, i.e. $5\times10^{-6}$ M by 74%). Corresponding to compound **5b** the pyridine derivative **6b** shows 92% inhibition at a concentration of $5\times10^{-5}$ M. At the same concentration the starting compound **4** also inhibits by 67-70%. Hence we propose that, the ability of the investigated compounds to inhibit the *in vitro* activity of glutathione-S-transferase requires a phenothiazine component in the molecule conjugated with a 2-methyleneindanedione group since the starting N-methylphenothiazine shows an inhibition of only 29% at a concentration of $5\times10^{-5}$ M.

However, the fact that **5b** is significantly more effective than **5a** shows that the effect of the remaining dihydropyridine part of the molecule must be taken into account.

## EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (in nujol), UV spectra were taken on a Specord M40 Carl Zeiss Jena spectrometer in ethanol. $^1$H NMR spectra were recorded on Bruker WH 90/DC (90 MHz) and Varian Mercury (200 MHz) instruments with TMS as internal standard. Monitoring of the course of the reaction and the purity of the synthesized compounds was carried out using TLC on Merck Silicagel 60 $F_{254}$ UV-254 plates with chloroform–hexane–acetone (9 : 7 : 1) as eluent. The basic characteristics of the compounds synthesized are given in Tables 1 and 2.

**10-Methyl-10H-phenothiazine** was prepared by a known method [24] from phenothiazine *via* alkylation with methyl iodide in hexametapol (HMPA).

**10-Methyl-10H-phenothiazine-3-carbaldehyde (1)** was prepared by Vilsmeier-Haack formylation of 10-methyl-10H-phenothiazine [25].

**3,5-Dimethoxycarbonyl-2,6-dimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-1,4-dihydropyridine (2a)**. Method B. A mixture of compound **1** (2.41 g, 10 mmol), methyl β-aminocrotonate (3.45 g, 30 mmol), ethanol (70 ml), and glacial acetic acid (2 ml) was refluxed for 8 h. Solvent was distilled of in vacuo and the residue was triturated with water (100 ml). The precipitated material was filtered off, dried, dissolved in acetone (20 ml), and passed thorough a silica gel column (l = 40 cm, *d* = 2 cm) using chloroform–hexane–acetone–ethanol (9 : 7: 2 : 1) as eluent. The fraction with $R_f$ 0.56 was collected. After removal of solvent the residue was crystallized from methanol to give the dihydropyridine **2a**. Yield 1.95 g (45%), mp 173-175°C.

**3,5-Diethoxycarbonyl-2,6-dimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-1,4-dihydropyridine (2b)**. A. A mixture of compound **1** (2.41 g, 10 mmol), acetoacetic ester (2.60 g, 20 mmol) and 25% aqueous ammonia solution (5 ml) in ethanol (100 ml) was refluxed for 8 h. Solvent was removed in vacuo and the residue was chromatographed as described before. The fraction with $R_f$ 0.66 was collected. After removal of solvent the residue was crystallized from aqueous methanol (~ 70%) to give the colorless dihydropyridine **2b.** Yield 1.95 g (42%), mp 164°C.

**3,5-Dimethoxycarbonyl-2,6-dimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-1,4-dihydropyridine (2a)** was prepared using method A from aldehyde **1** and methyl acetoacetate in 37% yield.

**5-Ethoxycarbonyl-3-methoxycarbonyl-2,6-dimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-1,4-dihydropyridine (2c)**. C. Compound **3** (3.53 g, 10 mmol) and methyl β-aminocrotonate (1.7 g, 15 mmol) were refluxed for 7 h in a mixture of ethanol (70 ml) and acetic acid (30 ml). Solvent was evaporated in vacuo and the oil produced was chromatographed as described before. The fraction with $R_f$ 0.62 was collected. The colorless substance was crystallized from aqueous methanol to give the dihydropyridine **2c.** Yield 3 g (65%), mp 169°C.

**3,5-Dimethoxycarbonyl-2,6-dimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-1,4-dihydropyridine (2a)** was prepared similarly from methyl 2-(10-methyl-10H-phenothiazin-3-ylmethylene)acetoacetate **3a** (3.39 g, 10 mmol). Yield 3 g (70%).

**Synthesis of 2-(10-Methyl-10H-phenothiazin-3-ylmethylene)acetoacetic acid esters (3a,b) (General Method).** Aldehyde **1** (2.41 g, 10 mmol) and the corresponding ester (10 mmol) in dry benzene (150 ml) with piperidine (0.2 ml) and glacial acetic acid (0.2 ml) were refluxed in a Dean and Stark apparatus for 3 h. The benzene solution was washed with water and dried with anhydrous sodium sulfate. Solvent was evaporated in vacuo and the residue was crystallized from ethanol to give orange colored crystals of **3a** or **3b.**

**2-(10-Methyl-10H-phenothiazin-3-ylmethylene)indane-1,3-dione (4)**. Indane-1,3-dione (1.46 g, 10 mmol) was dissolved with heating in glacial acetic acid (60 ml). Aldehyde **1** (2.41 g, 10 mmol) and piperidine (0.1 ml) were added to the hot solution and the product was refluxed for 10 min. After cooling, the dark-violet crystals formed were filtered off and crystallized from AcOH to give the dihydroindeno[1,2-*b*]-pyridine **5a.** Yield 0.96 g (69%), mp 255°C.

**3-(Ethylthio)carbonyl-2-methyl-4-(10-methyl-10H-phenothiazin-3-yl)-5-oxo-1H-4,5-dihydroindeno[1,2-*b*]- pyridine (5b)**. Compound **4** (1.1 g, 3 mmol) was dissolved in glacial AcOH (50 ml). S-ethyl acetothioacetate (1.46 g, 10 mmol) and ammonium acetate (2.5 g) were added and the mixture was refluxed for 10 min. Solvent was distilled off in vacuo to half volume. After cooling, the red crystals were filtered off and crystallized from AcOH to give the dihydroindeno[1,2-*a*]pyridine **5b**. Yield 1.0 g (70%), mp 180-183°C.

**Synthesis of 3-Substituted 2-Methyl-4-(10-methyl-10H-phenothiazin-3-yl)-5-oxoindeno[1,2-*b*]pyridines 6a,b (General Method)**. The corresponding dihydroindeno[1,2-*b*]pyridine **5a,b** (2 mmol) was dissolved in glacial AcOH (10 ml), sodium nitrite (1 g) was added portionwise, and the mixture was heated to 80°C over 10 min. After cooling, the product was diluted with water (20 ml) and the yellow crystalline precipitate was filtered off and recrystallized from a mixture of ethanol and AcOH (5 : 1 by volume) to give the pyridines **6a,b** as pale-yellow colored crystals.

**2-(10-Methyl-10H-phenothiazin-3-ylmethyl)-3-oxo-1,2-dihydro-1λ$^6$-benzo[b]thiophene 1,1-dioxide (7)**. The aldehyde **1** (1.2 g, 5 mmol) and benzo[*b*]thiophen-3(2H)-one 1,1-dioxide (0.95 g, 5.2 mmol) were refluxed in glacial AcOH (50 ml) in the presence of piperidine as catalyst (0.1 ml) for 30 min. After cooling the dark-violet crystals were filtered off and crystallized repeatedly from AcOH to give compound **7.** Yield 1.7 g (84%), mp 252-254°C.

**3-Methoxycarbonyl-2-methyl-4-(10-methyl-10H-phenothiazin-3-yl)-4,5-dihydro-1H-5λ$^6$-benzo[4,5]thieno- [3,2-*b*]pyridine 5,5-dioxide (8a)**. Compound **7** (0.81 g, 2 mmol) was dissolved with heating in glacial AcOH (30 ml) and taken to reflux. Methyl β-aminocrotonate (0.3 g, 2.5 mmol) was added and the solution was refluxed for 30 min. After cooling and addition of water the yellow crystals were filtered off and recrystallized from a mixture of ethanol and AcOH to give the methyl ester **8a.** Yield 0.56 g (56%), mp 200-254°C.

**3-Ethoxycarbonyl-2-methyl-4-(10-methyl-10H-phenothiazin-3-yl)-4,5-dihydro-1H-5λ$^6$-benzo[4,5]thieno-[3,2-*b*]pyridine 5,5-dioxide (8b)** was prepared similarly from the benzo[*b*]thiophen-3-one **7** and ethyl β-aminocrotonate in 69% yield. Mp 172-174°C.

## REFERENCES


1. R. M. Robertson and D. Robertson, in: J. G. Hardman, L. E. Limbird, P. M. Molinoff, R. W. Ruddon, A. Goodman and H. Gilman, (editors), *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, , McGraw-Hill Ryerson Ltd, Inc., (1996), p. 759.
2. R. Peri, S. Padmanabhan, A. Rutledge, S. Singhs, and D. I. Triggle, *J. Med. Chem.*, 2906 (2000).

3. V. I. Parinov, A. G. Odinec, A. P. Gilev, G. Duburs, D. H. Muceniece, J. J. Ozols, V. D. Shatz, M. P. Gavars, and B. A. Vigante, *Arzneim. –Forsch.*, **35**, 808 (1985).
4. D. J. Triggle, *Current Pharmaceutical Design*, **12**, 443 (2006).
5. G. Tirzitis, I. Kirule, and G. Duburs, *Fat. Sci. Technol.*, **10**, 411 (1988).
6. G. Tirzitis D. Tirzite, and Z. Hyvonen, *Czech. J. Food Sci*, **19**, 81 (2000).
7. K. Yao, Y. Ina, K. Nagashima, K. Ohmori, and T. Ohno, *Biol. Pharm. Bull.*, **23**, 766 (2000).
8. M. Inoye, T. Mio, and K. Sumino, *Eur. J. Clin. Pharmacol.*, **56**, 35 (2000).
9. A. Rampa, A. Chiarini, A. Bisi, R. Budriesi, and P. Valenti, *Arzneim.–Forsch.*, **41**, 707 (1991).
10. P. Valenti, A. Chiarini, F. Gasperi, and R. Budriesi, *Arzneim –Forsch.*, **40**, 122 (1990).
11. D. Tirzite, G. Tirzitis, B. Vigante, and G. Duburs, *Biochem. Pharmacology*, **46**, 773 (1993).
12. K. Fukuzumi, N. Ikeda, and M. Egawa, *J. Am. Oil Chem. Soc.*, **53**, 623 (1976).
13. S. Nagy, G. Argyclan, J. Molnar, M. Kawase, and N. Motohashi, *Anticancer Res.*, **16**, 1916 (1996).
14. B. Moosman, T. Skutella, K. Beyer, and C. Behl, *Biol. Chem.*, **382**, 1601 (2001).
15. C. Korth, B. May, F. E. Cohen, and S. B. Prusiner, *Proc. Natl. Acad. Sci. U. S.*, **98**, 9836 (2001).
16. M. Frigiero, A. Zaliani, C. Riva, G. Palmisano, T. Pilati, and C. A. Gandolfi, *Tetrahedron Lett.*, **29**, 6335 (1988).
17. B. A. Vigante, Ya. Ya. Ozols, and G. Ya. Dubur, *Izv. Akad. Nauk SSR, Ser. Khim.*, 707 (1980).
18. R. R. Dubure, B. A. Vigante, Ya. Ya. Ozols, G. Ya. Dubur, and G. I. Rozentale, *Khim. Geterotsikl. Soedin.*, 1563 (1986); [*Chem. Heterocycl. Comp.*, **22**, 1267 (1986)].
19. R. R. Dubure, R. O. Vitolina, J. J. Ozols, G. J. Duburs, A. A. Kimenis, and G. V. Zarins, USSR Inventor's certificate 1018396; *Chem. Abstr.*, **105**, 191950 (1986).
20. B. A. Vigante, Ya. Ya. Ozols (J. J. Ozols), G. O. Sileniece, A. A. Kimenis, and G. J. Dubur, USSR Inventor's certificate 794006; *Chem. Abstr.*, **95**, 704 (1981).
21. B. A. Vigante, J. J Ozols, R. O. Vitolina, H. O Sileniece, A. A. Kimenis, and G. J. Duburs, Ger. Offen 2909852; *Chem. Abstr.*, **94**, 15579 (1981).
22. E. A. Bisenieks, J. R. Uldrikis, G. J. Duburs, G. D. Tirzit, A. Z. Dauvarte, A. A. Zidermane, E. A. Ivanov, and T. V. Ponomareva, USSR Inventor's certificate 1050261; *Chem. Abstr.*, **124**, 333068 (1996).
23. B. A. Vigante, J. J. Ozols, and G. J. Duburs, USSR Inventor's certificate SU 1 198 067 (1985); *Chem. Abstr.*, **105**, 190979 (1986).
24. H. Normant, T. Cuvighy, J. Normant, and B. Angelo, *Bull. Soc. Chim. France*, **12**, 3446 (1965).
25. V. Farcasan, I. Oprean, and C. Bodea, *Rev. Roum. Chim.*, **15**, 1433 (1970).