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# Synthesis of New Chiral Heterocycles of the Pyrazole and 2-Isoxazoline Types from (+)-3-Carene.

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***Abstract:*** Preparation of chiral heterocyclic compounds of the pyrazole and 2-isoxazoline types starting from natural monoterpene hydrocarbon (+)-3-carene is described. Stereochemical assignment of the compounds synthesized is made by NMR spectroscopy and X-ray analysis together with the data obtained by molecular mechanics and quantum chemical calculations.

## INTRODUCTION

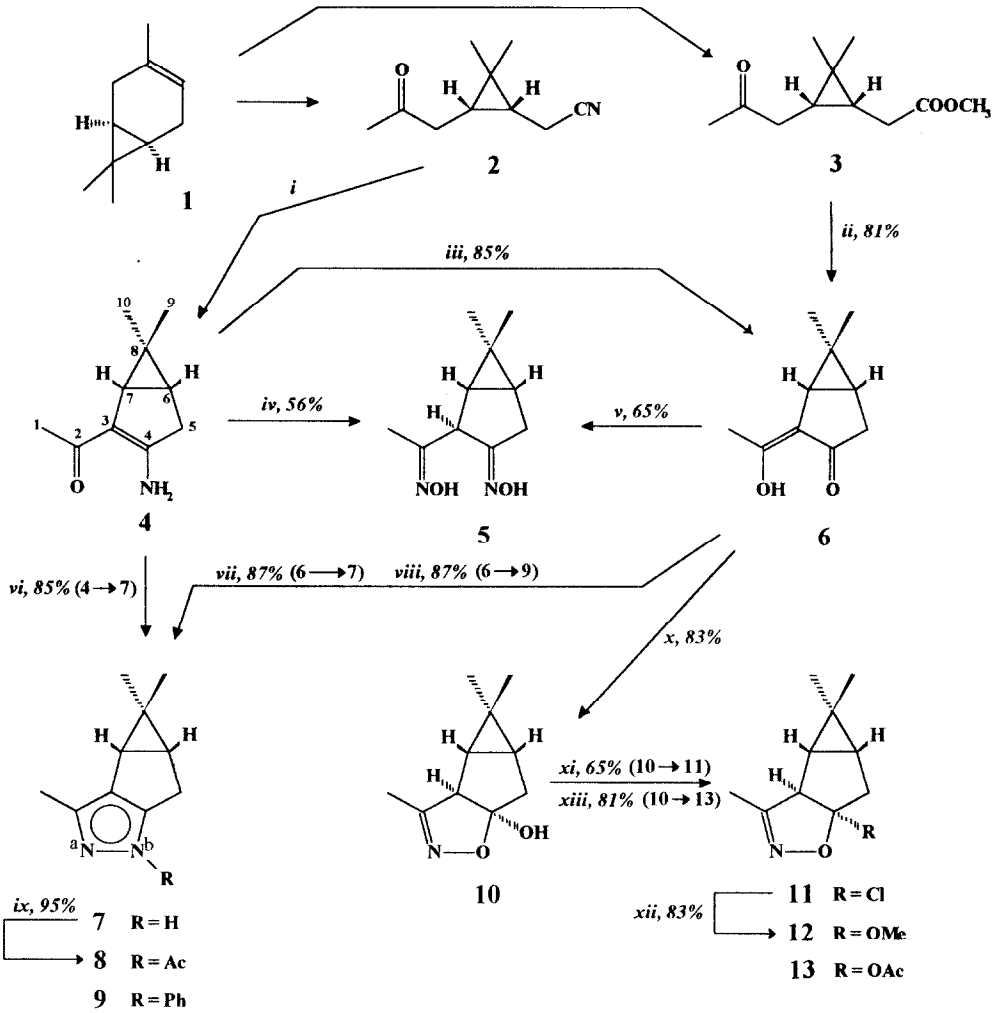
Certain organic compounds of natural origin are the primary source of chirality in organic synthesis and are used for preparing all the other chiral chemicals. Among the different types of chiral natural products, terpenes have received the less study. In spite of high enantiomeric purity of some terpenes and their accessibility "...the lack of functional group makes them less attractive as chiral auxiliary"[1]. This is true for natural terpenic hydrocarbons "as is", but what about their synthetic derivatives? Is there a possibility to transform wide spread terpenes to the effective chiral agents? Recently we have reported very simple method for preparing of cyclic enaminones[2] by cyclization of the corresponding ω-keto nitriles[3]. These enaminones are of interest from the viewpoint of their use as starting material for synthesis of chiral heterocyclic compounds. It is common knowledge that different five-membered nitrogen-containing heterocycles are excellent ligands, and the coordination chemistry of these compounds has been extensively studied[4,5,6]. At the same time, different complexes of transition metal ions with chiral nitrogen containing ligands are being studied as chiral auxiliary[7]. In this paper we report the synthesis of new chiral tricyclic compounds of the pyrazole and 2-isoxazoline types derived from natural monoterpene hydrocarbon (+)-3-carene. The compounds synthesized are prospective chiral auxiliary for enantioselective synthesis.

## RESULTS AND DISCUSSION

Highly regioselective synthesis of isoxazoles is known to be easily carried out with the use of enaminones as starting compounds[8]. We tried to prepare isoxazole derivatives by treatment of enaminone **4** with hydroxylamine.

## *Scheme 1.*

The numbering scheme does not coincide with the numbering of the cyclic systems according to IUPAC.




*i* see ref.[2]; *ii* NaOMe-MeOH/reflux/15 min; *iii* HCl-$H_2O$-MeOH/80°C/3h; *iv* $NH_2OH$×HCl-NaOAc-MeOH/reflux/8h; *v* $NH_2OH$×HCl-NaOAc-MeOH/reflux/3h; *vi* $NH_2NH_2$×$H_2O$-$HOCH_2CH_2OH$/100°C →reflux/6h; *vii* $NH_2NH_2$×$H_2O$-AcOH-MeOH/room temp./30 min; *viii* $PhNHNH_2$-AcOH-MeOH/ reflux/8h; *ix* $Ac_2O$-Py-$CHCl_3$/-5°C/1h; *x* $NH_2OH$×HCl-NaOAc-MeOH/room temp./20h; *xi* $SOCl_2$-Py-$C_6H_6$/reflux/8h; *xii* *p*-TsOH-MeOH/room temp./14h; *xiii* $Ac_2O$-$Et_3N$/room temp./36h.

***Table 1.*** **$^{13}$C NMR Data for Compounds 5 - 13[a].**

| | 5[b] | 6[c] | 7[c] | 8[d] | | 9[c,e] | 10[c] | 11[c] | 12[c,f] | 13[c,g] |
|---|---|---|---|---|---|---|---|---|---|---|
| *i* | $\delta C^i$ | $\delta C^i$ | $\delta C^i$ | $\delta C^i$ | $^1J_{Ci-Cj}$ (*j*), ±0.3 Hz | $\delta C^i$ | $\delta C^i$ | $\delta C^i$ | $\delta C^i$ | $\delta C^i$ |
| 1 | 10.90 | 19.61 | 10.16 | 13.04 | 51.6 (2) | 12.48 | 12.11 | 11.68 | 11.88 | 11.50 |
| 2 | 158.12* | 172.33 | 133.15* | 148.22 | 51.6 (1) 55.8 (3) | 140.10* | 158.80 | 160.58 | 158.24 | 158.38 |
| 3 | 47.40 | 111.20 | 122.61* | 131.38 | 55.8 (2) 61.5 (4) 59.3 (7) | 128.45 | 60.67 | 67.16 | 57.67 | 61.01 |
| 4 | 167.29* | 208.94 | 162.05 | 152.41 | 61.5 (3) 47.6 (5) | 144.26* | 123.83 | 117.76 | 126.95 | 123.79 |
| 5 | 27.39 | 36.66 | 24.07 | 27.32 | 47.6 (4) 40.8 (6) | 26.65 | 37.81 | 41.71 | 35.90 | 37.56 |
| 6 | 26.11 | 21.72 | 34.12 | 35.32 | 40.8 (5) 12.5 (7) 15.8 (8) | 34.55 | 28.96 | 30.17 | 28.19 | 28.38 |
| 7 | 30.24 | 28.25 | 25.73 | 26.13 | 59.3 (3) 12.5 (6) 15.3 (8) | 25.85 | 31.76 | 31.84 | 31.32 | 30.67 |
| 8 | 19.23 | 21.81 | 22.44 | 22.30 | 15.8 (6) 15.3 (7) 46.3 (10) 43.0 (9) | 22.03 | 19.48 | 19.49 | 19.31 | 19.33 |
| 9 | 26.60 | 26.12 | 26.52 | 26.50 | 43.0 (8) | 26.18 | 26.31 | 25.69 | 26.25 | 26.07 |
| 10 | 13.32 | 14.14 | 13.94 | 13.75 | 46.3 (8) | 13.57 | 13.89 | 14.24 | 13.76 | 13.78 |

[a] chemical shifts are given in ppm, 50.32 MHz, *c* = 100-120 mg/ml; assignments marked with asterisk may have to be reversed; [b] in **$CDCl_3$-$CD_3OD$** 4:1 v/v; [c] in **$CDCl_3$**; [d] 100.13 MHz, 300 mg/ml in **$CD_2Cl_2$**; acetyl group - 21.67 *q* and 169.31 *s* ($^1J_{C-C}$ = 54.3 Hz); [e] phenyl group - 118.12 *d* (ortho), 124.82 *d* (para), 129.03 *d* (meta), 149.12 *s* (ipso)*; [f] methoxy group - 51.29 *q*; [g] acetyl group - 21.07 *q* and 166.42 *s*.

Compound **4** does not react with **$NH_2OH$** at room temperature, the reaction takes place only at elevated temperatures to give dioxime **5**, no isoxazole derivatives being detected. The same dioxime **5** is formed when keto derivative **6** is treated with **$NH_2OH$** in boiling methanol.

Eight stereoisomeric dioximes of the type **5** may be formed. Reaction of either enaminone **4** or ketone **6** with hydroxylamine results in a mixture of four stereoisomers in ratio 18:55:22:5 having trans-1-hydroxyiminoethyl group (singlet signal of **H**-3 atom for all of these isomers corresponds to the trans-location of **H**-3 and **H**-7 atoms in cyclopentane ring). The main component **5** is obtained by crystallization of the crude product. Nothing is known about the configuration of both oxime groups in this compound.

It should be pointed out, that isoxazole derivatives are not formed in the reaction of keto derivative **6** with **$NH_2OH$** either at room or at elevated temperatures. In the reactions of the hydroxylamine addition "pH of the reaction medium can be very crucial to regio specificity of the reaction and the use of hydroxylamine hydrochloride without a base in acetic acid may lead to undesirable isomer"[6]. At the same time, prolonged treatment of ketone **6** with **$NH_2OH{\times}HCl$** or **$NH_2OH$** at room temperature results in isoxazolinol **10**, whose structure was solved by X-ray analysis of the corresponding **O**-acetyl derivative **13** (***Figure 1***). Although, isoxazolinols are known to be unstable intermediate products in the reactions of isoxazoles formation[9],

compound **10** is unprecedented stable one. Our attempts to perform dehydration of hydroxy derivative **10** failed.

*Table 2.* **$^1$H NMR Data for Compounds 5 - 13[a].**

| | $\delta_H{}^i$, ppm (*J*, Hz) | | | | |
|---|---|---|---|---|---|
| *i* | **5** | **6**[b] | **7** | **8**[c] | **9**[d] |
| 1 | 1.69 *s* | 1.93 *s* | 2.20 *s* | 2.16 *s* | 2.26 *s* |
| 3 | 3.16 *s* ($W_{1/2}$ 3.5Hz) | - | - | - | - |
| 5 | 2.48 *m* 2H | βH: 2.53 *dd* (19.0, 7.5); αH: 2.16 *d* (19.0) | βH: 2.80 *dd* (17.0, 6.5); αH: 2.52 *ddd* (17.0, 1.0, 1.0) | βH: 2.94 *ddd* (18.5, 5.5, 2.0) αH: 2.77 *ddd* (18.5, 1.8, 1.8) | βH: 3.05 *dd* (17.0, 6.5); αH: 2.76 *ddd* (17.0, 1.5, 1.5) |
| 6 | 1.21 *ddd* (7.0, 4.5, 2.0) | 1.17 *dd* (7.5, 7.5) | 1.69 *ddd* (6.5, 6.5, 1.0) | 1.75 *m* | 1.78 *m* |
| 7 | 0.98 *d* (7.0) | 1.66 *d* (7.5) | 1.76 *dd* (6.5, 1.0) | 1.75 *m* | 1.83 *m* |
| 9 | 0.89 *s* | 1.02 *s* | 1.06 *s* | 1.06 *s* | 1.09 *s* |
| 10 | 0.74 *s* | 0.73 *s* | 0.64 *s* | 0.64 *s* | 0.68 *s* |

| | $\delta_H{}^i$, ppm (*J*, Hz) | | | |
|---|---|---|---|---|
| *i* | **10**[e] | **11** | **12**[f] | **13**[g] |
| 1 | 1.96 *s* | 2.05 *s* | 1.96 *s* | 2.00 *d* (0.5) |
| 3 | 2.91 *s* ($W_{1/2}$ 3.5 Hz) | 3.27 *s* ($W_{1/2}$ 3.5 Hz) | 2.89 *s* ($W_{1/2}$ 3.5 Hz) | 3.21 *s* ($W_{1/2}$ 3.5 Hz) |
| 5 | βH: 1.86 *dd* (14.5, 7.5); αH: 2.51 *dd* (14.5, 2.0) | βH: 2.88 *dd* (15.0, 7.0); αH: 2.15 *dd* (15.0, 2.0) | βH: 2.45 *dd* (14.5, 7.5); αH: 1.87 *dd* (14.5, 2.0) | βH: 2.85 *dd* (15.5, 7.5); αH: 2.00 *dd* (15.5, 2.0) |
| 6 | 1.18 *ddd* (7.5, 7.5, 2.0) | 1.34 *ddd* (7.0, 7.0, 2.0) | 1.18 *ddd* (7.5, 7.5, 2.0) | 1.23 *ddd* (7.5, 7.5, 2.0) |
| 7 | 0.97 *dd* (7.5, 1.0) | 1.05 *dd* (7.0, 1.0) | 0.98 *dd* (7.5, 1.0) | 1.03 *dd* (7.5, 1.0) |
| 9 | 1.03 *s** | 1.02 *s** | 0.98 *s** | 0.96 *s** |
| 10 | 0.96 *s** | 0.98 *s** | 0.94 *s** | 0.95 *s** |

[a] 200.13 MHz; for solutions of just the same concentrations as given in ***Table 1***; assignments marked with asterisk may have to be reversed; [b] hydroxyl group - 12.0 br. 1**H**; [c] 400.13 MHz, acetyl group - 2.49 *s* 3**H**; [d] phenyl group - 7.14 *m* 1**H** (para), 7.36 *m* 2**H** (meta), 7.54 *m* 2**H** (ortho); [e] hydroxyl group - 5.0 br. 1**H**; [f] methoxy group - 3.15 *s* 3**H**; [g] acetyl group - 1.93 *s* 3**H**.

Thus, treatment of **10** with $SOCl_2$ in boiling benzene gives rise to chloro derivative **11** instead of dehydration[10]. The chloro derivative is quite unstable either at chromatography ($SiO_2$) or at the distillation procedures and we were not able to obtain satisfactory elemental analysis for this product. Reaction of **11** with $CH_3OH$ results in methoxy derivative **12**. This fact, together with the data of NMR (*Tables 1* and *2*) and IR spectra (see Experimental), supports the structure of chloro derivative **11**. Tolerance for dehydration of the hydroxy derivative seems to result from extremely unfavorable relative positions of the hydroxy group and H-3 atom. According to the X-ray data for O-acetyl derivative **13**, dihedral angle O2-C4-C3-H3 is about -17°. At the same time, there is a possibility of the proton elimination from the side chain of the isoxazolinol ring as it was demonstrated for certain derivatives of this type[11]. Nevertheless, such a product is not formed in the case of compound **10**. The reason is probably the same: dihedral angles O2-C4-C5-H5α and O2-C4-C5-H5β are 9° and -106° respectively (according to X-ray data for compound **13**). In addition, such a product with exo-cyclic carbon-carbon double bond (relative to the heterocycle)should be markedly strained. Treatment of isoxazolinol with an excess of $NH_2OH$ produces dioxime **5**. Equilibrium isoxazolinol = diketone mono oxime was reported[12], and the equilibrium may be the reason of formation of **5** from **10**.

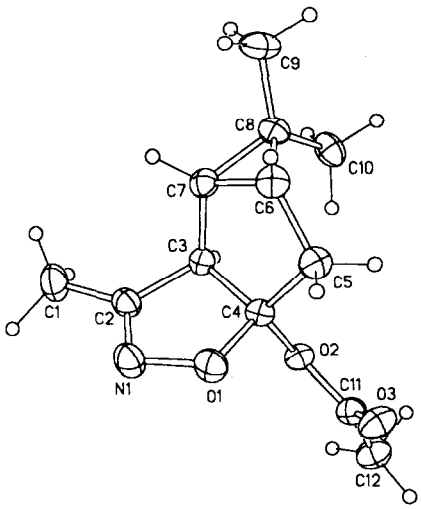



***Figure 1.***

Molecular structure of compound **13**. Thermal ellipsoids are shown at the 30% probability level. Selected bond lengths (Å) are as follows: O(1)-N(1) 1.443(4), O(1)-C(4) 1.422(4), N(1)-C(2) 1.275(5), O(2)-C(4) 1.453(4). Both five-membered cycles have envelope-like conformation, C-4 being out of the plane of both rings (by 0.231(5) Å for the carbon ring and by 0.216(5) Å for the heterocycle). Dihedral angle between the planes of the five-membered rings is 64.2(2)°.

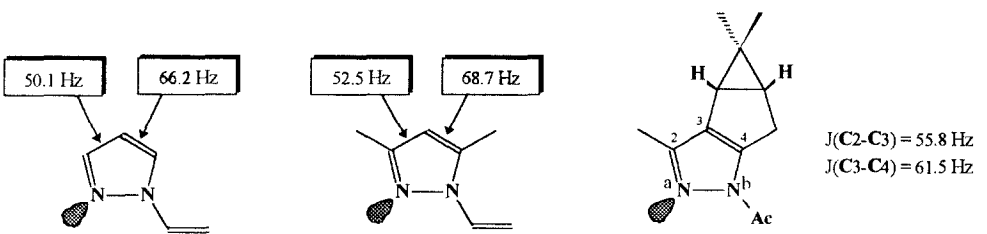
Enaminone **4** also demonstrates remarkable stability in usual hydrolytic conditions. In contrast to the known enaminones with primary amino group[13], compound **4** is rather stable in acidic medium and can be purified through hydrochloride[2]. Nevertheless, hydrolysis of enaminone **4** is possible under more drastic conditions: treatment of **4** with aqueous **HCl** in boiling methanol results in keto derivative **6**. The same product may result from the based-induced intramolecular addition to ester group in compound **3**. Possibility of the ketone **6** formation from keto ester **3** in the presence of a base has been discussed earlier[14] but the product has not been isolated. As one can see from $^1H$ and $^{13}C$ NMR spectra of compound **6** (*Tables 1* and *2*), only one of two possible enolic tautomers exists in a solution. Comparison of the $^1H$ and $^{13}C$ chemical shifts for compound **6** with those for enaminone **4** (see ref.[2]) supports the structure of 4-oxo derivative **6** for the condensation product.

β-Dicarbonyl compounds are useful starting material for the syntheses of 1,2-diazoles[5,15]. Treatment of keto derivative **6** with phenylhydrazine results in a complex mixture of the addition products, while the presence of acetic acid provides N-phenyl derivative **9** in good yield. Enaminone **4** is inert to phenylhydrazine either in the presence or in the absence of acetic acid, and the reaction does not take place at more rigorous conditions as well. Treatment of enaminone **4** with hydrazine hydrate yields pyrazole **7**, although this reaction takes place at more arduous conditions (reflux for 6h in ethylene glycol) than the reaction of keto derivative **6** requires (30 min at room temperature).

$^{1}$**H** and $^{13}$**C** NMR spectra of pyrazole and its **C**- and **N**-substituted derivatives have been studied[5,16]. However, comparison of the data published with those obtained for the pyrazole type derivatives **7-9** (***Tables 1*** and *2*) does not enable one to make an unambiguous assignment of the carbon resonances and so that to determine the place of attachment of a substituent in the heterocycle (to the nitrogen atom **N**-a or **N**-b).

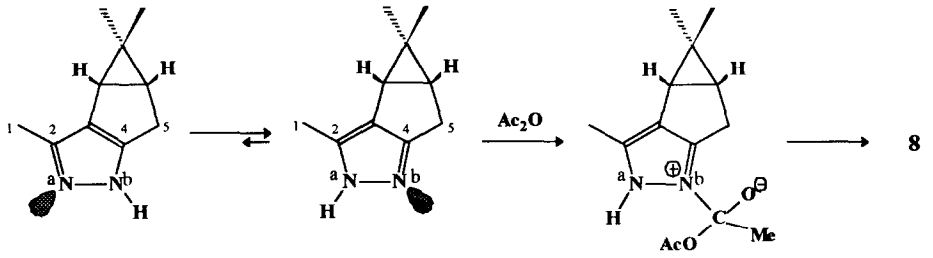
It is generally known, that acylation of pyrazole derivatives can give a pair of isomeric N-acylated products, but asymmetric substituted pyrazoles are usually converted to the less hindered one because, due to acylotropy, the less stable isomer is transformed in the reaction medium into the more stable one . Treatment of the pyrazole derivative **7** with $\mathbf{Ac_2O}$ at -5°C results in a single isomer. We failed to determine the acetyl group position in this compound using $^{1}$**H** and $^{13}$**C** chemical shifts and long range coupling constants. At the same time, values of one-bond coupling constants in the pyrazole ring are known to depend on the position of a substituent (at **N**-a or **N**-b). Comparison of the $^{1}J_{\mathbf{C\text{-}C}}$ values taken from ref.[17] and shown on ***Figure 2*** with those obtained for the acylated product **8** proves the structure of this compound having the acetyl group attached to the **N**-b atom.

***Figure 2.***




Formation of the **N**-b substituted derivative can be easily explained in terms of less steric hindrance of this position. Molecular mechanics and MNDO calculations for two tautomeric pyrazoles **7a** and **7b** show significant asymmetric deformation of exocyclic bond angles in the pyrazole ring of both forms. According to the calculations (***Scheme 2***), the value of the bond angle **C**5-**C**4-**N**b is by 12-17° larger than that of angle **C**1-**C**2-**N**a. So, the **N**-b position is less hindered to the attack of a reagent, and the possible intermediate adduct **14** should be more stable. In addition, tautomer **7b** leading to the acylation product is more stable. Thus, addition of the acethyl group to the **N**-b position not only leads to the more stable isomer, but also should proceed more rapidly.

*Scheme 2.*




**7a** **7b** **14**

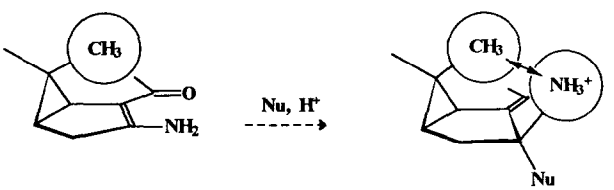
| | | |
|---|---|---|
| $\Delta H_f^o$ (kcal/mol): | | |
| PM3: | 57.3 | 55.8 |
| MMX: | 58.9 | 55.5 |
| $\theta$ (C1-C2-Na): | | |
| PM3: | 123.5° | 125.2° |
| MNDO: | 122.9° | 121.4° |
| $\theta$ (C5-C4-Nb): | | |
| PM3: | 140.2° | 137.3° |
| MNDO: | 136.4° | 139.5° |

Heats of formation and selected bond angles for tautomeric forms of compound 7 according to the molecular mechanics (MMX program[18]) and quantum chemical (MNDO program[19] with standard and PM3 parameterization[20]) calculations.

A correlation between the carbon chemical shifts of N-acylated derivative **8** and those of pyrazole **7** and N-phenyl derivative **9** shows the phenyl group to be attached to N-b atom in the latter compound. Formation of compound **9** as a single isomer may result from the higher stability of this product as compared with corresponding N-a-substituted isomer.

Stability of enaminone **4** to nucleophilic addition (hydrolysis, reactions with $NH_2OH$ or $NH_2NH_2$) may be due to the specific steric structure of this compound. Addition of different type nucleophiles to the enaminone conjugated system is known to proceed at the enamine fragment[8]. Nucleophilic addition at the C-4 atom in the enaminone molecule **4** requires intermediate formation of an adduct like **15** having tetrahedron carbon atom C-4. One of the methyls of the dimethylcyclopropane unit may inhibit this process (see *Scheme 3*).

*Scheme 3.*




**15**

## EXPERIMENTAL

*General experimental procedures* All the solvents used were reagent-quality. Petroleum ether refers to that fraction which boils in the range 40-70°C. Diethyl ether was freshly distilled. Removal of all solvents was carried out under reduced pressure and all commercial reagents were used without additional purification. Analytical TLC plates were **Silufol**® (Silpearl on aluminum foil, Czecho-Slovakia). Preparative column chromatography was performed on $SiO_2$ ("KSK", Russia, 100-200 mesh, air dried and activated at 140°C for 5h) or $Al_2O_3$ (Brockmann II, neutr., **Reanal**®, Hungary). IR spectra were obtained using a ***Specord M-80*** spectrometer. UV spectra were obtained for 1% solutions in **EtOH** using a ***Specord UV VIS*** spectrometer. A ***Polamat A*** polarimeter was used to measure optical rotation at 578 nm. Melting points were obtained using a ***Kofler*** melting point apparatus and are uncorrected. Mass spectra were obtained on a ***Finnigan MAT 8200*** instrument using the Electron Impact Ionization technique (50-150°C, 70eV). For some of the new compounds, precise mass determination for the molecular ion of a pure sample were obtained instead of combustion analyses. Purity was determined from constancy of melting point together with TLC and NMR data. $^1H$ and $^{13}C$ NMR spectra were recorded at room temperature for 5-10% solutions using standard Bruker NMR Software System on a ***Bruker AC 200*** instrument ($^1H$ 200.13 MHz, $^{13}C$ 50.32 MHz) and a ***Bruker AM-400*** instrument ($^1H$ 400.13 MHz, $^{13}C$ 100.61 MHz) locked to the deuterium resonance of the solvent ($CDCl_3$). The chemical shifts were calculated relative to the solvent signal using as internal standard: $\delta_H$ 7.24 ppm and $\delta_C$ 76.90 ppm. Carbon-carbon coupling constants $^1J_{CC}$ were measured by INADEQUATE techique.

*X-Ray crystallographic experiment.* Intensity data for compound **13** were collected at 298°K on a **SYNTEX-P2$_1$** diffractometer using graphite monochromated CuKα radiation (λ = 1.54178 Å). After absorption correction, the structure was solved using SHELX-86, refinement was carried out by full-matrix least-squares procedure using SHELX-93. The structure of the compounds is shown on ***Figure 1.***

Crystal data and structure refinement for compound **13**: $C_{12}H_{17}NO_3$, $M$ = 223.27, orthorhombic, space group $P2_12_12_1$, $a$ = 6.3540(10) Å, $b$ = 7.4270(10) Å, $c$ = 25.428(3) Å, $U$ = 1200.0(3) Å$^3$, Z = 4, $D_c$ 1.236 g×cm$^{-3}$, μ = 0.725 mm$^{-1}$, *F(000)* = 480. Crystal size 0.50×0.26×0.19 mm$^3$. Theta range for data collection: from 3.48 to 67.50°. Index ranges: 0≤h≤7, 0≤k≤8, 0≤l≤30. Reflections collected: 1280. Independent reflections: 1249 [R(int) = 0.0170]. Max. and min. transmission: 0.90 and 0.80. Data/restraints/parameters - 1249/0/214. Goodness-of-fit on $F^2$: 1.114. Final R indices [I>2σ(I)]: $R_1$ = 0.0495, $wR_2$ = 0.1446. R indices (all data): $R_1$ = 0.0545, $wR_2$ = 0.1503. Absolute structure parameter: 0.1(5). Extinction coefficient: 0.0030(12). Largest diff. peak and hole: 0.182 and -0.190 e.Å$^{-3}$.

Atomic coordinates, bond length and angles, and thermal parameters have been deposited in the Cambridge Crystallographic Data Center.

(*1R,3S*)-2,2-Dimethyl-3-(2-oxopropyl)-cyclopropanacetonitrile (**2**) and methyl (*1R,3S*)-2,2-dimethyl-3-(2-oxopropyl)-cyclopropanacetate (**3**) were purchased from JANSSEN CHIMICA.

*(1R,2R,5R)-6,6-Dimethyl-3-hydroxyimino-2-(1-hydroxyiminoethyl)-bicyclo[3.1.0]hexane* (**5**). Powdered **$NH_2OH$×HCl** (2.0 g, 29 mmol) and **NaOAc** (2.4 g, 29 mmol) were added to a stirred solution of enaminone **4** (1.0 g, 6.1 mmol) in **$CH_3OH$** (20 mml). The mixture was stirred at reflux for 8 h. The solvent was evaporated at reduced pressure, the residue was treated with 1N aq. **KOH** (50 ml) and extracted with ether (2×10 ml). The

aqueous phase was acidified with 20% aq. **HCl** (pH 3) and extracted with ether (3×20 ml). The combined ethereal extracts were dried over $Na_2SO_4$, filtered and concentrated to give 0.66 g (56%) of a *ca.* 18:55:22:5 mixture of the isomeric dioximes ($^1H$ NMR data for $CDCl_3$-solution; $\delta_{H-3}$, ppm: 3.18 *s*, 3.29 *s*, 3.61 *s*, 3.78 *s*), *the title compound* being the main component of the mixture. Crystallization of the crude product resulted in *the title compound* (0.25 g, 21%) as pale yellow solid: m.p. 159-160°C (aqueous isopropanol); $[\alpha]^{23}$ +49.2 (*c* 2.0, **EtOH**); IR (*c* 1% in $CHCl_3$): 3590 (**O-H**); 1650 (**C=N**), 940, 910; MS (*m/z*): 196.1213 {$C_{10}H_{16}N_2O_2$ requires 196.1212} ($M^+$, 94%), 179 ($M^+$-**OH**, 90), 164 (100), 147 (49), 141 (42), 138 (35), 124 (32), 122 (26), 121 (35), 120 (30), 106 (28).

Reaction of ketone **6** (0.60 g, 3.6 mmol) with $NH_2OH$×**HCl** (1.2 g, 17 mmol) and **NaOAc** (1.5 g, 18 mmol) in boiling $CH_3OH$ (5 ml) for 3 h gave ca. 16:58:21:6 mixture of stereoisomers of *the title compound* (0.46 g, 65%) as yellowish solid.

*(1R,5R)-6,6-Dimethyl-2-(1-hydroxyethylidene)-bicyclo[3.1.0]hexan-3-one* (**6**). Keto ester **3** (30.0 g, 0.15 mol) was added to a $NaOCH_3$ solution (6.0 g of **Na** + 150 ml of $CH_3OH$) and the mixture was stirred at reflux for 15 min. The reacton mixture was diluted with water (500 ml) and extracted with benzene (2×50 ml). The aqueous phase was acidified with 20% aq. **HCl** (pH 2) and extracted with ether. The organic extracts were washed with 5% aq. $NaHCO_3$ (2×50 ml), dried ($Na_2SO_4$) and concentrated to give *the title compound* (20.3 g, 81%) as dark yellow liquid: b.p. 75-78°C/2÷3 mm **Hg**; $[\alpha]^{22}$ -108 (*c* 5.66, $CHCl_3$); IR (*c* 1% in $CHCl_3$): 3600 (**O-H**), 3400-2400 (**O-H**, H-bonded), 3025 (**C-H**, cyclopropane), IR (film): 1665 (**C=O**), 1610 (**C=C**), 1225 (**C-O**); UV: 304 (ε 7300), 208 (ε 3400); MS (*m/z*): 166.0993 {$C_{10}H_{14}O_2$ requires 166.0994} ($M^+$, 59%), 151 (100), 133 (50), 109 (26), 105 (12), 95 (8), 79 (10).

A solution of enaminone **4** (5.0 g, 30 mmol) in a mixture of $CH_3OH$ (10 ml) and 0.054N aq. **HCl** (55 ml) was stirred at 80°C for 3 h to give *the title compound* (4.25 g, 85%).

*(1S,8R)-3,9,9-Trimethyl-4,5-diazatricyclo[6.1.0.0$^{2,6}$]non-2(6),3-diene* (**7**). Hydrazine hydrate (1.0 g, 20 mmol) was added dropwise at vigorous stirring to a hot (100°C) solution of enaminone **4** (0.30 g, 1.8 mmol) in ethylene glycole (5 ml). The mixture was stirred at reflux for 6 h to give *the title compound* (0.25 g, 85%) as yellowish solid: m.p. 119-120°C (after sublimation in vacuo); $[\alpha]^{20}$ +48.0 (*c* 4.66, $CHCl_3$); found **C** 74.04, **H** 8.64, **N** 17.42; $C_{10}H_{14}N_2$ requires **C** 74.03, **H** 8.70, **N** 17.27; IR (*c* 1% in $CHCl_3$): 3460 (**N-H**), 1630 (**C=C**, **C=N**); UV: 330 (ε 100), 292 (ε 160), 237 (ε 4800), 209 (ε 3600); MS (*m/z*): 162 (33), 147 (100), 132 (11), 120 (4), 119 (4), 106 (18), 79 (7), 77 (5).

Reaction of ketone 6 (1.00 g, 6.0 mmol) with hydrazine hydrate (0.35 g, 7.0 mmol) in a mixture of $CH_3OH$ (5 ml) and glacial **AcOH** (1 ml) for 1 h at room temperature and the 30 min at reflux gave *the title compound* (0.85 g, 87%).

*(1S,8R)-5-Acetyl-3,9,9-trimethyl-4,5-diazatricyclo[6.1.0.0$^{2,6}$]non-2(6),3-diene* (**8**). Reaction of pyrazole **7** (2.50 g, 15.4 mmol) with $Ac_2O$ (1.73 g, 16.9 mmol) and **Py** (1.33 g, 16.9 mmol) in $CHCl_3$ (20 ml) at -5°C for 1 h gave *the title compound* (3.00 g, 95%) as white chrystals: m.p. 106-107°C (hexane); $[\alpha]^{20}$ +219 (*c* 1.70, $CHCl_3$); IR (in **KBr**): 3025 (**C-H**, cyclopropane), 1705 (**C=O**), 1585 (**C=C**, **C=N**); UV: 270 (ε 7200), 242 (ε 7300), 205 (ε 6600); MS (*m/z*): 204.1270 {$C_{12}H_{16}N_2O$ requires 204.1263} ($M^+$, 10%), 189 ($M^+$-$CH_3$, 13), 162 (17), 147 (100), 106 (9).

*(1S,8R)-5-Phenyl-3,9,9-trimethyl-4,5-diazatricyclo[6.1.0.0$^{2,6}$]non-2(6),3-diene* (**9**). Reaction of ketone **6** (0.20 g, 1.2 mmol) with phenylhydrazine (0.14 g, 1.3 mmol) and **AcOH** (0.16 g, 2.7 mmol) in boiling $CH_3OH$

(3 ml) for 8 h resulted in *the title compound* (0.25 g, 87%) as red oil which was then purified by column chromatography on a silica gel column: $[\alpha]^{21}$+149 (*c* 1.07, **$CHCl_3$**); IR (*c* 1% in **$CHCl_3$**): 1600, 1650, 1510 (**C=N**, **C=C**); UV: 350 (ε 294), 275 (ε 14000), 236 (ε 8300), 208 (ε 16000); MS (*m/z*): 238.1470 {**$C_{16}H_{18}N_2$** requires 238.1470} ($M^+$, 18), 223 ($M^+$-**$CH_3$**, 100), 167 (12).

*(1R,2R,6R,8R)-6-Hydroxy-3,9,9-trimethyl-5-oxa-4-azatricyclo[6.1.0.0$^{2,6}$]non-3-ene* (**10**). Reaction of ketone **6** (4.50 g, 27.1 mmol) with **$NH_2OH$×HCl** (2.16 g, 32.0 mmol) and **NaOAc** (2.60 g, 32.0 mmol) in methanol (50 ml) at room temperature for 20 h resulted in *the title compound* (4.10 g, 83%) as yellowish crystals: m.p. 132-133°C (toluene-hexane); $[\alpha]^{21}$ -87.0 (*c* 6.44, **$CHCl_3$**); found **C** 66.07, **H** 8.78, **N** 7.66; **$C_{10}H_{15}NO_2$** requires **C** 66.27, **H** 8.34, **N** 7.73 IR (*c* 1% in **$CHCl_3$**): 3590 (**O-H**); IR (in KBr): 3025 (**C-H**, cyclopropane), 1630 (**C=N**), 1140 (**C-O**), 870; MS (*m/z*): 181 ($M^+$, 0.2%), 166 ($M^+$-**$CH_3$**, 17), 137 (22), 124 (32), 109 (100), 96 (24), 95 (24), 79 (24), 67 (36).

*(1R,2R,6S,8R)-6-Chloro-3,9,9-trimethyl-5-oxa-4-azatricyclo[6.1.0.0$^{2,6}$]non-3-ene* (**11**). A solution of isoxazolinol **10** (0.90 g, 5.0 mmol), **$SOCl_2$** (0.71 g, 6.0 mmol) and **Py** (1.96 g, 25 mmol) in benzene (10 ml) was stirred at reflux for 8 h to give *the title compound* (0.65 g, 65%) as brown oil, which was then purified by chromatography on a **$Al_2O_3$** column affording yellowish oil: *ca.* 95% of *the title compound* (according to $^1$**H** NMR), $[\alpha]^{21}$ -226 (*c* 2.10, **$CHCl_3$**); IR (film): 3025 (**C-H**, cyclopropane), 1630 (**C=N**), 865, 815 (**C-Cl**); MS (*m/z*): 199 ($M^+$, 1%).

*(1R,2R,6R,8R)-6-Methoxy-3,9,9-trimethyl-5-oxa-4-azatricyclo[6.1.0.0$^{2,6}$]non-3-ene* (**12**). A solution of *p*-toluenesulfonic acid (0.1 g) in **$CH_3OH$** (5 ml) was added to a solution of the crude chloride **11** (prepared from 0.9 g, 5 mmol of **10** and 0.71 g, 6 mmol of **$SOCl_2$** as described above) in benzene (10 ml) at 0°C. The reaction mixture was kept at room temperature for 14 h and concentrated at reduced pressure. The residue was extarcted with ether to give *the title compound* (0.53 g, 54%) as light brown oil which was then purified by column chromatography on a silica gel column: $[\alpha]^{21}$ -121 (*c* 5.38, **$CHCl_3$**); found **C** 67.62, **H** 8.82, **N** 7.26; **$C_{11}H_{17}NO_2$** requires **C** 67.66, **H** 8.78, **N** 7.17; IR (film): 3025 (**C-H**, cyclopropane), 1625 (**C=N**), 1120 (**C-O**), 890, 870; MS (*m/z*): 195 ($M^+$, 3%), 181 (8), 154 (7), 149 (5), 138 (22), 136 (20), 122 (100), 114 (11), 95 (31).

*(1R,2R,6R,8R)-6-Acetoxy-3,9,9-trimethyl-5-oxa-4-azatricyclo[6.1.0.0$^{2,6}$]non-3-ene* (**13**). Treatment of isoxazolinol **10** (0.90 g, 5.0 mmol) with **$Ac_2O$** (2.2 g, 21 mmol) and **$Et_3N$** (2.2 g, 24 mmol) at room temperature (36 h) resulted in *the title compound* (0.90 g, 81%) as yellow solid: m.p. 98-99°C (toluene-hexane); $[\alpha]^{21}$ -176 (*c* 5.26, **$CHCl_3$**); found **C** 64.61, **H** 7.93, **N** 6.22; **$C_{12}H_{17}NO_3$** requires **C** 64.55, **H** 7.67, **N** 6.27; IR (in KBr): 3025 (**C-H**, cyclopropane), 1740 (**C=O**), 1625 (**C=N**), 1245 and 1210 (**C-O-C**), 865; MS (*m/z*): 223 ($M^+$, 0.1%), 181 (41), 164 (43), 163 (68), 148 (100), 124 (50), 122 (82), 109 (39), 84 (54), 79 (21), 67 (10).

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