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# 5,5,6-Trimethylbicyclo[2.2.1]heptan-2-one in the Synthesis of Carbocyclic Analogs of Prostaglandin Endoperoxides

**F. S. Pashkovskii[1], F. A. Lakhvich[1], S. S. Koval'skaya[2], and N. G. Kozlov[2]**

[1] *Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, Belarus*

[2] *Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, ul. Surganova 13, Minsk, 220072 Belarus*

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**Abstract**—1,3-Dipolar cycloaddition of nitrile oxides to 5,5,6-trimethyl-*exo*-2-ethynylbicyclo[2.2.1]heptan-*endo*-2-ol yields the corresponding 2-(isoxazol-5-yl) derivatives. Opening of the isoxazole ring in the latter gives rise to prostanoid precursors with partially built up or completed side chain. 5,5,6-Trimethyl-3-methylenebicyclo[2.2.1]heptan-2-one reacts with nitromethane in the presence of tetramethylguanidine to afford 5,5,6-trimethyl-*exo*-3-(2-nitroethyl)bicyclo[2.2.1]heptan-2-one which can be converted into the corresponding nitrile oxide by the action of phenyl isocyanate in benzene in the presence of triethylamine as catalyst. 1,3-Dipolar cycloaddition of the nitrile oxide to ethyl 4-pentynoate yields 3-*exo*-[5-(2-ethoxycarbonylethyl)isoxazol-3-ylmethyl]-5,5,6-trimethylbicyclo[2.2.1]heptan-2-one. Treatment of the latter with hydroxyl amine leads to formation of the corresponding *Z*-oxime whose reaction with *n*-hexyl bromide results in transalkylation of the ester group to afford 3-*exo*-[5-(2-hexyloxycarbonylethyl)isoxazol-3-ylmethyl]-5,5,6-trimethylbicyclo[2.2.1]heptan-2-one oxime.

Prostaglandins are important bioregulators which participate in a large number of biochemical reactions and are capable of influencing cell metabolism [1, 2]. However, naturally occurring prostaglandins have not received wide application as pharmaceuticals for the following reasons: (1) concentration of prostaglandins in natural materials is very low, so that their isolation for use in medical practice seems to be unreasonable; (2) natural prostaglandins are characterized by low selectivity of the biological effect, which restricts possible scope of their application; and (3) prostaglandins are very labile compounds from the chemical and metabolic viewpoints. Therefore, an important problem is to obtain synthetic analogs of prostaglandins, possessing pronounced biological activity, high selectivity, and sufficient chemical stability.

In the recent years much efforts were made to synthesize prostaglandin analogs on the basis of compounds having a bicyclo[2.2.1]heptane (norbornane) skeleton. Such prostanoids are carbocyclic analogs of prostaglandin endoperoxides; in some cases, they showed desired biological activity, being incommensurably more stable than their natural analogs [3, 4]. In the present work we examined the possibility of using 5,5,6-trimethylbicyclo[2.2.1]heptan-2-one (**I**) as starting compound in the synthesis of prostaglandin analogs.

It is known that prostaglandin structure implies the presence of two vicinal side carbon chains at a five-membered ring, i.e., at the $C^2$ and $C^3$ atoms of the bicyclo[2.2.1]heptane skeleton. The carbonyl group in **I** can be converted into a prostanoid side chain via the isoxazole technique which was proposed previously. By reaction of ketone **I** with lithium acetylide we obtained *exo*-2-ethynyl-5,5,6-trimethylbicyclo[2.2.1]heptan-*endo*-2-ol (**II**) [5]. Compound **II** was brought into reaction with acetonitrile oxide which was generated *in situ* by the action of phenyl isocyanate on nitroethane in benzene in the presence of a catalytic amount of triethylamine. The addition was regioselective, and the reaction yielded 2-(5-isoxazolyl) derivative **III**. The isoxazole ring in **III** was cleaved by the action of sodium tetrahydridoborate in the presence of a Ni(II) salt as catalyst in methanol [6]. Enamino ketone **IV** was obtained in 65% yield (Scheme 1).

The structure of isoxazolyl derivative **III** and enaminoketone **IV** was established on the basis of the

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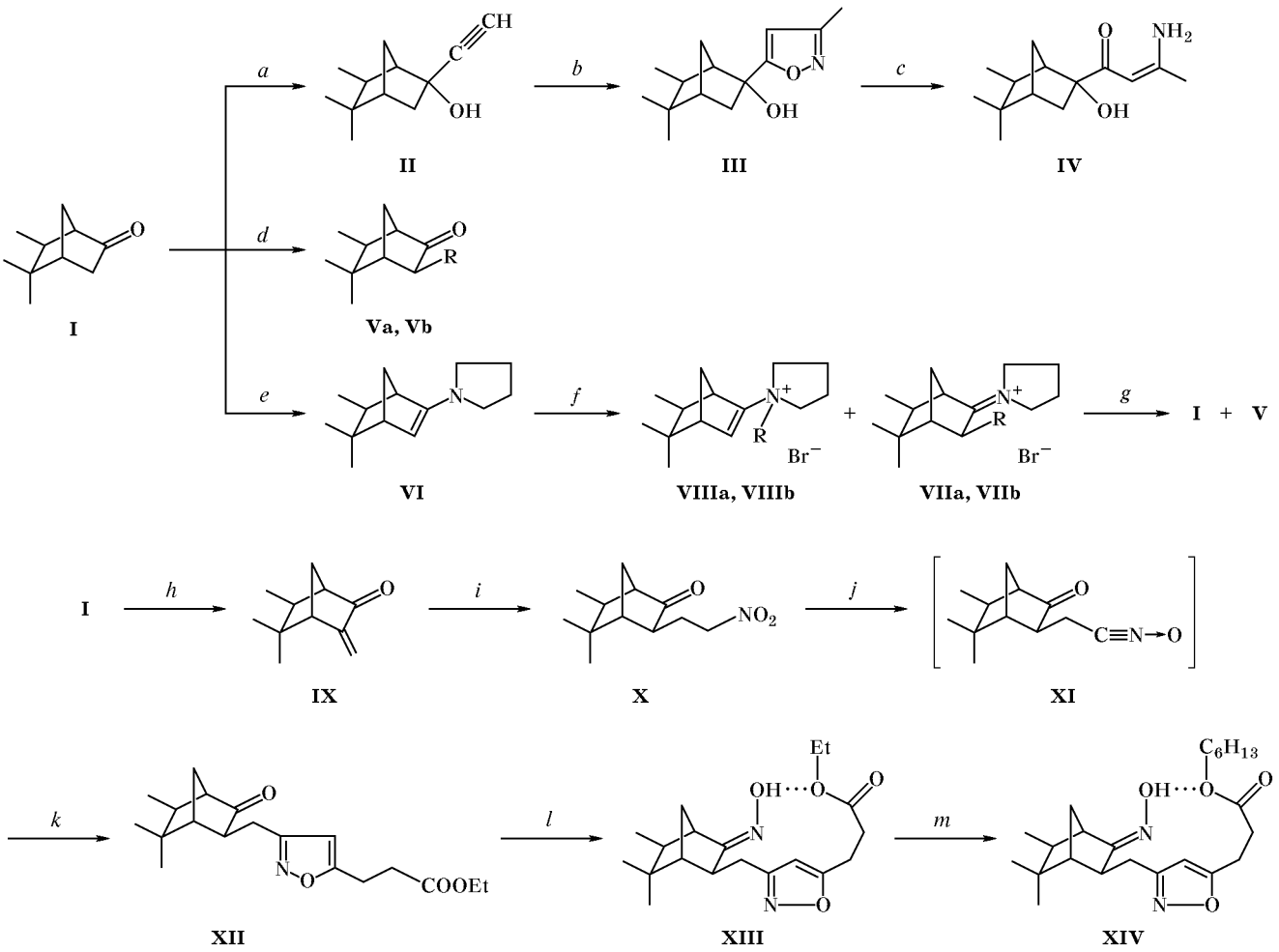
**Scheme 1.**



R = $CH_2CH{=}CH_2$ (**a**), $CH_2COOEt$ (**b**). *a*: $HC{\equiv}CLi$, THF; *b*: $CH_3C{\equiv}N{\rightarrow}O$, benzene; *c*: $NaBH_4/NiSO_4 \cdot 7H_2O$, MeOH; *d*: $BrCH_2CH{=}CH_2$ or $BrCH_2COOEt$, *t*-BuOK/*t*-BuOH; *e*: pyrrolidine, toluene, *p*-TsOH, Δ; *f*: $BrCH_2CH{=}CH_2$ or $BrCH_2COOEt$, *t*-BuOK/*t*-BuOH; *g*: $H_2O$; *h*: (1) $(CH_2O)_n$, $Me_2NH \cdot HCl$; (2) KOH, EtOH; (3) $CH_3I$, EtOH; (4) NaOH, EtOH, Δ; *i*: $CH_3NO_2$, $[(CH_3)_2N]_2C{=}NH$; *j*: PhNCO, $Et_3N$, benzene; *k*: $HC{\equiv}CCH_2CH_2COOEt$; *l*: $NH_2OH$, EtOH; *m*: $CH_3(CH_2)_5Br$.

$^1$H NMR and IR spectra. The IR spectrum of **III** contained a band at 3340 $cm^{-1}$, typical of hydroxy group vibrations, and a band at 1605 $cm^{-1}$, which can be assigned to vibrations of isoxazole ring. In the $^1$H NMR spectrum of **III** we observed signals from methyl groups in the norbornane moiety (see Experimental), a singlet from the methyl group in the isoxazole ring (δ 2.26 ppm), and a singlet at δ 5.98 ppm, belonging to 4-H of the isoxazole ring. The 1-H and *exo*-3-H signals are displaced strongly upfield, as compared with the spectrum of compound **II**, δ, ppm: 1.07 br.s and 1.02 d.d, $J$ = 14.0, 4.0 Hz). This is the result of shielding by the isoxazole ring, and we can conclude that the heteroring is located in the plane orthogonal to the $C^1{-}C^2$ and $C^2{-}C^3$ bonds.

Enamino ketone **IV** showed in the IR spectrum hydroxy group absorption at 3430 $cm^{-1}$, NH vibration bands at 3320 and 3220 $cm^{-1}$ (free NH group and that involved in intramolecular hydrogen bond), and bands at 1635 and 1620 $cm^{-1}$ from conjugated C=O and C=C bonds.

Unlike isoxazole derivative **III**, the $^1$H NMR signals from the norbornane fragment of **IV** have their usual positions (see Experimental). The terminal methyl protons give a signal at δ 1.92 ppm, whose position is typical of a methyl group located at a conjugated double bond. These data indicate that compound **IV** exists in the enamino form. This structure is also supported by the presence of two signals from the $NH_2$ protons, δ 9.55 ppm (chelated) and

δ 4.98 ppm (nonchelated), and of a singlet from the olefinic proton at δ 5.25 ppm.

Thus the reaction sequence consisting of 1,3-dipolar cycloaddition of nitrile oxide to ethynylcarbinol and opening of the isoxazole ring gives rise to prostaglandin α- or ω-chain, depending on the nitrile oxide structure. A group capable of being transformed into the second prostaglandin chain is often introduced into bicycloheptane skeletone through α-alkylation of appropriate oxo derivatives. As a rule, enolates derived from ketones by the action of strong bases or enamines obtained by condensation of ketone with secondary amines are alkylated with activated halogen derivatives, e.g., allyl bromide, 2-propynyl bromide, or ethyl bromoacetate. The substituent introduced in such a way into the α-position relative to the carbonyl group can be converted into a prostanoid side chain via known chemical methods.

However, in our case an attempt to follow this approach was unsuccessful. We failed to effect alkylation of ketone **I** with the above alkyl halides in the presence of potassium *tert*-butoxide: the yield of the target products did not exceed few percent. Also, the alkylation of enamine **VI** (Stork reaction) obtained from ketone **I** and pyrrolidine in the presence of *p*-toluenesulfonic acid did not resulted in formation of the target products with an acceptable yield. First, the formation of enamine is reversible, and the conversion of ketone **I** into compound **VI** did not exceed 50% even when liberated water was removed from the reaction mixture by azeotropic distillation. Second, the alkylation of enamine **VI** is characterized by low selectivity, and both 3- (**VII**) and *N*-alkylated (**VIII**) products were formed; moreover, the fraction of the latter was appreciably greater. Taking into account that hydrolysis of **VIII** leads to formation of initial ketone **I**, the yield of the target alkylation products was poor (see Experimental).

With the above in mind, we developed an alternative approach to 3-substituted 5,5,6-trimethylbicyclo[2.2.1]heptan-2-ones. We previously [7] reported on the synthesis of 5,5,6-trimethyl-3-methylenebicyclo[2.2.1]heptan-2-one (**IX**) by transformation of ketone **I** into the corresponding Mannich base and deamination of the latter (Hofmann rearrangement). The presence in molecule **IX** of an activated double bond led us to expect addition of CH acids according to Michael. In fact, enone **IX** reacted with nitromethane in the presence of tetramethylguanidine to give *exo*-3-(2-nitroethyl) derivative **X** in a preparative yield; the reaction was fairly fast. Presumably, skeletal strains inherent to the bicyclic ketone with two semicyclic double bonds favor formation of a compound with less strained skeleton. The *exo* orientation of the substituent on $C^3$ in nitro ketone **X** was deduced from the $^1$H NMR data. The 4-H signal appears as a broadened singlet (coupling constants for 4-H and neighboring protons do not exceed 2 Hz). Hence it is obvious that the proton on $C^3$ is oriented *endo*, otherwise (*exo*-3-H) its coupling constant with 4-H should be no less than 4 Hz. The steric structure of compound **X** is consistent with nitromethane addition from the spatially more accessible *exo* side of molecule **IX**, which conforms to the generally accepted views on the stereochemistry of Michael addition.

Further transformation of the nitroethyl group in **X** into prostaglandin α(ω)-chain implies application of the above noted nitrile oxide technique with the only difference that the nitro group resides in the bicycloheptane fragment. The transformation was effected by the standard procedure, i.e., by the action of phenyl isocyanate in benzene in the presence of a catalytic amount of triethylamine. Cycloaddition of the resulting nitrile oxide **XI**, e.g., to ethyl 4-pentynoate, gave *exo*-3-[2-(5-ethoxycarbonylethyl)isoxazol-3-ylmethyl]bicyclo[2.2.1]heptan-2-one (**XII**) which has a completed $C^7$-carboxyalkyl α-chain containing isoxazole fragment. The latter can be converted into open chain via numerous known methods (e.g., as described above).

However, this procedure cannot be applied to transformation of the carbonyl group in isoxazolyl ketone **XII** into prostanoid ω-chain, for molecule **XII** possesses other centers capable of reacting with organolithium compounds. First of all, such a reaction center is the ester group. Also, partial or complete cleavage of the isoxazole ring is possible: in the presence of bases isoxazole ring can behave as an equivalent of β-diketone or β-diketone monooxime. Therefore, the $C^2$=O carbonyl group in **XII** was converted into prostanoid side chain by a different procedure. For this purpose, ketone **XII** was treated with hydroxylamine to obtain oxime **XIII**. The *Z* configuration of the hydroxyimino group in **XIII** was established on the basis of the $^1$H NMR data. We previously showed [8] that the chemical shifts of 1-H in 5,5,6-trimethylbicyclo[2.2.1]heptan-2-one oximes are δ 2.46 and 3.11 ppm for the *E* and *Z* isomers, respectively. In the spectrum of *E* isomers, the 1-H signal is only slightly displaced to a weaker field relative to the 1-H signal of the initial ketone (δ 2.23 ppm). The $^1$H NMR spectrum of ketone **XII** contained two

broadened singlets at δ 2.31 and 2.35 ppm, which belong to the 1-H and 4-H protons in the bridgehead positions. The $^1$H signals of oxime **XIII** were assigned using double-resonance spectra. Oxime **XIII** showed in the spectrum only one broadened singlet at δ 2.04 ppm, obviously belonging to 4-H. Taking into account that the 1-H signal of *E* isomer should appear at δ ~2.5 ppm and that no such signal was present, we can conclude that only the *Z* isomer of **XIII** was formed. The 1-H signal of *Z*-**XIII** is located in a considerably weaker field and is overlapped by the multiplet at δ 3.07 ppm (4H). The selective formation of *Z* isomer was observed by us previously [9] in the oximation of *exo*-3-dimethylaminomethyl-5,5,6-trimethylbicyclo[2.2.1]heptan-2-one.

We planned to transform the hydroxyimino group in **XIII** into a prostaglandin-like chain by alkylation with *n*-hexyl bromide. As shown in [10], some heteroprostanoids with an analogous structure exhibit high biological activity. Insofar as the hydroxyimino group in **XIII** has *Z* configuration, its alkylation should not be complicated by the presence of a bulky group on C$^3$. However, instead of the expected alkylation of the hydroxyimino group, transalkylation of the ester moiety occurred, and the only product was hexyl ester **XIV**. Oxime alkylation products were not obtained even with an eightfold excess of the alkylating agent.

These unusual results may be explained as follows. Compound **XIII** is likely to adopt a conformation in which the ester and hydroxyimino group appear in the close vicinity to each other; moreover, these groups can form a hydrogen bond. On the one hand, such orientation of the α-chain hampers alkylation of the hydroxyimino group. On the other hand, hydrogen bonding induces polarization of the ester C–O bond thus favoring its dissociation and hence transalkylation.

## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Bruker AC-200 instrument at 200 MHz; the chemical shifts were measured relative to TMS as internal reference. The IR spectra were measured on Specord 75IR and UR-20 spectrometers. The melting points were determined on a Boetius device. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates and by GLC on a Chrom-5 chromatograph equipped with a 2000 × 2-mm column packed with N-AW-DMCS (0.16–0.20), stationary phase Apiezon L.

***exo*-2-Ethynyl-5,5,6-trimethylbicyclo[2.2.1]-heptan-*endo*-2-ol (II)** was synthesized by the action of lithium acetylide on ketone **I**, following the procedure reported by us in [5]. mp 37–38°C, bp 138–140°C (10 mm).

**5,5,6-Trimethyl-*exo*-2-(3-methylisoxazol-5-yl)bicyclo[2.2.1]heptan-*endo*-2-ol (III).** To a solution of 0.534 g (3 mmol) of *exo*-2-ethynyl-5,5,6-trimethylbicyclo[2.2.1]heptan-*endo*-2-ol (**II**) in 20 ml of benzene we added 0.29 ml (4 mmol) of nitroethane, 1.3 ml (12 mmol) of phenyl isocyanate, and 5 drops of triethylamine (until the solution became turbid). The mixture was stirred for 60 h at room temperature, the precipitate of diphenylurea was filtered off, and the filtrate was evaporated. The residue was subjected to column chromatography on aluminum oxide (gradient elution with hexane–diethyl ether). We isolated 0.68 g (96.4%) of isoxazole derivative **III** as a pale yellow transparent viscous oil. IR spectrum, ν, cm$^{-1}$: 3340 (OH); 2975, 2945, 2880 (C–H); 1605 (C=N). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 d (3H, $J$ = 7.5 Hz, 6-$CH_3$), 0.94 s (3H, 5-$CH_3$), 1.04 d.d (1H, *exo*-3-H, $^2J$ = 14.0, $^3J$ = 4.0 Hz), 1.07 br.s (1H, 1-H), 1.11 s (3H, 5-$CH_3$), 1.44 d.d (1H, *syn*-7-H, $^2J$ = 10.2, $^WJ$ = 1.5 Hz), 1.77 br.d (1H, 4-H, $^3J$ = 4.0 Hz), 1.96 q (1H, 6-H, $^3J$ = 7.5 Hz), 2.03 m (3H, *endo*-3-H, *anti*-7-H, OH), 2.26 s (3H, $CH_3$, isoxazole), 5.98 s (1H, 4-H, isoxazole).

***exo*-2-[(2*Z*)-3-Amino-2-butenoyl)-5,5,6-trimethylbicyclo[2.2.1]heptan-*endo*-2-ol (IV).** To a solution of 0.235 g (1 mmol) of isoxazole derivative **III** and 0.14 g (0.5 mmol) of $NiSO_4 \cdot 7H_2O$ in methanol, cooled to –30 to –15°C, we added in several portions 0.19 g (5 mmol) of sodium tetrahydridoborate. After 20 min, the cooling bath was removed, the mixture was allowed to warm up to room temperature, 25 ml of 25% aqueous ammonia was added, and the mixture was thoroughly stirred for 20 min and extracted with ether. The solvent was removed from the extract, and the residue was subjected to column chromatography on silica gel (gradient elution with hexane–ether) to isolate 0.155 g (65.4%) of enamino ketone **IV** as a viscous oily substance which became vitreous on storage. IR spectrum, ν, cm$^{-1}$: 3430 (OH); 3320 ($NH_2$); 3220 ($NH_2$); 2980, 2965, 2945, 2880 (C–H); 1635 (C=O); 1620 (C=C). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 d (3H, 6-$CH_3$, $^3J$ = 7.2 Hz), 0.93 s (3H, 5-$CH_3$), 1.04 s (3H, 5-$CH_3$), 1.52 d (1H, *anti*-7-H, $^2J$ = 10.2 Hz), 1.72 m (3H, *endo*-3-H, 4-H, *syn*-7-H), 1.92 s (3H, =$CCH_3$), 1.96 q (1H, 6-H, $^3J$ = 7.2 Hz), 2.20 s (1H, 1-H), 2.46 d.d (1H, *exo*-3-H,

$^2J$ = 14.0, $^3J$ = 4.0 Hz), 4.98 br.s (1H, NH, free), 5.27 s (1H, =CH), 6.78 s (1H, OH), 9.55 br.s (1H, NH, chelated).

**Alkylation of 5,5,6-trimethylbicyclo[2.2.1]heptan-2-one (I) with allyl bromide and ethyl bromoacetate in the presence of potassium *tret*-butoxide.** Metallic potassium, 1.85 g (50 mmol), was dissolved in 50 ml of anhydrous *tert*-butyl alcohol on heating to ~40°C, the solution was cooled to room temperature, and 7.6 g (50 mmol) of ketone **I** was added. Allyl bromide, 7.3 g (60 mmol), or ethyl bromoacetate, 10 g (60 mmol), was then added dropwise, and the mixture was heated under reflux. According to the GLC data, only a small part of initial ketone had reacted. The mixture was carefully diluted with water and extracted with ether, and the extract was dried over $CaCl_2$ and evaporated on a rotary evaporator. The residue (consisting of 95% of initial ketone and 5% of the alkylation product; GLC data) was distilled in vacuo.

***exo*-3-Allyl-5,5,6-trimethylbicyclo[2.2.1]heptan-2-one (Va).** Vacuum distillation gave 0.36 g (4%) of pure compound **Va**. bp 98–99°C (4 mm), $n_D^{15}$ = 1.4701. IR spectrum, ν, $cm^{-1}$: 2980, 2910, 2880 (C−H); 1750 (C=O); 1660 w (C=C). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.95 d (3H, $J$ = 7.0 Hz, 6-$CH_3$), 0.97 s (3H, 5-$CH_3$), 1.09 s (3H, 5-$CH_3$), 1.56 m (2H, 6-H, *anti*-7-H), 1.96 m (2H, 3-$CH_2$), 2.02 br.s (1H, 4-H), 2.08 d (1H, $^2J$ = 9.8 Hz, *syn*-7-H), 2.32 br.s (1-H), 2.87 t (1H, *endo*-3-H, $^3J$ = 7.2 Hz), 4.54 m (2H, =$CH_2$), 5.08 m (1H, CH=). Found, %: C 81.42; H 10.30. $C_5H_{20}O$. Calculated, %: C 81.25; H 10.42.

***exo*-3-Ethoxycarbonylmethyl-5,5,6-trimethylbicyclo[2.2.1]heptan-2-one (Vb).** Yield 0.48 g (4%). bp 156–157°C (4 mm), $n_D^{15}$ = 1.4748. IR spectrum, ν, $cm^{-1}$: 2980, 2920, 2880 (C−H); 1750 v.s (C=O, ketone, ester); 1170 s (C−O−C). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.98 d (3H, 6-$CH_3$, $J$ = 7.0 Hz), 0.99 s (3H, 5-$CH_3$), 1.10 s (3H, 5-$CH_3$), 1.17 t (3H, $CH_2C\mathbf{H}_3$, $^3J$ = 7.5 Hz), 1.58 m (2H, 6-H, *anti*-7-H), 2.12 br.s (1H, 4-H), 2.16 d (1H, *syn*-7-H, $^2J$ = 10.2 Hz), 2.36 d.d (1H, 11-H, $^2J$ = 16.0, $^3J$ = 9.2 Hz), 2.48 br.s (1H, 1-H), 2.80 d.d (1H, *endo*-3-H, $^3J$ = 9.2, $^3J$ = 5.0 Hz), 2.98 d.d (1H, 11-H, $^2J$ = 16.0, $^3J$ = 5.0 Hz), 4.12 q (2H, $COOCH_2$, $^3J$ = 7.5 Hz). Found, %: C 70.36; H 9.36. $C_{14}H_{22}O_3$. Calculated, %: C 70.59; H 9.24.

**5,5,6-Trimethyl-2-(1-pyrrolidinyl)bicyclo[2.2.1]-hept-2-ene (VI).** A mixture of 7.6 g (50 mmol) of ketone **I**, 50 ml of toluene, 7.1 g (100 mmol) of pyrrolidine, and 100 mg of *p*-toluenesulfonic acid was refluxed in a flask equipped with a Dean–Stark trap until water no longer separated. The solvent and excess pyrrolidine were distilled off, and the residue was distilled in vacuo. According to the GLC data, the conversion of **I** into enamine **VI** was no less than 50%; however, the product is very prone to undergo tarring, so that only 3.7 g (36%) of **VI** was isolated. bp 136–138°C (4 mm), $n_D^{20}$ = 1.5209. IR spectrum, ν, $cm^{-1}$: 3050 v.w (=C−H); 2980, 2920, 2880 (C−H); 1630 w (C=C).

**Alkylation of 5,5,6-trimethyl-2-(1-pyrrolidinyl)-bicyclo[2.2.1]hept-2-ene (VI).** Enamine **VI**, 3.2 g (15 mmol), was dissolved in 10 ml of toluene, and 20 mmol of allyl bromide or ethyl bromoacetate was added dropwise with care. The mixture warmed up, and an amorphous material separated. It was a mixture of bromides **VII** and **VIII** at a ratio of ~2:3 (GLC). The mixture was kept for 4 h at room temperature, 10 ml of water was added, and the mixture was left overnight to complete hydrolysis of **VII** and **VIII** to alkylation product **V** and ketone **I**, respectively. The products were separated by vacuum distillation. We isolated 1.06 g (37%, calculated on enamine **VI**, or 11%, calculated on the initial ketone) of 3-allyl derivative **Va**. Its physical constants and spectral parameters coincided with those given above. Compound **Vb** was isolated in an amount of 1.43 g (40%, calculated on enamine **VI**, or 12%, calculated on the initial ketone). It was identical to the product obtained as described above.

**5,5,6-Trimethyl-3-methylenebicyclo[2.2.1]heptan-2-one (IX)** was synthesized by the procedure reported in [7]; it included Mannich condensation of ketone **I** with dimethylamine hydrochloride and paraformaldehyde in ethanol, transformation of the resulting hydrochloride into methylammonium iodide, and cleavage of the latter according to Hofmann.

**Reaction of 5,5,6-trimethyl-3-methylenebicyclo-[2.2.1]heptan-2-one (IX) with nitromethane.** To a solution of 0.34 g (2.07 mmol) of compound **IX** in 1.1 ml (20.7 mmol) of nitromethane we added 0.05 ml (0.414 mmol) of 1,1,3,3-tetramethylguanidine. The mixture was stirred for 24 h at room temperature and diluted with ether. The ether layer was washed with cold 5% hydrochloric acid, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by chromatography on a small column charged with aluminum oxide (gradient elution with hexane–ether) to isolate 0.312 g (67%) of 5,5,6-trimethyl-*exo*-3-(2-nitroethyl)bicyclo[2.2.1]heptan-2-one (**X**) as a viscous oily substance. IR spectrum, ν, $cm^{-1}$: 2970, 2940, 2915, 2880 (C−H); 1745 (C=O); 1560,

1485, 1385 ($NO_2$). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.96 d (3H, 6-$CH_3$, $^3J$ = 7.0 Hz), 1.04 s (3H, 5-$CH_3$), 1.09 s (3H, 5-$CH_3$), 1.56 d (1H, *anti*-7-H, $^2J$ = 11.0 Hz), 1.62 q (1H, 6-H, $^3J$ = 7.0 Hz), 2.10 d (1H, *syn*-7-H, $^2J$ = 11.0 Hz), 2.22 br.s (1H, 4-H), 2.32 br.s (1H, 1-H), 2.34 m (3H, 3-H, 3-$CH_2$), 4.50 d.d.d (1H, $O_2NCH_2$, $^2J$ = 13.2, $^3J$ = 7.0, $^3J$ = 6.5 Hz), 4.62 d.t (1H, $O_2NCH_2$, $^2J$ = 13.2, $2^3J$ = 6.5 Hz).

***exo*-3-[5-(2-Ethoxycarbonylethyl)isoxazol-3-ylmethyl]-5,5,6-trimethylbicyclo[2.2.1]heptan-2-one (XII).** Nitroethyl derivative **X**, 0.27 g (1.2 mmol), and 0.454 g (3.6 mmol) of ethyl 4-pentynoate were dissolved in 20 ml of dry benzene, and 0.39 ml (3.6 mmol) of phenyl isocyanate and 6 drops of triethylamine (until the solution became turbid) were added. The mixture was stirred for 48 h at room temperature, the precipitate of diphenylurea was filtered off, and the filtrate was evaporated. The residue was subjected to column chromatography on aluminum oxide (gradient elution with hexane–ether) to isolate 0.218 g (54.5%) of isoxazolyl derivative **XII** as a viscous oily substance. IR spectrum, ν, $cm^{-1}$: 2980, 2945, 2915, 2880 (C−H); 1745 (C=O, ketone, ester); 1610 (C=N); 1490, 1450, 1190. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.98 d (3H, 6-$CH_3$, $^3J$ = 7.5 Hz), 1.00 s (3H, 5-$CH_3$), 1.14 s (3H, 5-$CH_3$), 1.28 t (3H, $CH_2C\mathbf{H}_3$, $^3J$ = 7.0 Hz), 1.56 d (1H, *anti*-7-H, $^2J$ = 11.0 Hz), 1.64 q (1H, 6-H, $^3J$ = 7.5 Hz), 2.09 d (1H, *syn*-7-H, $^2J$ = 11.0 Hz), 2.31 br.s (1H, 4-H), 2.35 br.s (1H, 1-H), 2.62 t (1H, 3-H, $^3J$ = 6.0 Hz), 2.71 t (3H, 5′-$CH_2$, EtOCOC$\mathbf{H}_2$, $^3J$ = 7.5 Hz), 3.06 m (3H, 3-$CH_2$, EtOCOC$\mathbf{H}_2$), 4.17 q (2H, $COOCH_2$), 6.00 s (1H, 4′-H, isoxazole).

***exo*-3-[5-(2-Ethoxycarbonylethyl)isoxazol-3-ylmethyl]-5,5,6-trimethylbicyclo[2.2.1]heptan-2-one oxime (XIII).** Hydroxylamine hydrochloride, 0.043 g (0.624 mmol), was dissolved in 1 ml of aqueous ethanol, and 0.24 ml of a 2 N aqueous solution of potassium hydroxide (0.48 mmol) was added. The mixture was kept for 20 min and was added with stirring to a solution of 0.16 g (0.48 mmol) of isoxazole derivative **XII** in 1 ml of anhydrous ethanol. The mixture was stirred for 96 h at room temperature and evaporated under reduced pressure, 10 ml of water was added to the residue, and the product was extracted into diethyl ether. The extract was dried over sodium sulfate and evaporated, and the residue was passed through a layer of aluminum oxide (gradient elution with hexane–diethyl ether) to isolate 0.16 g (95.8%) of oxime **XIII** as a light yellow viscous oily substance. IR spectrum, ν, $cm^{-1}$: 3335, 3145 (O−H); 2975, 2940, 2915, 2880 (C−H); 1740 (C=O, ester); 1610 (C=N, isoxazole). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 s (3H, 5-$CH_3$), 0.98 d (3H, 6-$CH_3$, $^3J$ = 7.5 Hz), 1.14 s (3H, 5-$CH_3$), 1.28 t (3H, $CH_2C\mathbf{H}_3$, $^3J$ = 7.0 Hz), 1.30 d (1H, *anti*-7-H, $J$ = 11.0 Hz), 1.36 m (1H, EtOCOC$\mathbf{H}_2$), 1.62 q (1H, 6-H, $^3J$ = 7.5 Hz), 1.90 d (1H, *syn*-7-H, $^2J$ = 11.0 Hz), 2.05 br.s (1H, 4-H), 2.74 t (2H, 5′-$CH_2$, $^3J$ = 7.5 Hz), 2.88 m (1H, 3-H), 3.07 m (4H, 3-$CH_2$, EtOCOC$\mathbf{H}_2$, 1-H), 4.17 q (2H, $COOCH_2$), 5.99 s (1H, 4′-H).

**Alkylation of *exo*-3-[5-(2-ethoxycarbonylethyl)-isoxazol-3-ylmethyl]-5,5,6-trimethylbicyclo[2.2.1]-heptan-2-one oxime (XIII) with hexyl bromide in the presence of aqueous sodium hydroxide.** To a solution of 0.139 g (0.4 mmol) of oxime **XIII** in 1 ml of dimethylformamide we added while stirring and cooling 0.16 ml of a 2.5 N aqueous solution of sodium hydroxide (0.4 mmol) at such a rate that the temperature of the mixture did not exceed 15°C. The mixture was stirred for 1 h, and 0.08 ml (0.57 mmol) of hexyl bromide was added. The mixture was stirred for 72 h at room temperature and diluted with 50 ml of 3% hydrochloric acid. The product was extracted into diethyl ether, the extracts were dried over sodium sulfate and evaporated, and the residue was subjected to column chromatography on silica gel (gradient elution with hexane–diethyl ether) to isolate 0.133 g (82%) of *exo*-3-[5-(2-hexyloxycarbonylethyl)isoxazol-3-ylmethyl]-5,5,6-trimethylbicyclo[2.2.1]heptan-2-one oxime (**XIV**) as an oily substance. IR spectrum, ν, $cm^{-1}$: 3340, 3150 (O−H); 2965, 2940, 2880 (C−H); 1750 (C=O, ester); 1615 (C=N, isoxazole). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.93 m [9H, 5-$CH_3$, 6-$CH_3$, $(CH_2)_5C\mathbf{H}_3$], 1.16 s (3H, 5-$CH_3$), 1.33 m [8H, $(C\mathbf{H}_2)_3CH_3$, *anti*-7-H, OCOCH], 1.60 m (3H, 6-H, $COOCH_2C\mathbf{H}_2$), 1.90 d (1H, *syn*-7-H, $^2J$ = 10.5 Hz), 2.04 br.s (1H, 4-H), 2.72 t (2H, 5′-$CH_2$), 2.90 m (1H, 3-H), 3.07 m (4H, 1-H, 3-$CH_2$, OCOCH), 4.08 t (2H, $COOCH_2$), 5.97 s (1H, 4′-H, isoxazole).

No products of alkylation of the hydroxyimino group were isolated from the reaction mixture. Also, we failed to alkylate the hydroxyimino group in **XIV** using 2 equiv of sodium hydroxide and 8 equiv of hexyl bromide, other conditions being equal. After appropriate treatment, we isolated almost unchanged initial compound.

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