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Reaction of 3-Methyleneisocamphanone with Derivatives of Malonic Acid

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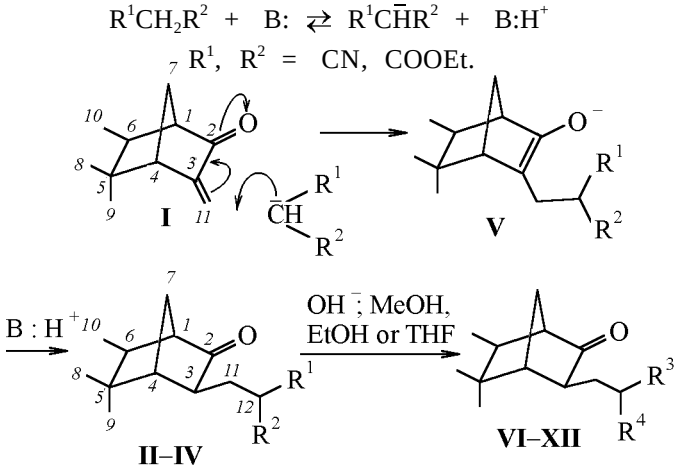
Abstract—Reaction of 3-methyleneisocamphanone with malononitrile, ethyl cyanoacetate or diethyl malonate in the presence of catalytic quantities of alkali or under catalysis with tetramethylguanidine in ethanol proceeds according to classical scheme of the Michael reaction and gives rise to 3-*exo*-(2,2-dicyanoethyl)-, 3-*exo*-(2-cyano-2-ethoxycarbonylethyl)-, or 3-*exo*-(2,2-diethoxycarbonylethyl)isocamphanone respectively. When the reaction with ethyl cyanoacetate and diethyl malonate is carried out in methanol occurs transalkylation of the ester groups resulting in the corresponding methyl esters, and in THF occurs hydrolysis to form carboxylic acids. In ethanol or methanol in the presence of equimolar or excess amounts of alkali compounds with cyano groups suffer cyclization into the corresponding 2-alkoxy-3-cyano- or 1-alkoxy-3-alkoxycarbonyl-7,7,8-trimethylbicyclo[2.2.1]hepteno[2.3-b]pyridines. In THF partially form analogous tricyclic 2-hydroxypyridines.

α,β-Unsaturated carbonyl compounds are extensively used in the organic synthesis due to their high reactivity. Terpene α,β-unsaturated ketones of the bicyclo[2.2.1]heptane series do not exist naturally, and their chemical properties are virtually unstudied. However in considering the reactions of the first representatives of these compounds we synthesized we found certain transformations previously unknown in the series of bicyclo[2.2.1]heptane derivatives [1, 2].

We investigated reactions of 3-methyleneisocamphanone (5,5,6-trimethyl-3-methylenebicyclo]-2.2.1]heptan-2-one) (**I**) [2] with the derivatives of malonic acid (dinitrile, diethyl ester, and mixed nitriloester) under conditions of a basic catalysis. It was presumed that since compound **I** possessed a structure of a classical substrate for the Michael reaction its treatment with CH-acids would provide various 3-substituted isocamphanone derivatives. The latter are promising synthons for preparation of analogs of some low-molecular bioregulators, in particular, prostaglandins.

The 3-methyleneisocamphanone actually readily reacted with the mentioned CH-acids. However depending on the structure of reagents and the reaction conditions can arise different compounds, and some of them have structures quite unlike that of the products forming in the Michael reaction. The reaction of 3-methyleneisocamphanone (**I**) with malononitrile, diethyl malonate, or ethyl cyanoacetate follows the classical scheme of the Michael reaction when the process is carried out in ethanol, methanol or THF and catalyzed by tetramethylguanidine. As a result arise 3-*exo*-(2,2-dicyanoethyl)isocamphanone (**II**), 3-*exo*-(2,2-diethoxycarbonylethyl)isocamphanone (**III**), or 3-*exo*-(2-cyano-2-ethoxycarbonylethyl)isocamphanone (**IV**) respectively.

The structure of the substances obtained was determined from IR, ^{1}H NMR, and mass spectra. In



II, $R^1 = R^2 =$ CN; **III**, $R^1 = R^2 =$ COOEt; **IV**, $R^1 =$ CN, $R^2 =$ COOEt; **VI**, $R^3 =$ COOEt, $R^4 =$ COOMe; **VII**, $R^3 = R^4 =$ COOMe; **VIII**, $R^3 =$ COOM, $R^4 =$ COOEt; **IX**, $R^3 = R^4 =$ COOM; X, $R^3 =$ COOM, $R^4 =$ H; **XI**, $R^3 =$ CN, $R^4 =$ COOMe; **XII**, $R^3 =$ CN, $R^4 =$ COOM; M = H (**a**), Na (**b**), K (**c**).

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Table 1. Melting points, IR and mass spectra of 3-*exo*-(2-R^1-2-R^2-ethyl)isocamphanones **II**–**IV, XI, XIIa** and 2,3-disubstituted 7,7,8-trimethylbicyclo[2.2.1]hepteno[2,3-*b*]pyridines (**XVII**–**XXII**)

Compd. no.	mp, °C	IR spectrum, cm^{-1}	Mass spectrum, *m/z* (I_{rel}, %)
II	146–147	2970, 2930, 2900, 2870 (C–H), 2250, 2240 v.w (C≡N), 1750 s (C=O)	230 $[M]^+$ (13), 215 $[M–Me]^+$, 202 $[M–2CH_2]^+$, 187 $[M–Me–2CH_2]^+$, 177, 165, 147, 123, 121, 108, 95 (100), 81, 70 55, 43
III	–	2990, 2950, 2920, 2880 (C–H), 1760 v.s (3C=O), 1200, 1175, 1050 (C–O–C)	324 $[M]^+$ (7), 309 $[M–Me]^+$, 295 $[M–Me–CH_2]$, 281 $[M–Me–2CH_2]$, 266, 261 $[M–COOEt]^+$, 246, 232, 218, 205, 177, 165, 147, 121, 108, 95 (100), 81, 70, 55, 43
IV	141–142	2990, 2950, 2930, 2880 (C–H), 2250 v.w (C≡N), 1750 v.s (2 C=O), 1175, 1110, 1040 (C–O–C)	277 $[M]^+$ (11), 262 $[M–Me]^+$, 248 $[M–Me–CH_2]^+$, 234 $[M–Me–2CH_2]^+$, 220, 207 (100), 178, 165, 147, 121, 108, 95, 82, 69, 55, 43
XI	137–139	2980, 2940, 2920, 2880 (C–H), 2250 v.w (C≡N), 1750 v.s (2 C=O), 1175, 1075, 1040 (C–O–C)	263 $[M]^+$ (7), 248 $[M–Me]^+$, 234 $[M–Me–CH_2]^+$, 220 $[M–Me–2CH_2]^+$, 207, 193 (100), 178, 165, 147, 132, 121, 108, 95, 82, 69, 55, 43
XIIa	142–143	3450 (COO–H), 2970, 2950, 2920, 2880 (C–H), 2250 v.w (C≡N), 1745 v.s (2 C=O)	249 $[M]^+$ (9), 234 $[M–Me]^+$ 220 $[M–Me–CH_2]^+$, 206 $[M–Me–2\ CH_2]^+$, 205 $[M–CO_2]^+$, 193, 179 (100), 165, 147, 121, 108, 95, 82, 69, 55, 43
XVII	178	3075 w (C–Harom), 3000, 2980, 2970, 2950, 2920, 2880 (C–H aliph), 2230 v.s (C≡N conjug.), 1600, 1550 (C=C arom), 1260, 1240, 1120, 1040, 1010 (C–O–C)	256 $[M]^+$ (7), 241 $[M–Me]^+$, 227 $[M–Me–CH_2]^+$, 213 $[M–Me–2\ CH_2]^+$, 197, 186, 158 (100), 142, 130, 115, 103, 91, 89, 76, 55, 43
XVIII	136	3075 w (C–H arom), 3000, 2990, 2970, 2950, 2930, 2910, 2880 (C–H aliph), 2230 v.s (C≡N conjug.), 1610, 1570 (C=C arom), 1270, 1260, 1130, 1050, 1020 (C–O–C)	242 $[M]^+$ (11), 227 $[M–Me]^+$, 199 $[M–Me–2CH_2]^+$, 185, 172 (100), 155, 143, 129, 117, 102, 91, 89, 77, 76, 55, 51, 43
XIX	108	3400 (OH), 3075 w (C–H arom), 3000, 2970, 2930, 2910, 2880 (C–H aliph), 2220 v.s (C≡N conjug.), 1610, 1560 (C=C arom)	228 $[M]^+$ (9), 213 $[M–Me]^+$, 199 $[M–Me–CH_2]^+$, 185 $[M–Me–2CH_2]^+$, 171, 158 (100), 141, 115, 103, 91, 89, 76, 55, 43
XX	161	3075 w (C–H arom), 3000, 2980, 2950, 2920, 2880 (C–H aliph), 1720 s (conjug. ester), 1275, 1210, 1175, 1120, 1075, 1020 (C–O–C)	303 $[M]^+$ (8), 287 $[M–Me]^+$, 273 $[M–Me–CH_2]^+$, 259 $[M–Me–2CH_2]^+$, 230 $[M–COOEt]^+$, 215, 201, 187, 172, 158 (100), 142, 130, 115, 103, 91, 89, 76, 55, 43
XXI	154	3075 w (C–H arom), 3000, 2970, 2940, 2910, 2880 (C–H aliph), 1720 s (conjug. ester), 1280, 1230, 1190, 1140, 1080, 1040 (C–O–C)	275 $[M]^+$ (10), 260 $[M–Me]^+$, 246 $[M–Me–CH_2]^+$, 232 $[M–Me–2CH_2]^+$, 206 [*M*–COOMe], 191, 177, 163, 143 (100), 129, 117, 102, 91, 89, 76, 55, 43
XXII	185 (decomp.)	3470 v.s (COOH + OH), 3075 w (C–H arom), 3000, 2970, 2950, 2930, 2910, 2880 (C–H aliph), 1710 (COOH arom)	247 $[M]^+$ (7), 232 $[M–Me]^+$, 218 $[M–Me–CH_2]^+$, 204 $[M–Me–2CH_2]^+$, 203 $[M–CO_2]$ (100), 185, 171, 157, 142, 116, 103, 91, 89, 76, 55, 43

their IR spectra appears a band at 1750 cm^{-1} corresponding to carbonyl vibrations, therewith in the spectra of compounds **III** and **IV** containing ester group the intensity of the band is considerably higher. In the IR spectra of compounds **II** and **IV** is present a band corresponding to vibrations of the aliphatic cyano group (~2250 cm^{-1}, very weak). In the mass spectra of the compounds appear peaks of the cor-

Table 2. ^{1}H NMR spectra of 3-*exo*-(2,2-dicyanoethyl)isocamphanone (**II**), 3-*exo*-diethoxycarbonylethyl)isocamphanone (**III**), 3-*exo*-(2-cyano-2-ethoxycarbonylethyl)isocamphanone (**IV**), 3-*exo*-(2-methoxycarbonyl-2-cyanoethyl)isocamphanone (**XI**), and 3-*exo*-(2-carboxy-2-cyanoethyl)isocamphanone (**XIIa**), δ, ppm, *J*, Hz[a]

Compd. no.	H^1	H^4	H^6	H^7_{syn}	H^7_{anti}	$H^3+H^{11}_2+H^{12}$	C^5–CH_3	C^6–CH_3	Other signals	$^2J(H^7_{syn}, H^7_{anti})$	$^3J(H^6, C^6CH_3)$
II	2.48 br.s	1.62 br.s	1.57 q	2.12 d	1.64 d	2.39 m	1.08 s, 1.05 s	0.98 d		10.0	7.0
III	2.48 br.s	2.17 br.s	1.56 q	2.06 d	1.48 d	2.26 m	1.17 s, 0.99 s	0.94 d	4.18 q (4H), 1.25 t (6H)	10.0	7.2
IV	2.35 br.s	2.02 br.s	1.55 q	2.10 d	1.56 d	2.26 m	1.03 s, 0.96 s	0.93 d	4.22 q (2H), 1.30 t (3H)	10.0	7.0
XI	2.36 br.s	2.14 br.s	1.54 q	2.06 d	1.60 d	2.30 m	1.02 s, 0.98 s	0.93 d	3.85 c (3H)	10.0	7.2
XIIa	2.30 m	1.98 br.s	1.52 q	2.12 d	1.54 d	2.30 m	1.01 s, 0.99 c	0.93 d	11.5 s (1H)	10.0	7.2

[a] All spectra were registered in $CDCl_3$.

responding molecular ions with intensity 7–13% relative to the maximal peak (Table 1).

In the ^{1}H NMR spectra alongside the proton signals characteristic of isocamphane skeleton appears a multiplet with the chemical shift ~2.30 ppm and integral intensity corresponding to 4 protons (C^3H + $C^{11}H_2$ + $C^{12}H$). In the spectra of ethyl esters **III** and **IV** are also present the signals from ethoxy group protons (Table 2). The *exo*-addition of the given CH-acids to the double bond of 3-methyleneisocamphanone (**I**) was established from the ^{1}H NMR spectra. Since the vicinal coupling constant for proton attached to C^4 with the *exo*-directed proton at C^3 in the 3-substituted ketones of the bicyclo[2.2.1]heptane series amounts to ~4.8 Hz [3], in case of endo-orientation of the substituent at C^3 the signal of the proton at C^4 should appear as a doublet with the corresponding coupling constant. In our case this constant is notably smaller (the signal of proton at C^4 looks like a broadened singlet); obviously the proton at C^3 has endo-orientation, and consequently the $R^1R^2CHCH_2$ group has *exo*-orientation. This spatial structure of products is well consistent with the common understanding of the stereochemistry of the Michael reaction for the addition of the CH-acids is presumed to occur from the less hindered side of the molecule, in our case from the *exo*-side [4, 5].

Note that compound **IV** formally contains an additional asymmetric atom C^{12}, and thus stereoisomeric products might form. However all our attempts to isolate or detect (e.g., with the use of NMR spectroscopy) the corresponding isomers failed. This is apparently due to the fact that this compound is prone to enolization. Since the enol form of the nitriloester does not contain the corresponding asymmetric atom, the isolated product obviously is an equilibrium mixture of the stereoisomeric nitriloesters **IV**. The observed signals in the ^{1}H NMR spectrum correspond to the weighted mean of the chemical shifts of the protons in the interconverting 12*R*- and 12*S*-isomeric nitriloesters. It cannot also be excluded that the reaction product is a single more thermodynamically stable stereoisomer arising as a result of the enolization, and therefore the second isomer cannot be detected.

The tendency of compounds **III** and **IV** to enolization is fully observed at the attempt to carry out the addition at catalysis with alkali (NaOH or KOH). Whereas the addition of malononitrile in the presence of the catalytic amount of alkali (no more than 0.1 g-equiv.) in ethanol, methanol or THF yields the same product, dicyanoketone **II**, the addition of two other CH-acids occurs cleanly only in ethanol. The reaction of 3-methyleneisocamphanone (**I**) with diethyl malonate in methanol proceeds with concomitant transalkylation of ester groups to furnish unseparable mixture of esters **III**, **VI**, and **VII**.

The formation of such mixture as a result of the reaction was established by GLC where were detected in the reaction mixture at least three products. The ^{1}H NMR spectrum of the mixture also differs from the spectrum of diethyl ester **III**: the integral intensity

of the ethoxy group signals (triplet at ~1.25 ppm and quartet at ~4.18 ppm) is reduced by about 60% with simultaneous increase of line number in the corresponding multiplets; besides in the region of 3.8 ppm appear three singlets from the ester methoxy groups. The overall integral intensity of the latter (~3.6H) corresponds to transformation of 60% of COOEt groups into COOMe.

The reaction carried out in THF is followed by hydrolysis resulting in four products. Three among them are carboxylic acids **VIIIa–Xa**, partially as potassium and sodium salts. The only individual compound isolated from the reaction mixture was substance **III** that was extracted into ether after alkalinization of the reaction mixture and diluting it with water. The salts **VIIIb**, **c–Xb, c** therewith remain in the water layer. On acidifying the latter (see Experimental) was obtained a mixture of the corresponding carboxylic acids **VIIIa–Xa**.

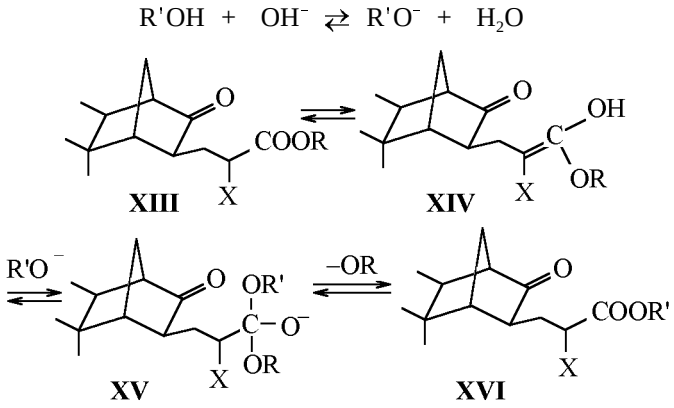
In the ^{1}H NMR spectrum of the mixture are present signals from ethoxy group corresponding by integral intensity to approximately 60% content in the mixture of a semiester **VIIIa**. Apart the signal from the carboxy group of this compound (δ 11.84 ppm, 0.6H) in the spectrum are observed 3 more signals of carboxy groups. The peak at the chemical shift 11.24 ppm and of integral intensity 0.3H belongs obviously to acid **Xa** originating from decarboxylation of the dicarboxylic acid **IXa**. The latter is a minor component of the reaction mixture [δ(COOH) 11.65 and 11.72, each 0.1H].

In the reaction of 3-methyleneisocamphanone (**I**) with ethyl cyanoacetate in methanol or THF in the presence of catalytic amounts of alkali was also observed transalkylation or hydrolysis of the ester group; however here the intermediate contained a single ester group, and therefore the competing reactions are lacking. Thus the transalkylation (or hydrolysis) of the ethoxycarbonyl group occurs virtually completely, and the process gives rise to individual compounds: methyl ester **XI** or cyanocarboxylic acid **XIIa**, in part as sodium **XIIb** or potassium **XIIc** salt.

The structure of compounds **XI** and **XIIa** was established from IR and ^{1}H NMR spectra. The IR spectrum of methyl ester **XI** is similar to that of ethyl ester **IV** (Table 1). In the mass spectrum is present the molecular ion peak M^+ 263 of integral intensity 7% related to the most abundant peak. In the ^{1}H NMR spectrum instead of ethoxy group signals appears a singlet at 3.84 ppm with integral intensity corresponding to three protons of the ester methoxy group. The multiplicity and position of the other signals in the ^{1}H NMR spectrum hardly change (Table 2).

In the IR spectrum of cyanocarboxylic acid **XIIa** alongside the bands observed in the spectra of esters appears a strong band at 3450 cm^{-1} corresponding to vibrations of the carboxy group. In the mass spectrum is present the molecular ion peak M^+ 249 of integral intensity 8% related to the most abundant peak. In the ^{1}H NMR spectrum (Table 2) is observed a signal from the proton of carboxy group at δ 11.5 ppm.

The transalkylation or hydrolysis occurring during the synthesis of esters is due as already mentioned to the high tendency to enolization of the intermediate compounds.



R = Et; R' = H, Me; X = CN, COOEt.

The reaction of the enolized form **XIV** of the initially formed ester **XIII** with the solvent (or alkali) apparently takes the route of classical solvolysis (hydrolysis) of esters. Note that in solvolysis all the stages of the process are reversible; however since the solvent R'OH concentration is many times greater than that of liberating ethanol the equilibrium is strongly shifted to the side of transalkylated product **XVI**. At X = COOEt occurs partial transalkylation of the second ester group as we already mentioned.

Thus the reaction of 3-methyleneisocamphanone with the malonic acid derivatives in the presence of catalytic quantities of alkali (no more than 0.1 g-equiv.) follows overall classical scheme of the Michael reaction, but the initially arising labile addition products undergo further transformations of the functional groups of the original CH-acids.

When the reaction with CH-acids containing cyano groups is carried out in the presence of greater amounts of alkali the transformation of the intermediate compounds results in tricyclic pyridine

Table 3. ^{1}H NMR spectra of 7,7,8-trimethylbicyclo[2.2.1]hepteno[2,3-*b*]pyridines **XVII**–**XXII**, δ, ppm; *J*, Hz[a]

Compd. no.	H^4	H^6	H^8	H^5	H^{10}_{syn}	H^{10}_{anti}	C^7–CH_3-*exo*	C^7–CH_3-*endo*	C^8–CH_3	C^2–OR	C^3–R'	$^2J(H^{10}_{syn}, H^{10}_{anti})$	$^3J(H^8, C^8–CH_3)$
XVII	7.50 s	2.72 br.s	1.21 q	2.83 br.s	2.13 d	1.73 d	1.11 s	0.54 s	1.08 d	4.47 q (2H), 1.42 t (3H)	–	10.0	7.0
XVIII	7.52 s	2.73 br.s	1.19 q	2.87 br.s	2.14 d	1.75 d	1.10 s	0.54 s	1.08 d	4.04 s (3H)	–	10.0	7.2
XIX	7.53 s	2.73 br.s	1.18 q	2.88 br.s	2.14 d	1.76 d	1.10 s	0.54 s	1.08 d	8.05 s (1H)	–	10.0	7.2
XX	7.53 s	2.73 br.s	1.20 q	2.83 br.s	2.14 d	1.74 d	1.10 s	0.55 s	1.08 d	4.48 q (2H) 1.42 t (3H)	4.35 q (2H) 1.31 t (3H)	10.0	7.0
XXI	7.54 s	2.73 br.s	1.19 q	2.87 br.s	2.14 d	1.75 d	1.10 s	0.55 s	1.08 d	4.05 s (3H)	3.98 s (3H)	10.0	7.0
XXII	7.55 s	2.75 br.s	1.18 q	2.88 br.s	2.16 d	1.77 d	1.09 s	0.55 s	1.09 d	8.50 s (1H)	11.8 s (1H)	9.8	7.2

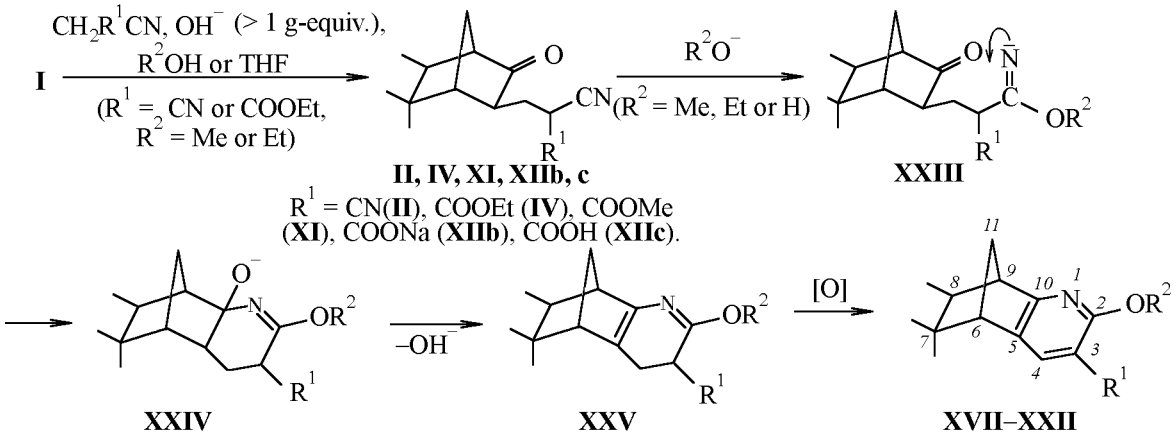
[a] All spectra were registered in $CDCl_3$.

derivatives, and at significant increase in alkali concentration this reaction path becomes a single one.

For instance, from 3-methyleneisocamphanone and malononitrile in the presence of 1 g-equiv. of NaOH or KOH in ethanol or methanol we obtained in preparative yield 7,7,8-trimethyl-3-cyano-2-ethoxy- or 7,7,8-trimethyl-3-cyano-2-methoxy-3-cyanobicyclo[2.2.1]hepteno[2,3-b]pyridines (**XVII, XVIII**).

When the reaction is carried out in THF tricyclic hydroxypyridine **XIX** and noncyclic dinitrile **II** are formed in comparable amounts. About the same ratio of cyclic reaction products **XX, XXI** and the corresponding cyanoesters **IV, XI** arises in reaction of ketone **I** with ethyl cyanoacetate in the presence of 1 g-equiv. of alkali. The increase of the alkali quantity to 2 g-equiv. results in prevailing formation of tricyclic compounds **XX**, **XXI**. Hydroxyacid **XXII** under all conditions remains a minor component of the reaction products.

The structure of tricyclic pyridine derivatives **XVII**–**XXII** was established from ^{1}H NMR (Table 3), IR, UV (Table 4), and mass spectra.



XVII, R^1 = CN, R^2 = Et; **XVIII**, R^1 = CN, R^2 = Me; **XIX**, R^1 = CN, R^2 = H; **XX**, R^1 = COOEt, R^2 = Et; **XXI**, R^1 = COOMe, R^2 = Me; **XXII**, R^1 = COOH, R^2 = H.

Table 4. UV spectra of 2-R^2O-3-R^3-7,7,8-trimethylbicyclo[2.2.1]hepteno[2,3-*b*]pyridines **XVII**–**XXII**[a]

R^2	R^3	λ, nm	log ε
Me	CN	208.6	4.26
		240.6	3.80
		307.5	3.99
Et	CN	208.8	4.28
		241.0	3.81
		307.8	4.00
H	CN	206.6	4.20
		240.8	3.80
		307.7	3.96
Me	COOMe	208.8	4.28
		244.8	3.80
		308.2	4.02
Et	COOEt	208.9	4.29
		244.9	3.80
		308.5	4.02
H	COOH	206.9	4.24
		244.4	3.82
		308.3	3.99

[a] Spectra were registered in ethanol solution, $c \sim 10^{-4}$ mol l^{-1}.

In the IR spectra of cyanopyridines **XVII, XVIII** the carbonyl absorption band is lacking but are present two bands characteristic of pyridine ring vibrations (~1600 and 1560 cm^{-1}). The band of cyano group vibrations shifts to lower frequencies (2230 cm^{-1}), and its intensity sharply grows due to conjugation with an aromatic heterocycle. In the spectra of compounds **XX, XXI** appear the bands belonging to the pyridine ring vibrations and also a band of the conjugated ester group (1730 cm^{-1}). In the spectra of hydroxy derivatives **XIX** and **XXII** apart of the above bands is also observed a band at 3400 cm^{-1} from the hydroxy group vibrations (Table 1). In the mass spectra of these compounds are always present the peaks of the appropriate molecular ions with integral intensity of 7–11% from that of the most abundant peak. In the UV spectra of compounds obtained are registered three absorption bands in the regions ~208, ~240, and ~307 nm [log ε ~4.2, 3.8, and 4.0 respectively (Table 4)].

The data on ^{1}H NMR spectra of compounds **XVV**–**XXII** are presented in Table 3. In the spectra is present a signal at ~7.50 ppm characteristic of H^4 proton in the pyridine ring. The signals from methyl group C^7–CH_3-*endo* and also from the proton H^8-*endo* are strongly shifted upfield for they occur in the region screened by the aromatic heterocycle. The chemical shifts and multiplicity of the other signals are consistent with the assumed structure of compounds **XVII**–**XXII**.

The tricyclic pyridine derivatives **XVII**–**XXII** presumably result from the following transformations. The addition to the cyano group of alcoholate anion formed in some quantity at high concentration of alkali, or of hydroxide ion (at reaction in THF) transforms the initial adducts **II, IV, XI, XII** into anion **XXIII** with a negative charge on nitrogen. Similar anions arise during alcoholysis (hydrolysis) of nitriles under basic catalysis [6]. The addition of the anionic nitrogen to the carbonyl carbon gives rise to tricyclic anion **XXIV**. The latter ejects a hydroxide ion and gives dihydropyridine intermediate **XXV** that transforms into more stable aromatic derivative by oxidation with air oxygen.

This scheme shows that compounds **IV, XI**, and **XII** are less prone to cyclization than dinitrile **II** not only due to the presence in the structure of the latter of two cyano groups (kinetic factor): The ester group of compounds **IV, XI** is also capable to take up alcoholate anion forming therewith anions with no tendency to cyclization. The probability of intermediate **XXIII** formation required for cyclization is considerably reduced, and therewith decreases the rate of reaction providing the corresponding tricyclic compounds. With compounds **XIIb, c** the carboxylate anion even more reduces the possibility of anion formation with a negative charge on nitrogen. Therefore even in the presence of large amounts of alkali the corresponding tricyclic derivative **XXII** arises in small quantity.

The assumed scheme also explains why the cyclization under mild conditions (without boiling) results in sharp increase in tarring. The above scheme includes a stage of oxidation with air oxygen as a way to the final products. At boiling and active access of oxygen to the reaction mixture the aromatization of the azadiene intermediate **XXV** dominates over polymerization.

Thus the reaction of 3-methylisocamphanone (**I**) with the derivatives of malonic acid depending on solvent, on the nature and concentration of the basic catalyst can furnish various products, either derivatives of 3-*exo*-substituted isocamphanone with different functional groups in the side chain or tricyclic pyridine derivatives with different substituents in the heterocycle.

EXPERIMENTAL

NMR spectra were registered on spectrometer Tesla BS-567 at operating frequency 100 MHz, internal reference HMDS. IR spectra were recorded on spectrophotometer Specord 75IR, UV spectra on spectrophotometer Specord UV Vis. Mass spectra were measured on an instrument Chrom-mas GC/MS Hewlett Packard 5890/5972, column HP-5MS (70 eV). The reaction monitoring and checking the purity of the products synthesized was performed by GLC on chromatograph Chrom-5 with a glass column (2×2000 mm), stationary phase Apiezon L on the carrier N-AW-DMCS (0.16–0.20).

Michael reaction was performed along one of the following procedures. (a) To a solution of 1.64 g (10 mmol) of 3-methyleneisocamphanone (**I**) in 10 ml of ethanol, methanol, or THF was added 12 mmol of an appropriate CH-acid and 115 mg (1 mmol) of tetramethylguanidine. The reaction mixture was boiled till completion of the reaction, commonly for several hours (monitoring with GLC). On cooling the reaction mixture was diluted with water, the reaction products were extracted into a large volume of ether, and the extracts were dried on $CaCl_2$.

(b) The procedure is as described above, but as catalyst was used 40 mg of NaOH or 56 mg of KOH (1 mmol). (c) The procedure is as described above, but as catalyst was used 10 (20) mmol of alkali. In this case the products were extracted into chloroform since the tricyclic pyridine derivatives, in particular compounds **XVII** and **XVIII**, are hardly soluble in ether.

3-*exo*-(2,2-Dicyanoethyl)isocamphanone (II) was obtained by reaction of 3-methyleneisocamphanone with malononitrile along procedure a or b in 88 and 84% yield respectively, purified by crystallization from ethanol.

3-*exo*-(2,2-Diethoxycarbonylethyl)isocamphanone (III) was obtained by reaction of 3-methyleneisocamphanone with diethyl malonate along procedure a in 85% yield, purified by distillation in vacuo, bp 208–210°C (4 mm Hg). n_D^{20} 1.4615.

By procedure b in ethanol was also obtained diester **III** in 82% yield. In methanol formed a mixture of three compounds in ~2:2:1 ratio (GLC data). As show the ^{1}H NMR data discussed above the diethyl ester **III** is the minor component (~20%), and two other components (about 40% each) are methyl ethyl ester **VI** and dimethyl ester **VII**. We failed to separate the compounds by fractional distillation in vacuo for they comprise an azeotrope.

In the reaction of 3-methyleneisocamphanone with diethyl malonate according to procedure b in THF we obtained a mixture of 4 substances. After dilution of the reaction mixture and alkalinization (for transformation of the carboxylic acids into salts soluble in water) by extraction with ether was separated diethyl ester **III** contained in the mixture in 20% amount. Then the reaction mixture was cautiously acidified with HCl and again extracted with ether. The mixture separated from the extract contained 3 compounds that according to ^{1}H NMR data were monoethyl ester of dicarboxylic acid **VIII** (~60% of the mixture), dicarboxylic acid **IX** (~10%), and monocarboxylic acid **X** (~30%).

3-*exo*-(2-Cyano-2-ethoxycarbonylethyl)isocamphanone (IV) was obtained by reaction of 3-methyleneisocamphanone with ethyl cyanoacetate along procedure a in 86% yield or by procedure b in 82% yield, purified by crystallization from ethanol.

3-*exo*-(2-Methoxycarbonyl-2-cyanoethyl)isocamphanone (XI) was obtained by reaction of 3-methyleneisocamphanone with ethyl cyanoacetate along procedure b in methanol in 80% yield, purified by crystallization from methanol.

3-*exo*-(2-Carboxy-2-cyanoethyl)isocamphanone (XIIa) was obtained by reaction of 3-methyleneisocamphanone with ethyl cyanoacetate along procedure b in THF. The reaction mixture containing alongside acid **XIIa** its sodium **XIIb** or potassium **XIIc** salt was cautiously acidified with HCl before extracting. Yield of acid **XIIa** 76%, purified by crystallization from acetonitrile.

7,7,8-Trimethyl-3-cyano-2-ethoxybicyclo[2.2.1]-hepteno[2.3-b]pyridine (XVII) was obtained by reaction of 3-methyleneisocamphanone with malononitrile along procedure c in ethanol, yield 72%, purified by crystallization from chloroform.

7,7,8-Trimethyl-2-methoxy-3-cyanobicyclo-[2.2.1]hepteno[2.3-b]pyridine (XVIII) was obtained by reaction of 3-methyleneisocamphanone with malononitrile along procedure c in methanol, yield 69%, purified by crystallization from chloroform.

In the reaction of 3-methyleneisocamphanone with malononitrile in THF in the presence of 1g-equiv. of alkali was obtained a mixture in ~45:55 ratio of 2-hydroxy-7,7,8-trimethyl-3-cyanobicyclo[2.2.1]-hepteno[2.3-b]pyridine (**XIX**) and noncyclic compound **XIIb, c** that was washed out with ethanol. The residue was purified by crystallization from chloroform. Yield 36%.

7,7,8-Trimethyl-2-ethoxy-3-ethoxycarbonylbicyclo[2.2.1]hepteno[2.3-b]pyridine (XX) was obtained by reaction of 3-methyleneisocamphanone with ethyl cyanoacetate in ethanol in the presence of 2 g-equiv. of alkali, yield 68%, purified by crystallization from ethanol. The reaction in the presence of 1 g-equiv. of alkali gave rise to a mixture of compound **XX** and noncyclic product **IV** in ~5 : 4 ratio.

2-Methoxy-3-methoxycarbonyl-7,7,8-trimethylbicyclo[2.2.1]hepteno[2.3-b]pyridine (XXI) was obtained by reaction of 3-methyleneisocamphanone with ethyl cyanoacetate along procedure c in methanol in the presence of 2 g-equiv. of alkali, purified by crystallization from ethanol. Yield 66%. As in the preceding case the reaction in the presence of 1 g-equiv. of alkali gave rise to a mixture of compound **XX** and noncyclic product **IV** in ~5 : 4 ratio.

In reaction of 3-methyleneisocamphanone with ethyl cyanoacetate in THF arise predominantly noncyclic compound **XIIb** or **XIIc**. The corresponding tricyclic compound, 2-hydroxy-3-carboxy-7,7,8-trimethylbicyclo[2.2.1]hepteno[2.3-b]pyridine (**XXII**) even in the presence of 5 g-equiv. of alkali formed in yield no more than 6%, and the use of so large concentration of the catalyst results in considerable tarring. Therefore the product was isolated from the reaction mixture obtained in the presence of 2 g-equiv. of alkali. The mixture was acidified, noncyclic compound was washed out with ether, and the residue was crystallized from ethanol. Yield 4%.

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