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# From 4,5,6,7-tetrahydroindole to functionalized furan-2-one–4,5,6,7-tetrahydroindole–cyclobutene sequence in two steps

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ABSTRACT

Ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)propynoate, readily available from 4,5,6,7-tetrahydroindole and ethyl bromopropynoate, when treated with dichlorodicyanobenzoquinone (DDQ) in methanol affords furan-2-one–4,5,6,7-tetrahydroindole–cyclobutene sequence in a 52% yield. As kinetic and minor products, a furan-2-one isomer along with bicycloheptadienone have been either isolated or identified. The reaction has been shown to proceed via the isolable intermediate the [2+2]-cycloadduct of ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)propynoate with DDQ. Other alcohols react with the [2+2]-cycloadduct in a similar way. The effect of the alcohol structure on the products ratio has been analyzed. All the intermediates and products are formed as single diastereomer, thus indicating a concerted character of the rearrangement.



## 1. Introduction

Functionalized multicyclic sequence, which combine fundamentally important heterocyclic systems in one molecule represent rewarding targets for medicinal and material chemistry as well as methodology of organic synthesis. The functionalized furan-2-one–4,5,6,7-tetrahydroindole-cyclobutene sequence belongs to such group of compounds.

The furanone moiety is known to be a common structural unit of numerous pharmaceutically important compounds (anti-AIDS drugs, such as d4T [1-(2,3-dideoxy-γ-D-glyceropent-2-enofuranosyl)thymine] and AZT {1-[4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl]-5-methyl-pyrimidine-2,4-(1*H*,3*H*)-dione},[1] vitamin C,[2] tetronic acids, and their thiol analogues[3]). This fragment occurs in cardenolides[4] (cardioactive steroid lactones), dysidiolide—the only known natural inhibitor of a protein phosphatase cdc25A[5]—as well as in a great variety of other natural molecules, such as sesterterpenes[6] and pulvinic acid derivatives.[7] In strigol and its analogues, the furanone part is primarily responsible for the germination of seeds.[8]

The indole and pyrrole scaffolds are also frequently met in many fundamental compounds, important from the biological point of view, such as chlorophyll, hemoglobin, vitamin B12, alkaloids and others, which play a pivotal role in the accumulation of solar energy, oxygen transfer processes, and other life-sustaining reactions.[9]

At the present time, the exhaustively substituted cyclobutenes still remain rare and exotic compounds, albeit, some of them have been successfully involved as key intermediates in Corey's brefeldin A synthesis.[10]

The combination of furan-2-one, 4,5,6,7-tetrahydroindole, and cyclobutene moieties in a one molecule may result in synergism of properties of these important chemical structures and substantially expand the fields of application of the newly synthesized functionalized compounds as effective building blocks for organic and medicinal chemistry.

However a short-cut to such diversified and multicyclic molecules represents a challenge for organic synthesis.

## 2. Results and discussion

Here we report on a two-step reaction sequence, which leads to densely functionalized compounds comprising all the above-mentioned heterocyclic systems.

For the synthesis, only the available 4,5,6,7-tetrahydroindole **1**[11] and a newly discovered[12] though well-elaborated ethynylation of the pyrrole ring are required. Ethyl 3-(4,5,6,7-tetrahydroindol-2-yl) propynoate **2** when treated with DDQ in methanol afforded the

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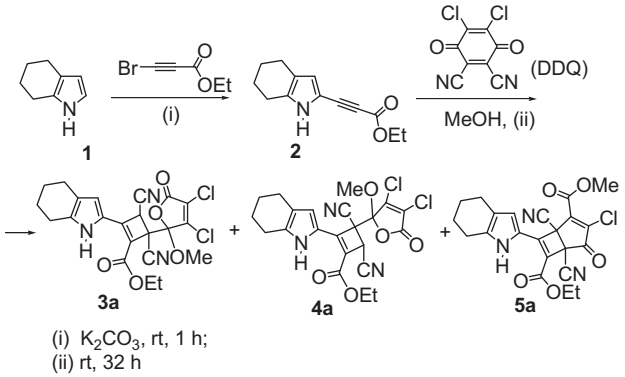
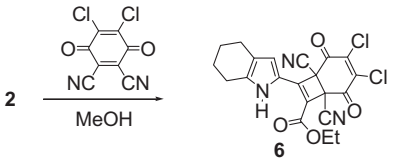
furan-2-one **3a** in 52% yield (Scheme 1). As minor products furan-2-one **4a** and bicycloheptadienone **5a** were formed (Scheme 1).



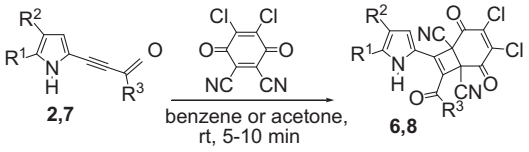

**Scheme 1.**

Apparently, the [2+2]-cycloadduct of ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)propynoate **2** with DDQ **6** is the intermediate of this reaction (Scheme 2).




**Scheme 2.**

Recently, we have shown[13] that the cycloadducts of the type **6** (the cycloadducts **8**) can be isolated in almost quantitative yields when 2-ethynylpyrroles **2,7** are allowed to contact with DDQ in aprotic solvent (benzene, acetone) at room temperature (Scheme 3).

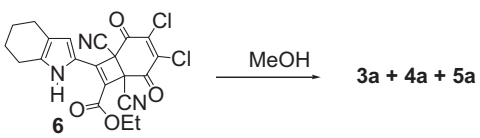



**7,8**: $R^1$ = Ph, 4-$ClC_6H_4$, 4-$MeOC_6H_4$, $R^2$ = H;
$R^1$-$R^2$ = $(CH_2)_4$; $R^3$ = Ph, 4-$NO_2C_6H_4$

**Scheme 3.**

Upon ethanolysis the cycloadducts **8** rearranged mostly to bicycloheptadienones, but furan-2-ones of the type **3** were identified by $^1$H NMR only (though in case of tetrahydroindole derivative **2** this compound was isolated in a larger quantitative yield that made it possible to grow a single crystal for X-ray analysis), while furan-2-ones of the type **4** were not detected at all.[14]

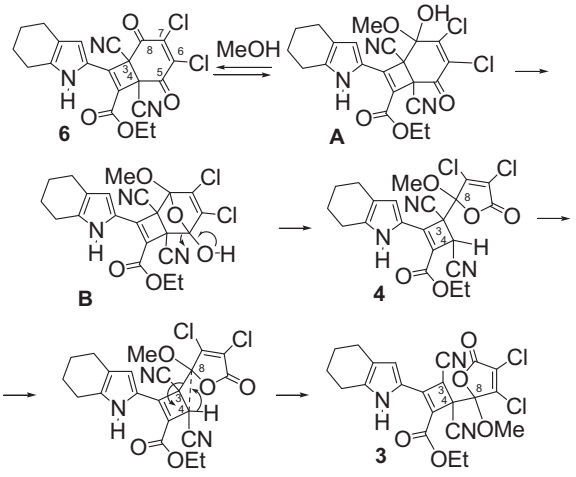
Here it has been revealed that the [2+2]-cycloadduct **6** upon action of methanol (rt, 24 h or 55–56 °C, 15 min) did rearrange to the furan-2-one **3a** as a major product, the minor ones being isomeric furan-2-one **4a** and bicycloheptadienone **5a**. (Scheme 4)




**Scheme 4.**

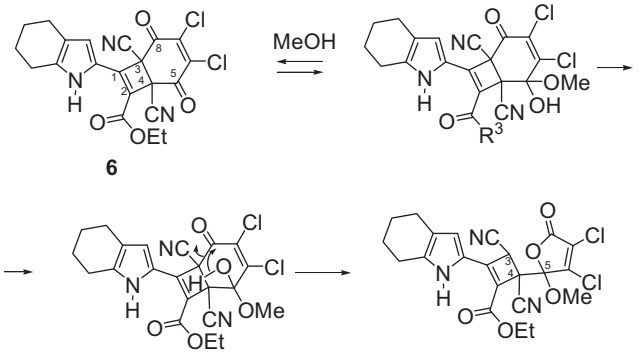
In the beginning of the rearrangement, the **4a**/**3a** isomers ratio was in favor of isomer **4a** and then changes with time in favor of isomer **3a**: 1.7 (15 min), 1.4 (30 min), 1.2 (60 min), 0.8 (90 min), and 0.7 (120 min). Thus, the isomer **4a** appears to be a kinetic product and isomer **3a** is a thermodynamic one. This becomes particularly clear upon the attempted separation of these two isomers. When the isomers mixture (**3a**/**4a**=1:8) was chromatographed ($SiO_2$ column, eluent $CH_2Cl_2$, 1 h), almost pure (98% purity) isomer **3a** was isolated, the mass of the sample remaining close to the initial one.

Obviously, the formation of furan-2-ones **3** and **4** represents a typical domino process (Scheme 5), triggered by the addition of methanol to the carbonyl group adjacent to the position 3 of the cyclobutene ring. The hemiacetal **A** attacks by its hydroxyl group the opposite carbonyl function (at carbon atom C5) and in hemiacetal **B**, thus formed, the cleavage of the C4–C5 bond occurs. This is accompanied by the simultaneous proton transfer from hydroxyl to anionic carbon atom C4 to finally give the labile (kinetic) isomer **4**.




**Scheme 5.**

The latter (as follows from experiment) rearranges to the more stable (thermodynamic) isomer **3**. Although this rearrangement might be rationalized as proceeding via the cleavage of the C3–C8 and C4-H bonds and the concerted formation of the C4–C8 and C3-H bonds, the activation energy of such a process (if not concerted) is expected to be high. Meanwhile, the alternative pathway for the formation of **3** can also be envisaged. Indeed, if methanol attacks another carbonyl group of compound **6**, followed by a similar sequence of steps as shown in Scheme 5, compound **3** will be formed directly (Scheme 6). However, initially as shown above product **4** is formed in a larger quantity than its isomer **3**. If the fragmentation **B**→**4** is reversible, the isomerization **4**→**3** could be understood without admitting the concerted process (Scheme 5).




**Scheme 6.**

The structure of furan-2-one of type **3** was previously unambiguously established by a single crystal X-ray analysis.[14] Here, all the spectral data ($^1$H, $^{13}$C NMR, HMBC, HSQC) for isomer **3a** are in agreement with those determined for the tricyclic compounds of the type **3**. For isomer **4a**, in the $^{13}$C NMR spectra signals of the carbon atoms C3 and C4 in the cyclobutene ring (49.1 and 35.8 ppm) and those of the two carbonyl carbons at 162.0 and 160.4 ppm were observed. In the $^1$H NMR spectrum of furanone **4a** the proton of the cyclobutene ring appeared at 4.30 ppm and displayed long range correlations (2D HMBC) with the carbon atoms at 49.1, 104.7, 105.3, 114.1 (CN), and 144.8 (C2 of pyrrole ring). The NOEs between this proton and the protons of the $OCH_3$ (3.45 ppm) and $OCH_2$ groups were observed in the 2D NOESY spectrum.

The structure of bicycloheptadienone **5a** including its relative stereochemistry and preferred conformation in crystal state has been determined by its single crystal X-ray analysis (Fig. 1). Also, the $^1$H and $^{13}$C NMR spectra entirely support the structure of bicycloheptadienone **5a**.

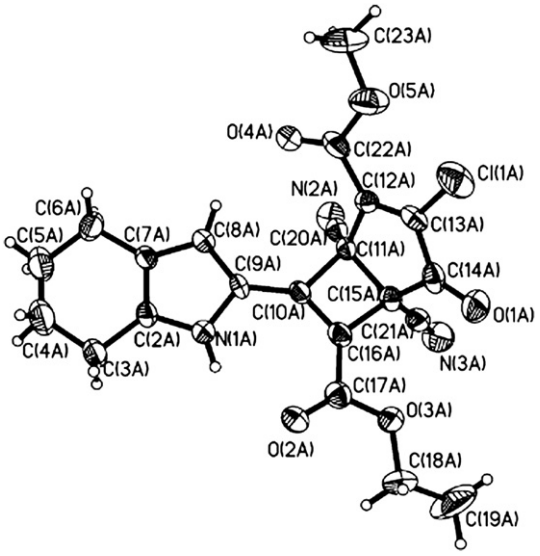
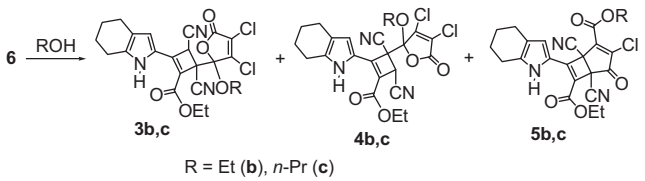


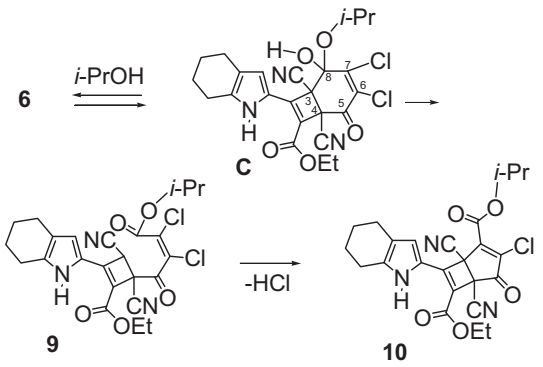

**Fig. 1.** X-ray crystal structure of bicycloheptadienone **5a**.

Similarly, [2+2]-cycloadduct **6** reacted with ethanol and *n*-propanol (Scheme 7), though as preliminary reported,[14] with ethanol the **3b**/**5b** ratio was almost the same. The yields of compounds **3c** and **5c**, the products of rearrangements of cycloadduct **6** in *n*-propanol (55–56 °C, 2 h), were 55% and 2%, correspondingly. The isomer **4c** was detected in the initial stage of the reaction only ($^1$H NMR).



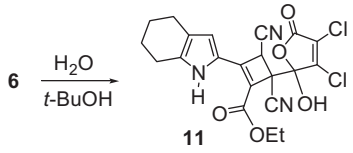

**Scheme 7.**

The reaction of [2+2]-cycloadduct **6** with *iso*-propanol (rt, 7 days or 55–56 °C, 2 h) led to the mixture of open-chained ester **9** and bicycloheptadienone **10** (Scheme 8). The ester **9** appeared to be the precursor of its cyclic isomer: when their 1:1 mixture was passed through the silica gel column (eluent $CH_2Cl_2$), the complete rearrangement **9**→**10** took place. Evidently, in this case, the intermediate hemiacetal **C** rearranges via the cleavage of the C3–C8 bond with simultaneous proton transfer from hydroxyl group to C3 anionic atom to deliver the open-chained ester **9**. The latter is further transformed to its cyclic isomer **10** via the proton abstraction from the position 3 (under the action of *iso*-propanol as a base) followed by the nucleophilic attack at the opposite C–Cl bond to release chlorine anion as a good fugitive group.




**Scheme 8.**

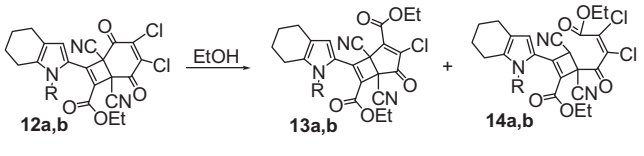
*tert*-Butanol did not react with [2+2]-cycloadduct **6** under even harsher conditions (reflux, 2 h). In this case, instead of the expected products, a new unstable furan-2-one–4,5,6,7-tetrahydroindole–cyclobutene **11** with hydroxy group in place of *tert*-butoxy substituent has been isolated in 24% yield that may result from similar reactions with trace water (Scheme 9). Such an assumption is supported by the isolation of the same cyclic hemiacetal from the reaction of cycloadduct **6** with water in dioxane (reflux, 2 h).




**Scheme 9.**

In the transformation depicted by Schemes 1–9, the free NH-indole function plays obviously an important if not a key role since the *N*-methyl- (**12a**) and *N*-benzyl- (**12b**) protected congeners of [2+2]-cycloadducts do not form furan-2-ones, only the bicycloheptadienones **13a**,**b** being isolated in moderate yields (Scheme 10). This implies a hydrogen bonding effect with the participation of NH and carbonyl functions that may fix favorable conformations and facilitate the proton transfers. Apart from bicycloheptadienones **13a**,**b**, the reaction mixtures contained also their precursors **14a**,**b**. The latter is transformed on $SiO_2$ to bicycloheptadienones **13a**,**b**.

## 3. Conclusion




**Scheme 10.**

An efficient two-step methodology for the diastereoselective synthesis of the polyfunctionalized linked-tricyclic systems comprising 4,5,6,7-tetrahydroindole, alkoxycarbonyldicyanocyclobutene, and dichloroalkoxyfuran-2-one moieties has been developed. The methodology includes the transition metal-free coupling of now readily available 4,5,6,7-tetrahydroindole and ethyl bromopropynoate followed by the three component domino reaction between ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)propynoate, dichlorodicyanobenzoquinone, and alcohols under mild conditions (20–56 °C). Apart from the major compounds, furan-2-one–4,5,6,7-tetrahydroindole–cyclobutenes, as minor products, bicycloheptadienones and their precursors have been isolated. As the pivotal intermediate of the methodology, [2+2]-cycloadduct of 2-ethynyl-4,5,6,7-tetrahydroindole and DDQ, is isolable which further undergoes the domino type alcoholysis and rearrangements. All the isolated and identified products represent single diastereomers thus indicating the concerted character of the cleavage and formation of the C–C- and C–H-bonds involved into the domino reactions.

The methodology elaborated opens an exceptionally concise and synthetically attractive atom and step economic route to novel promising families of building blocks for drug design.

## 4. Experimental section

### 4.1. General information

IR spectra were obtained in KBr pellets. $^1$H and $^{13}$C NMR spectra were recorded at 400.13 MHz and 101.6 MHz, respectively. The concerted application of $^1$H–$^1$H 2D homonuclear experiments COSY and NOESY and also $^1$H–$^{13}$C 2D heteronuclear experiments HSQC and HMBC were used for the distinction of the carbon and proton resonances in all cases. The X-ray diffraction study of **5a** was carried out with using a Bruker SMART APEX2 CCD diffractometer at room temperature (Mo Kα radiation). Crystalline structure of compound **5a** was solved by direct methods followed by Fourier synthesis using SHELXS-97.[15] All non-hydrogen atoms were refined using anisotropic full-matrix approximation using SHELXL-97.[15] The coordinates of the hydrogen atoms were calculated from geometric conditions. Atom coordinates, bond lengths, and angle values were deposited at Cambridge Crystallographic Data Centre (CCDC). These data are available via www.ccdc.cam.uk/conts/retrieving.html (or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0) 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 805575.

*4.1.1. Reaction of ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)propynoate (**2**) with DDQ in methanol.* A solution of ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)propynoate (**2**) (0.109 g, 0.5 mmol) in methanol (20 mL) was added to a solution of DDQ (0.114 g, 0.5 mmol) in methanol (10 mL). The reaction mixture was allowed to stand at room temperature for 32 h. The formed crystals were filtered off and dried to give 0.037 g of the mixture of furanones **3a** (12%) and **4a** (88%). After passing this mixture through column with $SiO_2$ (eluent—$CH_2Cl_2$), furanone **3a** (0.035 g, the purity is 95%, the impurity is furanone **4a**) was isolated. The residue after removal of methanol (0.207 g) containing furanone **3a** (35%), furanone **4a** (39%), bicycloheptadienone **5a** (19%), and cycloadduct **6** (7%) was passed through $SiO_2$ ($CH_2Cl_2$) and furanone **3a** (0.084 g) and bicycloheptadienone **5a** (0.010 g, 4%) were isolated. The total yield of furanone **3a** is 0.119 g (52%).

*4.1.2. Reaction of ethyl 3,4-dichloro-1,6-dicyano-2,5-dioxo-8-(4,5,6,7-tetrahydro-1H-indol-2-yl)bicyclo[4.2.0]octa-3,7-diene-7-carboxylate (**6**) with methanol. Method A.* A solution of cycloadduct **6** (0.100 g, 0.23 mmol) in MeOH (20 mL) was heated to reflux for 15 min and allowed to stand at room temperature for 24 h. Then the formed crystals were filtered off and dried to give 0.027 g of the mixture of furanones **3a** (41%) and **4a** (59%). This mixture was passed through column with $SiO_2$ (l–60 cm, eluent—$CH_2Cl_2$) to afford 0.025 g of furanone **3a**, the purity is 96%, the impurity is furanone **4a**. The residue after removing methanol (0.061 g) containing furanone **3a** (39%), furanone **4a** (36%), and bicycloheptadienone **5a** was fractionated by silica column chromatography (eluent—$CH_2Cl_2$) to afford compounds **3a** (0.035 g) and **5a** (0.006 g, 6%). The total yield of furanone **3a** is 0.060 g (56%).

*Method B.* A solution of cycloadduct **6** (0.111 g, 0.25 mmol) in methanol (20 mL) was stirred at room temperature for 24 h. The formed crystals were filtered off and dried to give the mixture (0.020 g) of furanones **3a** (14%) and **4a** (86%). After passing this mixture through column with $SiO_2$ (eluent—$CH_2Cl_2$) furanone **3a** (0.018 g, the purity is 96%, the impurity is furanone **4a**) was isolated. The residue after removing methanol (0.084 g) containing furanones **3a** (17%), **4a** (39%), and bicycloheptadienone **5a** (37%) was passed through $SiO_2$ (eluent—$CH_2Cl_2$) and furanone **3a** (0.044 g, the purity is 95%, the impurity is furanone **4a**) and bicycloheptadienone **5a** (0.07 g, 7%) were isolated. The total yield of furanone **3a** is 0.062 g (58%).

*4.1.3. Ethyl 3,4-dicyano-4-(3,4-dichloro-2-methoxy-5-oxo-2,5-dihydrofuran-2-yl)-2-(4,5,6,7-tetrahydro-1H-indol-2-yl)cyclobut-1-enecarboxylate (**3a**).* Yield 52–58%; yellow plates, mp 209–210 °C; [Found: C, 55.74; H, 4.12; Cl, 14.53; N, 8.89. $C_{22}H_{19}Cl_2N_3O_5$ requires C, 55.48; H, 4.02; Cl, 14.89; N, 8.82%]; $R_f$ (30% $Et_2O$/*n*-hexane) 0.86; $\nu_{max}$ (KBr) 3320 (NH), 2247 (CN), 1806 (CO), 1689 (CO), 1624 cm$^{-1}$ (C=C); $\delta_H$ (400.13 MHz, $CDCl_3$) 10.71 (1H, br s, N*H*), 6.60 (1H, d, *J* 2.0 Hz, $H^3$), 4.33 (1H, s, C*H*–CN), 4.24 (2H, m, $CH_2$C=O), 3.40 (3H, s, $CH_3$O), 2.67 (2H, m, $CH_{2^7}$), 2.53 (2H, m, $CH_{2^4}$), 1.82 (2H, m, $CH_{2^5}$), 1.74 (2H, m, $CH_{2^6}$), 1.35 (3H, t, *J* 7.1 Hz, $CH_3$); $\delta_C$ (101.6 MHz, $CDCl_3$) 162.0, 160.6, 147.9, 144.6, 140.1, 125.1, 123.0, 121.7, 117.2, 113.9, 113.8, 105.7, 104.9, 61.8, 52.4, 50.3, 34.3, 23.4, 23.0, 22.5, 22.4, 14.2.

*4.1.4. Ethyl 3,4-dicyano-3-(3,4-dichloro-2-methoxy-5-oxo-2,5-dihydrofuran-2-yl)-2-(4,5,6,7-tetrahydro-1H-indol-2-yl)cyclobut-1-enecarboxylate (**4a**).* $\delta_H$ (400.13 MHz, $CDCl_3$) 10.71 (1H, br s, N*H*), 6.68 (1H, s, $H^3$), 4.30 (1H, s, C*H*–CN), 4.24 (2H, m, $CH_2$C=O), 3.45 (3H, s, $CH_3$O), 2.67 (2H, m, $CH_{2^7}$), 2.53 (2H, m, $CH_{2^4}$), 1.82 (2H, m, $CH_{2^5}$), 1.74 (2H, m, $CH_{2^6}$), 1.35 (3H, t, *J* 7.1 Hz, $CH_3$); $\delta_C$ (101.6 MHz, $CDCl_3$) 162.2, 160.8, 148.0, 144.8, 140.3, 125.7, 123.3, 121.9, 117.6, 114.1, 113.9, 105.3, 104.7, 62.0, 52.5, 49.1, 35.8, 23.6, 23.2, 22.7, 22.6, 14.4.

*4.1.5. 6-Ethyl 2-methyl 3-chloro-1,5-dicyano-4-oxo-7-(4,5,6,7-tetrahydro-1H-indol-2-yl)bicyclo[3.2.0]hepta-2,6-diene-2,6-dicarboxylate (**5a**).* Yield 4–7%; red needles, mp 239–240 °C; [Found: C, 59.72; H, 4.27; Cl, 8.00; N, 9.28. $C_{22}H_{18}ClN_3O_5$ requires C, 60.07; H, 4.12; Cl, 8.06; N, 9.55%]; $R_f$ (30% $Et_2O$/*n*-hexane) 0.83; $\nu_{max}$ (KBr) 3346 (NH), 2248 (CN), 1756, 1724, 1684 (CO), 1615 cm$^{-1}$ (C=C); $\delta_H$ (400.13 MHz, $CDCl_3$) 10.89 (1H, br s, N*H*), 6.97 (1H, d, *J* 1.9 Hz, $H^3$), 4.31 (2H, q, *J* 7.1 Hz, C*H*$_2$O), 4.02 (3H, s, O$CH_3$), 2.68 (2H, m, $CH_{2^7}$), 2.55 (2H, m, $CH_{2^4}$), 1.82 (2H, m, $CH_{2^5}$), 1.75 (2H, m, $CH_{2^6}$), 1.38 (3H, t, *J* 7.1 Hz, $CH_3$); $\delta_C$ (101.6 MHz, $CDCl_3$) 182.9, 162.8, 161.0, 148.2, 143.9, 142.3, 142.0, 124.1, 121.6, 119.2, 112.0, 111.3, 105.8, 62.3, 53.9, 52.1, 47.4, 23.8, 23.3, 22.9, 22.6, 14.3.

*4.1.6. Reaction of ethyl 3,4-dichloro-1,6-dicyano-2,5-dioxo-8-(4,5,6,7-tetrahydro-1H-indol-2-yl)bicyclo[4.2.0]octa-3,7-diene-7-carboxylate (**6**) with n-propanol. Method* A. The solution of cycloadduct **6** (0.200 g, 0.45 mmol) in *n*-propanol (20 mL) was left at room temperature for 7 days. The formed crystals were filtered off and dried to give 0.063 g of mixture of furanone **3c** (73%) and bicycloheptadienone **5c** (27%). After passing the crystals through column with $SiO_2$ (eluent—hexane/ether, from 4:1 to 1:1) furanone **3c** (0.036 g, the purity is 93%, the impurity is bicycloheptadienone **5c**) was isolated. The residue after removing *n*-propanol (0.141 g)

containing furanone **3c** (79%), furanone **4c** (9%), and bicycloheptadienone **5c** (12%) was passed through $SiO_2$ (hexane/ether, from 4:1 to 1:1) and furanone **3c** (0.101 g) was isolated. The total yield of furanone **3c** is 0.134 g (59%).

*Method B*. The solution of cycloadduct **6** (0.100 g, 0.23 mmol) in *n*-propanol (10 mL) was heated (55–56 °C) for 2 h. The reaction mixture was diluted with brine (100 mL) and extracted with diethyl ether (5×40 mL). The ether extracts were washed with water and dried over $Na_2SO_4$. The residue after removing solvent (0.112 g) containing furanones **3c** (68%), **4c** (16%), and bicycloheptadienone **5c** (16%) was passed through $SiO_2$ (eluent—hexane/$CH_2Cl_2$, from 4:1 to 1:1) to give furanone **3c** (0.063 g, 55%). Bicycloheptadienone **5c** was isolated only as single crystals together with furanone **3c**.

*4.1.7. Ethyl 3,4-dicyano-4-(3,4-dichloro-2-n-propoxy-5-oxo-2,5-dihydrofuran-2-yl)-2-(4,5,6,7-tetrahydro-1H-indol-2-yl)cyclobut-1-enecarboxylate (**3c**).* Yield 55–59%; yellow needles, mp 169–170 °C; [Found: C, 56.78; H, 4.34; Cl, 13.86; N, 8.56. $C_{24}H_{23}Cl_2N_3O_5$ requires C, 57.15; H, 4.60; Cl, 14.06; N, 8.33%]; $R_f$ (30% $Et_2O$/*n*-hexane) 0.85; $\nu_{max}$ (KBr) 3321 (NH), 2255 (CN), 1807 (CO), 1682 (CO), 1625 $cm^{-1}$ (C=C); $\delta_H$ (400.13 MHz, $CDCl_3$) 10.71 (1H, br s, N*H*), 6.60 (1H, d, *J* 1.8 Hz, $H^3$), 4.32 (1H, s, C*H*–CN), 4.22 (2H, m, $CH_2$C=O), 3.46 (2H, m, O$CH_2$ of Pr), 2.67 (2H, m, $CH_{2^7}$), 2.53 (2H, m, $CH_{2^4}$), 1.83 (2H, m, $CH_2$), 1.74 (4H, m, $CH_{2^{5,6}}$), 1.35 (3H, t, *J* 7.3 Hz, $CH_3$), 0.99 (3H, t, *J* 7.3 Hz, $CH_3$ of Pr); $\delta_C$ (101.6 MHz, $CDCl_3$) 162.1, 160.8, 148.4, 144.7, 140.1, 124.9, 123.1, 121.9, 117.3, 114.1, 113.9, 106.0, 104.7, 67.3, 61.9, 50.6, 34.5, 23.6, 23.2, 22.6, 22.5, 22.4, 14.3, 10.3.

*4.1.8. 6-Ethyl 2-n-propyl 3-chloro-1,5-dicyano-4-oxo-7-(4,5,6,7-tetrahydro-1H-indol-2-yl)bicyclo[3.2.0]hepta-2,6-diene-2,6-dicarboxylate (**5c**).* Yield 2%; red prisms, mp 220–221 °C; $R_f$ (30% $Et_2O$/*n*-hexane) 0.84; $\nu_{max}$ (KBr) 3318 (NH), 2255 (CN), 1754, 1720, 1682 (CO), 1622 $cm^{-1}$ (C=C); $\delta_H$ (400.13 MHz, $CDCl_3$) 10.86 (1H, br s, N*H*), 7.00 (1H, d, *J* 1.9 Hz, $H^3$), 4.37 (2H, q, *J* 6.2 Hz, O$CH_2$), 4.31 (2H, t, *J* 7.1 Hz, O$CH_2$), 2.67 (2H, m, $CH_{2^7}$), 2.54 (2H, m, $CH_{2^4}$), 1.82 (4H, m, $CH_{2^{5,6}}$), 1.73 (2H, m, $CH_2$), 1.38 (3H, t, *J* 6.2 Hz, $CH_3$), 1.02 (3H, t, *J* 7.1 Hz, $CH_3$).

*4.1.9. Reaction of ethyl 3,4-dichloro-1,6-dicyano-2,5-dioxo-8-(4,5,6,7-tetrahydro-1H-indol-2-yl)bicyclo[4.2.0]octa-3,7-diene-7-carboxylate (**6**) with iso-propanol. Method A*. A solution of cycloadduct **6** (0.100 g, 0.23 mmol) in *iso*-propanol (20 mL) was allowed to stand at room temperature for 7 days. Then *iso*-propanol was removed and the residue (0.109 g) containing bicycloheptadienone **10** and its precursor **9** was passed through $SiO_2$ ($CH_2Cl_2$) to afford compounds **9** (0.038 g, 33%) and **10** (0.023 g, 22%).

*Method B*. The solution of cycloadduct **6** (0.100 g, 0.23 mmol) in *iso*-propanol (10 mL) was heated (55–56 °C) for 2 h and allowed to stand at room temperature for 60 h. The formed crystals of the mixture of compounds **9** and **10** (0.027 g, the ratio **9**/**10**, 1:1) were filtered off and passed through column with $SiO_2$ (eluent—$CH_2Cl_2$) to afford bicycloheptadienone **10** (0.021 g). After removal of *iso*-propanol (0.072 g), the residue was fractionated by column chromatography ($SiO_2$, l–30 cm, eluent—$CH_2Cl_2$) and the mixture (0.020 g) of compounds **9** and **10** (the ratio **9**/**10**, 3:1) was isolated. Repeated fractionation of this mixture gave 0.014 g of bicycloheptadienone **10**. The total yield of bicycloheptadienone **10** is 0.035 g (33%).

*4.1.10. (Z)-Ethyl 3,4-dicyano-4-(2,3-dichloro-4-isopropoxy-4-oxobut-2-enoyl)-2-(4,5,6,7-tetrahydroindol-2-yl)cyclobut-1-enecarboxylate (**9**).* Yield 33%; yellow prisms, mp 172–173 °C; [Found: C, 56.78; H, 4.31; Cl, 14.41; N, 8.69. $C_{24}H_{23}Cl_2N_3O_5$ requires C, 57.15; H, 4.60; Cl, 14.06; N, 8.33%]; $R_f$ (30% $Et_2O$/*n*-hexane) 0.84; $\nu_{max}$ (KBr) 3327 (NH), 2252, 2203 (CN), 1725, 1691 (CO), 1633 $cm^{-1}$ (C=C); $\delta_H$ (400.13 MHz, $CDCl_3$) 10.59 (1H, br s, N*H*), 6.58 (1H, d, *J* 2.0 Hz, $H^3$), 5.19 (1H, m, C*H*($CH_3$)$_2$), 4.42 (1H, s, C*H*–CN), 4.27 (2H, m, $CH_2$C=O), 2.67 (2H, m, $CH_{2^7}$), 2.53 (2H, m, $CH_{2^4}$), 1.82 (2H, m, $CH_{2^6}$), 1.74 (2H, m, $CH_{2^5}$), 1.42 (3H, d, *J* 6.3 Hz, $CH_3$ of *i*-Pr), 1.35 (3H, d, *J* 6.2 Hz, $CH_3$ of *i*-Pr), 1.32 (3H, t, *J* 7.1 Hz, $CH_3$); $\delta_C$ (101.6 MHz, $CDCl_3$) 188.5, 162.2, 161.7, 143.8, 139.3, 138.1, 127.8, 122.8, 121.8, 116.6, 115.2, 114.3, 111.1, 73.9, 61.8, 52.4, 38.4, 23.6, 23.3, 22.8, 22.7, 21.7, 21.6, 14.4.

*4.1.11. 6-Ethyl 2-isopropyl 3-chloro-1,5-dicyano-4-oxo-7-(4,5,6,7-tetrahydro-1H-indol-2-yl)bicyclo[3.2.0]hepta-2,6-diene-2,6-dicarboxylate (**10**).* Yield 23–33%; red needles, mp 223–224 °C; [Found: C, 61.32; H, 4.56; Cl, 7.84; N, 9.28. $C_{24}H_{22}ClN_3O_5$ requires: C, 61.61; H, 4.74; Cl, 7.58; N, 8.98%]; $R_f$ (30% $Et_2O$/*n*-hexane) 0.83; $\nu_{max}$ (KBr) 3423 (NH), 2248 (CN), 1759, 1709, 1684 (CO), 1613 $cm^{-1}$ (C=C); $\delta_H$ (400.13 MHz, $CDCl_3$) 10.84 (1H, br s, N*H*), 7.02 (1H, d, *J* 1.9 Hz, $H^3$), 5.32 (1H, m, C*H*($CH_3$)$_2$), 4.31 (2H, q, *J* 7.1 Hz, $CH_2$O), 2.68 (2H, m, $CH_{2^7}$), 2.55 (2H, m, $CH_{2^4}$), 1.82 (2H, m, $CH_{2^5}$), 1.75 (2H, m, $CH_{2^6}$), 1.43 (3H, d, *J* 6.4 Hz, CH$CH_3$), 1.38 (3H, d, *J* 6.4 Hz, CH$CH_3$), 1.37 (3H, t, *J* 7.1 Hz, $CH_3$); $\delta_C$ (101.6 MHz, $CDCl_3$) 182.9, 162.7, 160.1, 148.2, 144.6, 141.7, 141.5, 123.8, 121.5, 119.3, 111.9, 111.2, 105.8, 72.7, 62.1, 52.0, 47.4, 23.8, 23.2, 22.7, 22.6, 21.7 (2Me), 14.2.

*4.1.12. Reaction of ethyl 3,4-dichloro-1,6-dicyano-2,5-dioxo-8-(4,5,6,7-tetrahydro-1H-indol-2-yl)bicyclo[4.2.0]octa-3,7-diene-7-carboxylate (**6**) with tert-butanol.* A solution of cycloadduct **6** (0.100 g, 0.23 mmol) in *t*-BuOH (20 mL) was heated to reflux for 2 h and the solvent was removed at vacuo. The residue (0.098 g), containing only hydroxyfuranone **11** ($^1$H NMR) was dissolved in ethanol and left to stand at room temperature for 24 h. The formed white crystals were filtered off and washed with cold ethanol to give 0.025 g (24%) of hydroxyfuranone **11**.

*4.1.13. Ethyl 3,4-dicyano-4-(3,4-dichloro-2-hydroxy-5-oxo-2,5-dihydrofuran-2-yl)-2-(4,5,6,7-tetrahydroindol-2-yl)cyclobut-1-enecaboxylate (**11**).* Yield 24%; white prisms, mp 133–134 °C; [Found: C, 54.18; H, 3.98; Cl, 14.98; N, 8.79. $C_{21}H_{17}Cl_2N_3O_5$ requires C, 54.56; H, 3.71; Cl, 15.34; N, 9.09%]; $\nu_{max}$ (KBr) 3463 (OH), 3329 (NH), 2256 (CN), 2203 (CN), 1805 (CO), 1682 (CO), 1630 $cm^{-1}$ (C=C); $\delta_H$ (400.13 MHz, $CDCl_3$) 10.63 (1H, br s, N*H*), 6.59 (1H, s, $H^3$), 4.40 (1H, s, C*H*CN), 4.31 (1H, br s, O*H*), 4.22 (4H, m, 2O$CH_2$), 2.66 (2H, m, $CH_{2^7}$), 2.52 (2H, m, $CH_{2^4}$), 1.80 (2H, m, $CH_{2^5}$), 1.73 (2H, m, $CH_{2^6}$), 1.34 (3H, t, *J* 7.3 Hz, $CH_3$); $\delta_C$ (101.6 MHz, $CDCl_3$) 162.3, 161.7, 150.0, 144.2, 139.8, 123.7, 122.6, 121.8, 117.1, 114.4, 114.3, 107.0, 104.0, 61.9, 50.7, 34.3, 23.4, 23.0, 22.5, 22.4, 14.1.

*4.1.14. Reaction of ethyl 3,4-dichloro-1,6-dicyano-2,5-dioxo-8-(1-methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)bicyclo[4.2.0]-octa-3,7-diene-7-carboxylate (**12a**) with ethanol.* The solution of cycloadduct **12a** (0.100 g, 0.22 mmol) in EtOH (20 mL) was allowed to stand at room temperature for 24 h. Then the solution was poured into brine (100 mL) and extracted with diethyl ether (5×20 mL). The ether extracts were washed with water and dried over $Na_2SO_4$. After removing diethyl ether, the residue (0.084 g) containing bicycloheptadienone **13a** and intermediate **14a** (the ratio **13a**/**14a**, 1:2) was passed through $SiO_2$ (eluent—$CH_2Cl_2$) to give 0.044 g (43%) of bicycloheptadienone **13a**.

*4.1.15. Diethyl 7-(1-methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-3-chloro-1,5-dicyano-4-oxobicyclo[3.2.0]hepta-2,6-diene-2,6-dicarboxylate (**13a**).* Yield 43%; red needles, mp 158–160 °C; [Found: C, 61.32; H, 4.58; Cl, 7.75; N, 8.64. $C_{24}H_{22}ClN_3O_5$ requires C, 61.61; H, 4.74; Cl, 7.58; N, 8.98%]; $R_f$ (30% $Et_2O$/*n*-hexane) 0.76; $\nu_{max}$ (KBr) 2244, 2199 (CN), 1758, 1724, 1702 (CO), 1625 $cm^{-1}$ (C=C); $\delta_H$ (400.13 MHz, $CDCl_3$) 6.93 (1H, s, $H^3$), 4.33 (4H, m, 2O$CH_2$), 3.49 (3H, s, N*Me*), 2.53 (4H, m, $CH_{2^{4,7}}$), 1.85 (2H, m, $CH_{2^5}$), 1.71 (2H, m, $CH_{2^6}$), 1.38 (3H, t, *J* 7.3 Hz, $CH_3$), 1.35 (3H, t, *J* 7.3 Hz, $CH_3$); $\delta_C$ (101.6 MHz, $CDCl_3$) 182.8, 160.2, 160.1, 146.4, 145.0, 144.0, 141.6, 123.4, 122.5, 119.6, 112.6, 111.5, 109.6, 63.6, 61.9, 51.9, 48.5, 33.6, 23.1, 23.0, 22.9, 22.5, 14.2, 13.9.

*4.1.16. Reaction of ethyl 3,4-dichloro-1,6-dicyano-2,5-dioxo-8-(1-benzyl-4,5,6,7-tetrahydro-1H-indol-2-yl)bicyclo[4.2.0]octa-3,7-diene-7-carboxylate (**12b**) with ethanol.* Cycloadduct **12b** (0.100 g, 0.19 mmol) was heated to reflux in EtOH (20 mL) for 2 min and allowed to cool to room temperature. Then the solution was poured into brine (100 mL) and extracted with diethyl ether (5×20 mL). The ether extracts were washed with water and dried over $Na_2SO_4$. After removing diethyl ether the residue (0.096 g) containing bicycloheptadienone **13b** and compound **14b** (the ratio **13b**/**14b**, 1:1.5) was passed through $SiO_2$ (eluent—$CH_2Cl_2$) to give 0.027 g (26%) of bicycloheptadienone **13b**.

*4.1.17. Diethyl 7-(1-benzyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-3-chloro-1,5-dicyano-4-oxobicyclo[3.2.0]hepta-2,6-diene-2,6-dicarboxylate (**13b**).* Yield 26%; red prisms, mp 135–136 °C; [Found: C, 65.92; H, 4.59; Cl, 6.21; N, 7.44. $C_{30}H_{26}ClN_3O_5$ requires C, 66.24; H, 4.82; Cl, 6.52; N, 7.72%]; $R_f$ (30% $Et_2O$/*n*-hexane) 0.78; $\nu_{max}$ (KBr) 2244, 2199 (CN), 1753, 1724, 1704 (CO), 1625 $cm^{-1}$ (C=C); $\delta_H$ (400.13 MHz, $CDCl_3$) 7.12 (3H, m, C*H*$^{3,4,5}$ Ph), 7.02 (1H, s, *H*$^3$), 6.45 (2H, m, C*H*$^{2,6}$), 5.59 (1H, d, *J* 16.8 Hz, C$H_2$Ph), 5.04 (1H, d, *J* 16.8 Hz, C$H_2$Ph), 4.34 (4H, m, 2OC$H_2$), 2.60 (4H, m, C$H_{2\,4,7}$), 1.78 (4H, m, C$H_{2\,5,6}$), 1.38 (3H, t, *J* 7.3 Hz, C$H_3$), 1.35 (3H, t, *J* 7.3 Hz, C$H_3$); $\delta_C$ (101.6 MHz, $CDCl_3$) 182.3, 160.5, 159.7, 146.6, 144.4, 143.5, 140.8, 137.3, 128.8, 127.9, 125.3, 122.8, 122.5, 120.4, 112.4, 111.7, 111.3, 63.3, 62.1, 49.1, 48.7, 48.2, 23.1, 23.0, 22.9, 22.6, 14.2, 14.0.

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