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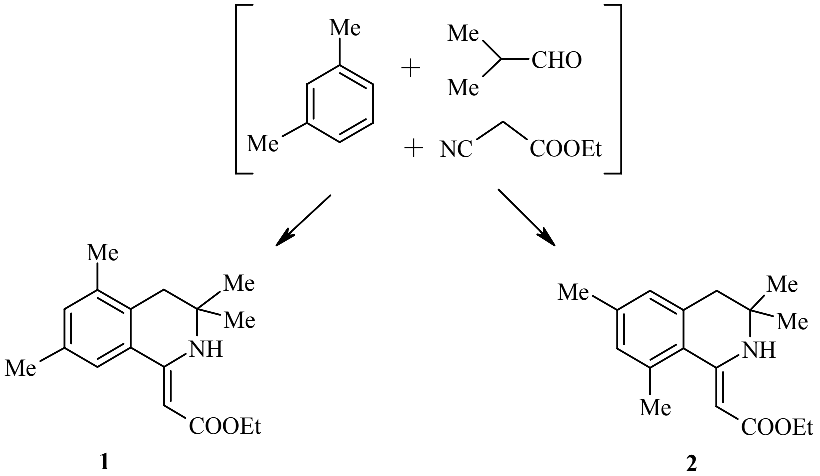
A NOVEL SPIROHETEROCYCLIZATION: SYNTHESIS OF 1-ETHOXYCARBONYLMETHYLIDENE-8-(2'-ETHOXYCARBONYLMETHYLIDENE-5',5'-DIMETHYL-3'-PYRROLIDINYLIDENE)-3,3,6-TRIMETHYL-2-AZASPIRO[4,5]DECA-6,9-DIENE

Yu. V. Shklyaev[1], Yu. V. Nifontov[1], M. I. Kodess[2], and M. A. Ezhikova[2]

It was shown that isobutyraldehyde and cyanoacetic ester enter into reaction with meta-xylene initially at the fourth carbon atom with the formation of a spiropyrroline ring and then at the newly formed exomethylene bond with closure of the 1-ethoxycarbonylmethylidene-8-(2'-ethoxycarbonylmethylidene-5',5'-dimethyl-3'-pyrrolidinylidene)-3,3,6-trimethyl-2-azaspiro[4,5]deca-6,9-diene system.

Keywords: isobutyraldehyde, *meta*-xylene, cyanoacetic ester, Ritter reaction, spiroheterocyclization.

The reaction of *ortho*- and *para*-xylenes, isobutyraldehyde, and nitriles leads to the production of 1-substituted 3,3,6,7- or 3,3,5,8-tetramethyl-3,4-dihydroisoquinolines [1]. It seemed of interest to bring *meta*-xylene also into reaction with nitriles.



On general considerations a concerted orientation of the substituents (*ortho*-, *para*-) could be expected for the reaction, and this should lead to the formation of 1-substituted 3,3,5,7-tetramethyl-3,4-dihydroisoquinolines **1**. By virtue of steric hindrances the formation of 1-substituted 3,3,6,8-tetramethyl-3,4-

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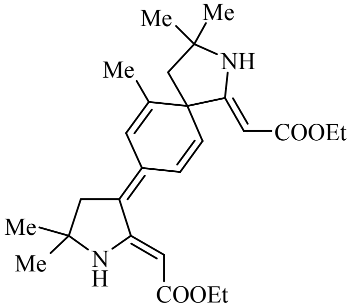
[1] Institute of Technical Chemistry, Urals Branch of the Russian Academy of Sciences, Perm. [2] Institute of Organic Synthesis, Urals Branch, Russian Academy of Sciences, Ekaterinburg; e-mail: onchup@ios.ural.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1487-1491, October, 2004. Original article submitted October 23, 2001.

dihydroisoquinolines **2** could be expected in so far as the substituent in the forthcoming position 8 of the ring does not prevent the formation of isoquinoline [2].

In fact, during the three-component reaction between *meta*-xylene, isobutyraldehyde, and cyanoacetic ester after neutralization of the reaction mass a product having basic character was isolated. In the ^1H NMR spectra all the signals of the aliphatic protons are split, but the methyl groups in the aromatic ring give one signal corresponding in intensity to only one methyl group. The mass spectrum gave a molecular ion peak at 440 (with *I* 70%), indicating the participation of two molecules of isobutyraldehyde and two molecules of cyanoacetic ester to one molecule of *meta*-xylene in the reaction.

It can be concluded from the experimental data that the reaction leads to the production of compounds **3** or **4**.

It should be noted that the two proposed versions have different directions for the initial attack by the protonated form of the isobutyraldehyde, i.e., at the position with highest electron density (the *ortho*-*ortho* orientation, position 2 of the ring) and at position 4 of the ring (*ortho*-*para* concerted orientation).



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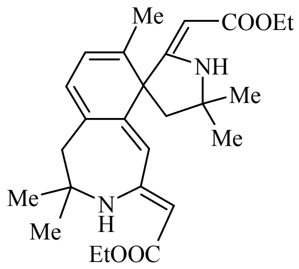

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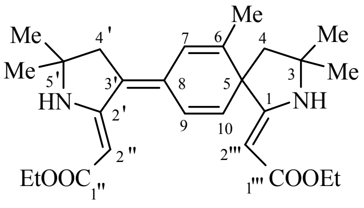
As shown by the data from 1D and 2D NMR experiments, the investigated compound has structure **3**:



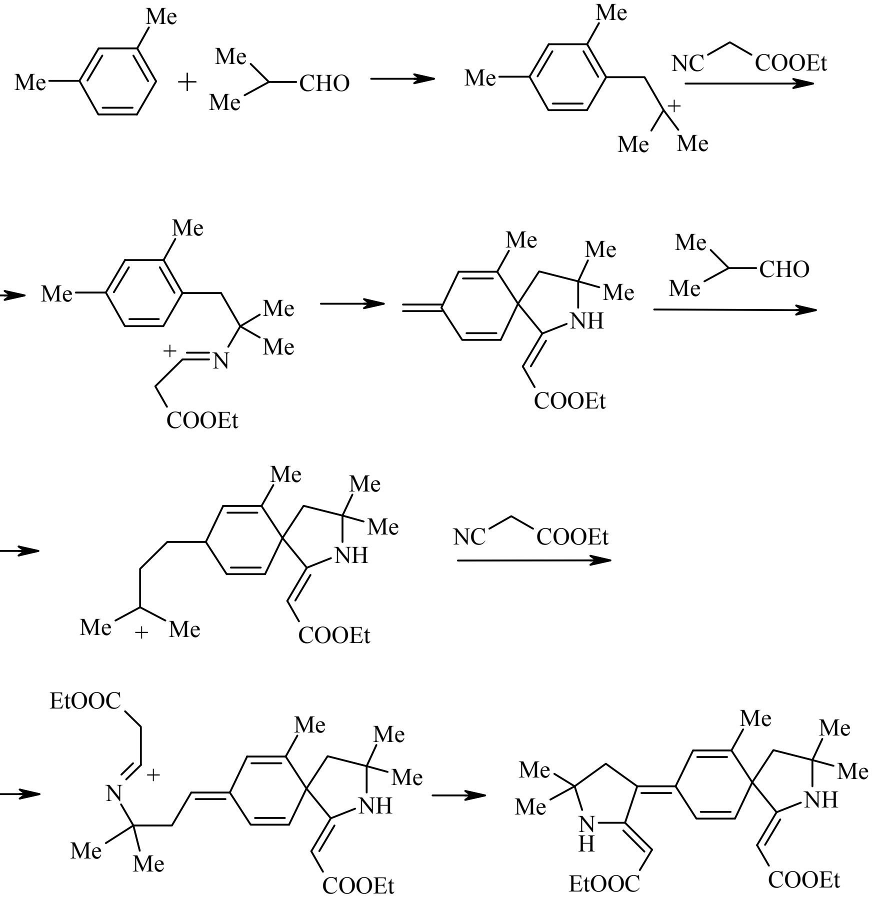
In the ^1H NMR spectrum it was possible to detect fine structure in the resonance signals of the $H_{(7)}$, $H_{(9)}$, and $CH_3–C_{(6)}$ protons. The signal of the $H_{(7)}$ proton at δ 6.18 ppm is split into a doublet of quartets on account of long-range interactions (^4J) with the $H_{(9)}$ proton and with the protons of the methyl group at $C_{(6)}$, while the signal of the $H_{(9)}$ proton at 6.97 ppm is split into a doublet of doublets. The spin–spin couplings between the discussed protons are supported by $^1H\{^1H\}$ double resonance experiments.

The signals of the protonated carbon atoms were assigned by means of a HETCOR heteronuclear correlation 2D experiment.

The data from an inversion HMBC 2D experiment, based on the long-range spin–spin couplings $^2J_{C–H}$ and $^3J_{C–H}$, made it possible to assign the quaternary carbon atoms and to confirm the structure of compound **3**. In the HMBC spectra there cross peaks between the nodal atoms $C_{(5)}$ and the $H_{(7)}$, $H_{(9)}$, $H_{(10)}$, and $C_{(6)}–CH_3$ protons of the six-membered ring and the $N_{(2)}H$ and $C_{(4')}H_2$ protons. In addition correlation is observed on account of interactions through two and three bonds between the protons and carbon atoms in each individual ring and the corresponding side chains. It was not possible to make an unambiguous assignment on account of the overlap of the signals of the carbonyl and ethyl groups.

Information on the steric proximity of the protons, obtained from the 2D NOESY spectrum, made it possible on the one hand to confirm the assignment of the resonance signals of the protons and on the other to draw conclusions about the configuration of the double bonds in the molecule of compound **3**. In particular, correlation on account of dipole–dipole interaction is observed for the following pairs of protons: $H_{(2'')}$ and $H_{(9)}$, $C_{(4')}H_2$ and $H_{(7)}$, $H_{(2'''')}$ and $C_{(6)}–CH_3$, and $H_{(10)}$ and one of the methyl groups at the $C_{(3)}$ atom. Thus, clearly, the steric hindrances created by the two methyl groups make attack at the fourth and not the second carbon atom (the position with the highest electron density) energetically more favorable.

The scheme for the formation of the product **3** can be represented as follows:



A special feature of compound **3** is its comparatively high hydrolytic stability in sulfuric acid at the isolation stage. During isolation the 1-R-3,3-dimethyl-2-azaspiro[4,5]deca-1,6,9-trien-8-ones that we described [3] with R groups other than thiomethyl undergo dienone–phenol rearrangement and give open-chain products – derivatives of 2-(4'-hydroxyphenyl)ethylamine – exclusively.

Thus, we have shown for the first time that not only alkoxyarenes but also alkyl aromatic compounds can enter into spiroheterocyclization, and this opens up broad possibilities for the use of α-branched aldehydes in these reactions.

TABLE 1. The ^{1}H and ^{13}C NMR Spectra of Compound **3**

Atom/ group	^{1}H NMR spectrum, δ, ppm (J, Hz)	^{13}C NMR spectrum, δ, ppm.	Atom/ group	^{1}H NMR spectrum, δ, ppm (J, Hz)	^{13}C NMR spectrum, δ, ppm.
C=O	—	171.29	$C_{(3)}$	—	61.01
C=O	—	171.08	OCH_2	4.12 (q, $J = 7.1$)	58.64
$C_{(1)}$	—	166.81	OCH_2	4.07 (center of AB system)	58.64
$C_{(2')}$	—	159.59	$C_{(5')}$	—	58.28
$C_{(6)}$	—	140.97	$C_{(5)}$	—	55.79
$C_{(10)}H$	5.94 (d, $J = 10$)	135.96	$C_{(4)}H_2$	2.15, 1.87 (AB system, $J_{AB} = 13.8$)	47.95
$C_{(8)}$	—	130.34	$C_{(4')}H_2$	2.68, 2.62 (AB system, $J_{AB} = 15.6$)	43.73
$C_{(3')}$	—	129.93	$C_{(3)}(CH_3)_2$	1.41, 1.40	32.06, 30.78
$C_{(7)}H$	6.18 (dq, $^4J = 1.5$, $^4J = 1.3$)	124.55	$C_{(5')}(CH_3)_2$	1.31, 1.30	29.51, 29.50
$C_{(9)}H$	6.97 (dd, $^3J = 10$, $^4J = 1.5$)	120.08	$C_{(6)}CH_3$	1.86 (d, $J = 1.3$)	19.90
$C_{(2'')}H$	4.92	78.84	$CH_3(C_2H_5)$	1.27 (t, $J = 7.1$)	14.71
$C_{(2''')}H$	4.21	77.23	$CH_3(C_2H_5)$	1.24 (t, $J = 7.1$)	14.58

EXPERIMENTAL

The IR spectrum was recorded in vaseline oil on a UR-20 spectrophotometer. The ^{1}H NMR spectra were obtained on a Bruker AM 300 spectrophotometer (300 MHz) in deuterochloroform with TMS as internal standard. The 1D and 2D NMR experiments in deuterochloroform solution were conducted on a Bruker DRX-400 spectrometer (400 and 100 MHz for ^{1}H and ^{13}C) using the standard pulse sequences contained in the Bruker software. The mass spectrum was recorded on a Finnigan MAT instrument (electron impact, 70 eV) under standard conditions. The course of the reaction and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates (9:1 chloroform–acetone) with a 0.5% solution of chloranil in toluene as developer.

1-Ethoxycarbonylmethylidene-8-(2'-ethoxycarbonylmethylidene-5',5'-dimethyl-3'-pyrrolidinylidene)-3,3,6-trimethyl-2-azaspiro[4,5]deca-6,9-diene (3). A mixture of *meta*-xylene (50 mmol), isobutyraldehyde (7.2 g, 100 mmol), and cyanoacetic ester (100 mmol) was added dropwise with stirring at 0-5°C over 15-20 min to concentrated sulfuric acid (50 ml). The mixture was stirred for 30 min, poured into water (300 ml), and extracted with toluene (50 ml). The organic layer was rejected, and the aqueous layer was neutralized to pH 8-9 with ammonium carbonate. The separated substance was filtered off, washed with water, dried, and crystallized. We obtained 19.8 g (45%) of compound **3**; mp 178-179°C (ethanol). IR spectrum, ν, cm^{-1}: 3355, 3335, 1735, 1723, 1650, 1600, 1580, 1500. Mass spectrum *m/z* (I_{rel}, %): 440 $[M]^+$ (100); 425 $[M - CH_3]^+$ (10); 395 $[M - OEt]^+$ (20); 367 $[M - COOEt]^+$ (45); 327 $[M - NCCH_2COOEt]^+$ (98); 312 $[M - NCCH_2COOEt - CH_3]^+$ (95). Found %: C 71.00; H 8.10; N 6.47. $C_{26}H_{36}N_2O_4$. Calculated %: C 70.91; H 8.18; N 6.36.

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