

## Synthesis of Dialkyl 2-(Alkylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylates

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Dialkyl 2-(alkylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylates are prepared in a one-pot three-component reaction of alkyl isocyanide, dialkyl acetylenedicarboxylate, and  $\alpha$ -tropolone (=2-hydroxycyclohepta-2,4,6-trienone). The reaction proceeds smoothly at room temperature and under neutral conditions to afford tropolone derivatives in high yield.

**Introduction.** – Heterocycle-fused tropolones, an important class of compounds with varied pharmacological and biological properties have attracted great attention since the beginning of tropoid chemistry [1–4]. The cyclohepta[*b*]pyran ring system is the backbone of some natural products such as paulitine (*Fig.*), which displays several biological activities, and some derivatives of this system exhibit platelet anti-aggregating, HIV protease inhibition, anesthetic, histaminic response-reducing, antimalarial, anti-inflammatory, and analgesic activities [5–8]. Only a few methods have been reported for the construction of cyclohepta[*b*]pyran ring systems. In a first method, a cyclohepta[*e*][1,3,2]dioxaborin ring is formed by reaction of cycloheptanone with  $\text{Ac}_2\text{O}$  in presence of  $\text{BF}_3$ , and subsequent reaction with *Vilsmeier* reagent provides the cyclohepta[*b*]pyran system [6]. In a second method, reaction of 3-acetyltropolone with benzaldehydes yields 3-cinnamoyltropolones, which are cyclized to 2-arylcyclohepta[*b*]pyran-4,9-diones in presence of oxidizing reagents such as  $\text{SeO}_2$  [9], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [10],  $\text{HClO}_4$  [11],  $\text{Br}_2$  [12], and  $\text{I}_2/\text{DMSO}/\text{H}_2\text{SO}_4$  [13]. Also the reaction of chloro(phenyl)ketene with 2-(aminomethylidene)cycloheptanones, followed by dehydrochlorination of the primary adducts, yields 4-amino-6,7,8,9-tetrahydro-3-phenylcyclohepta[*b*]pyran-2(5*H*)-ones [14].

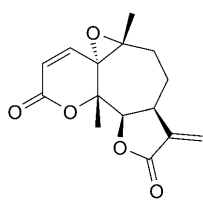
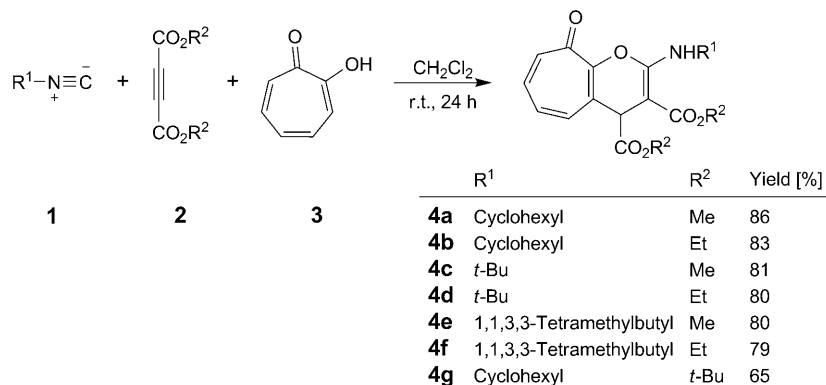


Figure. Molecular structure of paulitine (see text)

In continuation of our previous studies on the development of new routes to heterocyclic systems (see [15] and refs. cit. therein), we now report an efficient and facile synthetic route to dialkyl 2-(alkylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylates **4** using  $\alpha$ -tropolone (=2-hydroxycyclohepta-2,4,6-trienone; **3**), alkyl isocyanides **1**, and dialkyl acetylenedicarboxylates **2** without any catalyst (*Scheme 1*).

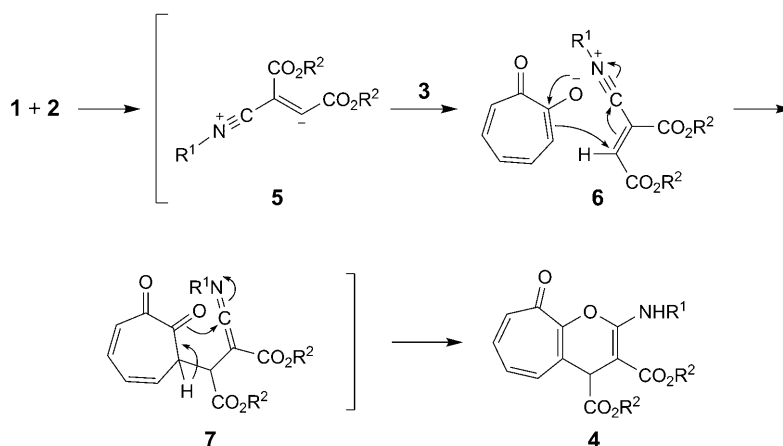
Scheme 1. Synthesis of Tropolone Derivatives **4** from Alkyl Isocyanide **1**, Dialkyl Acetylenedicarboxylate **2**, and Tropolone (**3**)



**Results and Discussion.** – The three-component reaction of alkyl isocyanide **1**, dialkyl acetylenedicarboxylate **2**, and **3** proceeded in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature and was completed after 24 h to afford dialkyl 2-(alkylamino)-4,9-dihydro-9-oxocyclohepta[*b*]pyran-3,4-dicarboxylates **4** in yields of 65–86% (*Scheme 1*).

The structures of the products **4a–4g** were deduced from their IR, <sup>1</sup>H- and <sup>13</sup>C-NMR, and MS data. For example, the mass spectrum of **4a** displayed the molecular-ion peak at 373 *m/z*, which is consistent with a 1:1:1 adduct of **1a**, **2a**, and **3**. The <sup>1</sup>H-NMR spectrum of **4a** exhibited a *multiplet* for the cyclohexyl substituent ( $\delta$ (H) 1.16–2.07), two *singlets* for two MeO groups ( $\delta$ (H) 3.63 and 3.68), a *multiplet* for (CH<sub>2</sub>)<sub>5</sub>CH–N ( $\delta$ (H) 3.99), a *singlet* for H–C(4) ( $\delta$ (H) 4.55) and two *multiplets* for three H-atoms of the tropone ring ( $\delta$ (H) 6.83–6.91 and  $\delta$ (H) 7.12–7.20), and a *doublet* ( $\delta$ (H) 7.06, <sup>3</sup>*J* = 11.2), as well as a broad *singlet* for NH ( $\delta$ (H) 8.26). The <sup>1</sup>H-decoupled <sup>13</sup>C-NMR spectrum of **4a** showed 20 distinct resonances, partial assignments of these resonances is given in the *Exper. Part*. The <sup>1</sup>H- and <sup>13</sup>C-NMR spectra of **4b–4g** are similar to those of **4a**, except for *N*-alkyl and esters moieties.

Although the mechanism of this reaction has not been established experimentally, a reasonable proposal is depicted in *Scheme 2*. On the basis of isocyanide chemistry [16], the zwitterionic intermediate **5** from reaction of alkyl isocyanide **1** and dialkyl acetylenedicarboxylate **2** is protonated by OH of **3**. Subsequent reaction of the nitrilium ion **6** with the deprotonated tropolone produces ketenimine **7**. This addition product may tautomerize and then cyclize, under the employed reaction conditions, to form tropolone derivatives **4**.

Scheme 2. Proposed Mechanism for the Formation of Tropolone Derivatives **4**

**Conclusions.** – We have developed a new and efficient synthetic method for the preparation of dialkyl 2-(alkylamino)-4,9-dihydro-9-oxocyclohepta[b]pyran derivatives. The present method has the advantage that the reaction is performed under neutral conditions with easily available starting materials to give high yields.

#### Experimental Part

*General.* Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland), and were used without further purification. Column chromatography (CC): Merck silica-gel powder. M.p.: Electrothermal 9100 apparatus; uncorrected. IR Spectra: Shimadzu IR-460 spectrometer; in KBr.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra ( $\text{CDCl}_3$  soln.): BRUKER DRX-250 AVANCE spectrometer at 250.0, and 62.9 MHz, resp. MS: Agilent-Technologies-(HP)-5973 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses: Heraeus CHN-O-Rapid analyzer.

*General Procedure for the Preparation of Compounds 4.* To a magnetically stirred soln. of tropolone (**3**, 1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 ml) was added a soln. of alkyl isocyanide **1** (1 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (2 ml). The mixture was stirred for 24 h. The solvent was evaporated, and the residue was purified by CC using petroleum ether/AcOEt mixtures.

*Dimethyl 2-(Cyclohexylamino)-4,9-dihydro-9-oxocyclohepta[b]pyran-3,4-dicarboxylate (4a).* Yield 320 mg (86%). Brown semisolid. IR: 3292 (NH), 2924, 1744, 1684, 1620, 1441, 1269, 1084.  $^1\text{H}$ -NMR: 1.16–2.07 (*m*, 5  $\text{CH}_2$  of cyclohexyl); 3.63 (*s*, MeO); 3.68 (*s*, MeO); 3.90–4.11 (*m*, N–CH); 4.55 (*s*, CH); 6.83–6.91 (*m*, 1 H of tropone); 7.06 (*d*,  $J = 11.2$ , 1 H of tropone); 7.12–7.20 (*m*, 2 H of tropone); 8.26 (*br. s*, NH).  $^{13}\text{C}$ -NMR: 24.40, 24.45, 25.47, 33.44, 33.62 (5  $\text{CH}_2$  of cyclohexyl); 45.52 (CH); 50.20 (CH–NH); 50.94, 52.73 (2 MeO); 70.22, 125.66, 130.34, 135.37, 135.97, 139.57, 154.67, 159.46 (C of alkene and tropone); 168.53, 172.32, 177.87 (3 C=O). EI-MS: 373 (2,  $M^+$ ), 314 (100,  $[M - \text{CO}_2\text{Me}]^+$ ), 232 (48,  $[314 - \text{C}_6\text{H}_{10}]^+$ ), 200 (14,  $[M + \text{H} - \text{CO}_2\text{Me} - \text{C}_6\text{H}_{10} - \text{MeO}]^+$ ), 172 (19,  $[200 - \text{CO}]^+$ ), 157 (9,  $[172 - \text{NH}_2]^+$ ). Anal. calc. for  $\text{C}_{20}\text{H}_{23}\text{NO}_6$  (373.40): C 64.33, H 6.21, N 3.75; found: C 64.26, H 6.13, N 3.68.

*Diethyl 2-(Cyclohexylamino)-4,9-dihydro-9-oxocyclohepta[b]pyran-3,4-dicarboxylate (4b).* Yield 330 mg (83%). Brown semisolid. IR: 3281 (NH), 2932, 1737, 1682, 1616, 1440, 1229, 1086.  $^1\text{H}$ -NMR: 1.15 (*t*,  $J = 7.0$ , Me); 1.22 (*t*,  $J = 7.2$ , Me); 1.23–2.10 (*m*, 5  $\text{CH}_2$  of cyclohexyl); 3.90–4.00 (*m*, N–CH); 3.99–4.20 (*m*, 2  $\text{CH}_2\text{O}$ ); 4.51 (*s*, CH); 6.80–6.92 (*m*, 1 H of tropone); 7.07 (*d*,  $J = 11.40$ , 1 H of tropone); 7.12–7.31 (*m*, 2 H of tropone); 8.25 (*br. s*, NH).  $^{13}\text{C}$ -NMR: 14.07, 14.56 (2 Me); 24.40, 24.42, 25.48, 33.45,

33.59 (5 CH<sub>2</sub> of cyclohexyl); 45.65 (CH); 50.11 (CH–NH); 59.36, 61.47 (2 CH<sub>2</sub>O); 70.34, 125.59, 130.16, 135.38, 135.95, 139.48, 154.58, 159.22 (C of alkene and tropone); 168.23, 172.00, 177.93 (3 C=O). EI-MS: 401 (1, *M*<sup>+</sup>), 328 (100, [*M* – CO<sub>2</sub>Et]<sup>+</sup>), 246 (46, [328 – C<sub>6</sub>H<sub>10</sub>]<sup>+</sup>), 218 (12, [246 – Et]<sup>+</sup>), 200 (12, [246 – EtO]<sup>+</sup>), 172 (15, [200 – CO]<sup>+</sup>), 157 (6, [172 – NH<sub>2</sub>]<sup>+</sup>). Anal. calc. for C<sub>22</sub>H<sub>27</sub>NO<sub>6</sub> (401.46): C 65.82, H 6.78, N 3.49; found: C 65.73, H 6.83, N 3.34.

*Dimethyl 2-(tert-Butylamino)-4,9-dihydro-9-oxocyclohepta[b]pyran-3,4-dicarboxylate (4c)*. Yield 280 mg (81%). Yellow powder. M.p. 115–117°. IR: 3314 (NH), 2954, 1731, 1676, 1616, 1430, 1166, 1081. <sup>1</sup>H-NMR: 1.51 (*s*, *t*-Bu); 3.65, 3.69 (2*s*, 2 MeO); 4.56 (*s*, CH); 6.83–6.94 (*m*, 1 H of tropone); 7.07 (*d*, *J* = 11.5, 1 H of tropone); 7.11–7.21 (*m*, 2 H of tropone); 8.51 (*br. s*, NH). <sup>13</sup>C-NMR: 29.95 (3 Me); 45.32 (CH); 51.01, 52.77 (2 MeO); 53.16 (C–NH); 70.70, 125.35, 130.35, 135.44, 135.91, 139.66, 154.67, 160.54 (C of alkene and tropone); 168.71, 172.38, 177.82 (3 C=O). EI-MS: 347 (2, *M*<sup>+</sup>), 288 (56, [*M* – CO<sub>2</sub>Me]<sup>+</sup>), 232 (100, [288 – Me<sub>2</sub>CCH<sub>2</sub>]<sup>+</sup>), 200 (17, [232 – MeO]<sup>+</sup>), 172 (23, [200 – CO]<sup>+</sup>), 157 (9, [172 – NH<sub>2</sub>]<sup>+</sup>). Anal. calc. for C<sub>18</sub>H<sub>21</sub>NO<sub>6</sub> (347.37): C 62.24, H 6.09, N 4.03; found: C 62.32, H 5.91, N 3.92.

*Diethyl 2-(tert-Butylamino)-4,9-dihydro-9-oxocyclohepta[b]pyran-3,4-dicarboxylate (4d)*. Yield 300 mg (80%). Yellow powder. M.p. 118–120°. IR: 3260 (NH), 2979, 1733, 1673, 1613, 1433, 1185, 1087. <sup>1</sup>H-NMR: 1.160 (*t*, *J* = 7.0, Me); 1.22 (*t*, <sup>3</sup>*J* = 7.2, Me); 1.48 (*s*, *t*-Bu); 4.01–4.20 (*m*, 2 CH<sub>2</sub>O); 4.51 (*s*, CH); 6.79–6.92 (*m*, 1 H of tropone); 7.06 (*d*, *J* = 11.6, 1 H of tropone); 7.11–7.18 (*m*, 2 H of tropone); 8.49 (*br. s*, NH). <sup>13</sup>C-NMR: 14.06, 14.55 (2 Me); 29.93 (3 Me); 45.47 (CH); 53.01 (C–NH); 59.41, 61.47 (2 CH<sub>2</sub>O); 70.82, 125.30, 130.17, 135.42, 135.88, 139.55, 154.59, 160.31 (C of alkene and tropone); 168.34, 172.04, 177.84 (3 C=O). EI-MS: 375 (1, *M*<sup>+</sup>), 302 (59, [*M* – CO<sub>2</sub>Et]<sup>+</sup>), 246 (100, [302 – Me<sub>2</sub>CCH<sub>2</sub>]<sup>+</sup>), 218 (10, [246 – Et]<sup>+</sup>), 200 (12, [246 – EtO]<sup>+</sup>), 172 (17, [200 – CO]<sup>+</sup>), 157 (6, [172 – NH<sub>2</sub>]<sup>+</sup>). Anal. calc. for C<sub>20</sub>H<sub>25</sub>NO<sub>6</sub> (375.42): C 63.99, H 6.71, N 3.73; found: C 64.12, H 6.83, N 3.61.

*Dimethyl 4,9-Dihydro-9-oxo-2-[(1,1,3,3-tetramethylbutyl)amino]cyclohepta[b]pyran-3,4-dicarboxylate (4e)*. Yield 330 g (80%). Yellow powder. M.p. 156–158°. IR: 3380 (NH), 2947, 1727, 1669, 1604, 1436, 1161, 1079. <sup>1</sup>H-NMR: 0.99 (*s*, Me<sub>3</sub>C); 1.56 (*s*, Me<sub>2</sub>C); 1.95 (*AB*, *J* = 15.6, CH<sub>2</sub>); 3.65, 3.70 (*s*, 2 MeO); 4.57 (*s*, CH); 6.83–6.95 (*m*, 1 H of tropone); 7.08 (*d*, *J* = 11.2, 1 H of tropone); 7.12–7.24 (*m*, 2 H of tropone); 8.57 (*br. s*, NH). <sup>13</sup>C-NMR: 30.65, 30.98 (2 Me); 31.41 (Me<sub>3</sub>C); 31.60 (C); 45.43 (CH); 50.97 (MeO); 52.20 (CH<sub>2</sub>); 52.71 (MeO); 56.63 (C–NH); 70.38, 125.40, 130.33, 135.42, 135.87, 139.68, 154.59, 160.42 (C of alkene and tropone); 168.74, 172.43, 177.74 (3 C=O). EI-MS: 401 (1, [*M* – 2]<sup>+</sup>), 344 (9, [*M* – CO<sub>2</sub>Me]<sup>+</sup>), 328 (100, [344 – Me]<sup>+</sup>), 246 (40, [344 – C<sub>7</sub>H<sub>14</sub>]<sup>+</sup>), 232 (31, [246 – Me]<sup>+</sup>), 200 (15, [232 – MeO]<sup>+</sup>), 172 (17, [200 – CO]<sup>+</sup>), 157 (8, [172 – NH<sub>2</sub>]<sup>+</sup>). Anal. calc. for C<sub>22</sub>H<sub>29</sub>NO<sub>6</sub> (403.48): C 65.49, H 7.24, N 3.47; found: C 65.38, H 7.32, N 3.58.

*Diethyl 4,9-Dihydro-9-oxo-2-[(1,1,3,3-tetramethylbutyl)amino]cyclohepta[b]pyran-3,4-dicarboxylate (4f)*. Yield 340 mg (79%). Yellow powder. M.p. 154–156°. IR: 3269 (NH), 2952, 1727, 1669, 1615, 1434, 1177, 1082. <sup>1</sup>H-NMR: 0.96 (*s*, Me<sub>3</sub>C); 1.160 (*t*, *J* = 7.0, Me); 1.23 (*t*, *J* = 7.0, Me); 1.53 (*s*, Me<sub>2</sub>C); 1.92 (*AB*, *J* = 14.2, CH<sub>2</sub>); 4.01–4.17 (*m*, 2 CH<sub>2</sub>O); 4.52 (*s*, CH); 6.80–6.92 (*m*, 1 H of tropone); 7.08 (*d*, *J* = 11.6, 1 H of tropone); 7.11–7.19 (*m*, 2 H of tropone); 8.58 (*br. s*, NH). <sup>13</sup>C-NMR: 14.07, 14.55, 30.71, 30.96 (4 Me); 31.42 (Me<sub>3</sub>C); 31.60 (C); 45.60 (CH); 52.11 (CH<sub>2</sub>); 56.48 (C–NH); 59.35, 61.43 (2 CH<sub>2</sub>O); 70.53, 125.30, 130.13, 135.41, 135.84, 139.57, 154.56, 160.13 (C of alkene and tropone); 168.41, 172.08, 177.77 (3 C=O). EI-MS: 431 (1, *M*<sup>+</sup>), 358 (29, [*M* – CO<sub>2</sub>Et]<sup>+</sup>), 328 (4, [358 – 2 Me]<sup>+</sup>), 246 (100, [358 – CMe<sub>2</sub>CH<sub>2</sub>CMe<sub>3</sub>]<sup>+</sup>), 218 (9, [246 – Et]<sup>+</sup>), 200 (15, [246 – EtO]<sup>+</sup>), 172 (19, [200 – CO]<sup>+</sup>), 157 (8, [172 – NH<sub>2</sub>]<sup>+</sup>). Anal. calc. for C<sub>24</sub>H<sub>33</sub>NO<sub>6</sub> (431.53): C 66.80, H 7.71, N 3.24; found: C 66.92, H 7.64, N 3.31.

*Di(tert-butyl) 2-(Cyclohexylamino)-4,9-dihydro-9-oxocyclohepta[b]pyran-3,4-dicarboxylate (4g)*. Yield 300 mg (65%). Yellow semisolid. IR: 3305 (NH), 2931, 1729, 1674, 1619, 1443, 1156, 1086. <sup>1</sup>H-NMR: 1.10–2.15 (*m*, 5 CH<sub>2</sub> of cyclohexyl); 1.38 (*s*, Me<sub>3</sub>C); 1.48 (*s*, Me<sub>3</sub>C); 3.87–4.04 (*m*, H–C–N); 4.35 (*s*, CH); 6.81–6.92 (*m*, 1 H of tropone); 7.12 (*d*, *J* = 11.3, 1 H of tropone); 7.13–7.25 (*m*, 2 H of tropone); 8.18 (*br. s*, NH). <sup>13</sup>C-NMR: 24.73, 25.56 (2 CH<sub>2</sub> of cyclohexyl); 27.89 (Me<sub>3</sub>C); 27.99 (CH<sub>2</sub>); 28.59 (Me<sub>3</sub>C); 32.74, 33.77 (2 CH<sub>2</sub> of cyclohexyl); 47.23 (CH); 50.26 (CH–NH); 77.22, 79.31, 81.46 (2 C and C of alkene); 126.07, 129.68, 135.72, 135.85, 139.41, 154.18, 158.86 (C of alkene and tropone); 168.21, 171.35, 178.11 (3 C=O). EI-MS: 457 (1, *M*<sup>+</sup>), 356 (29, [*M* – CO<sub>2</sub>*t*-Bu]<sup>+</sup>), 300 (100, [356 – *t*-Bu]<sup>+</sup>), 218 (33, [300 – C<sub>6</sub>H<sub>10</sub>]<sup>+</sup>), 57 (17, [*t*-Bu]<sup>+</sup>). Anal. calc. for C<sub>26</sub>H<sub>35</sub>NO<sub>6</sub> (457.57): C 68.25, H 7.71, N 3.06; found: C 68.37, H 7.62, N 3.11.

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