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Prototropic Isomerization of Spiro[2,3]hexanes 1,1,5-Trisubstituted with Electron-acceptor Groups into 1,3-Disubstituted Bicyclo[1.1.0]butanes

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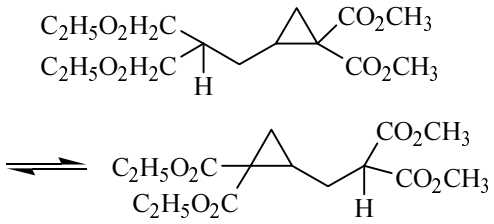
Abstract—1,1-Dicyano- and 1,1-dialkoxycarbonylspiro[2.3]hexane-1-carbonitriles treated with lithium diisopropylamide or potassium *tert*-butylate in THF undergo a prototropic isomerization into 3-(2,2-dicyanoethyl)- and 3-(2,2-dialkoxycarbonylethyl)bicyclo[1.1.0]butane-1-carbonitriles respectively.

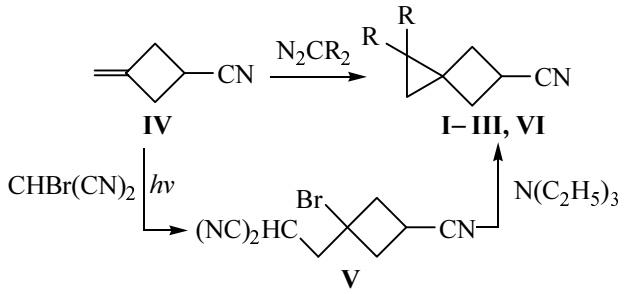
Cyclopropanes containing two electron-acceptor substituents at the same atom of the ring (activated cyclopropanes) are known [1] to enter into addition reactions with various nucleophilic agents, among them also with C-nucleophiles. It was established [2] that activated cyclopropanes with a third substituent possessing a CH-acid moiety under the action of bases underwent a prototropic isomerization resulting in building up a new ring instead of the opened three-membered one. Danishefsky *et al*. [3] discovered a cyclopropane-cyclopropane isomerization presented below effected by sodium dimsyl in DMSO.



This approach (building of a three-carbon ring at a sacrifice of opening another one) we have used in the present study where we report on the new preparation method for 1,3-disubstituted bicyclobutanes by prototropic isomerization of spiro[2.3]hexanes 1,1,5-trisubstituted with electron-acceptor groups.*

We studied the behavior of three substituted spirohexanes **I–III** in the presence of strong bases, lithium diisopropylamide or potassium *tert*-butylate in THF. Bis(alkoxycarbonyl) derivatives **I** and **II** were obtained from available methylenecyclobutane (**IV**) by a carbene reaction involving the corresponding ester of diazomalonic acid. Trinitrile **III** was prepared from the same precursor along Boldt procedure [5] in two stages: first was carried out a photochemical addition of bromomalononitrile, and then adduct **V** was subjected to dehydrobromination. The substituted spirohexanes **I** and **II** were obtained as two diastereomers that were not separated.

The precursor of spirohexane **III**, bromide **V**, was also



obtained as a mixture of diastereomers. The main *E*-isomer **Va** was isolated from the mixture by crystallization. The treatment of the latter with triethylamine resulted in an individual diastereomer of spirohexane **III** that was assigned *Z*-configutation **IIIb** in keeping with the expected stereospecific elimination, cf. [6]. In its turn the configuration assigned to bromide **Va** was assumed based on the close values of the chemical shifts of H^1 (3.65 ppm) in **Va** spectrum and that of the model *E*-3-bromo-3-methylcyclobutane-1-carbonitrile (3.46 ppm) taking into account that in the spectrum of the *Z*-isomer of the model the corresponding signal appeared upfield from 3.17 ppm, cf.

* For preliminary communication see [4].

[7]. The structure of compounds **I–III** was proved using ^{1}H and ^{13}C NMR spectroscopy. The spectral identification of the spirohexane skeleton of these compounds was performed by comparison with the data on model nitrile **VI** prepared by cyclopropanation of compound **IV** with diazomethane. The assignment of configuration in diastereomers **I–III** was based on the difference in the chemical shifts of the carbons in the four-membered ring analogous to that in the diastereomers 1-oxaspiro[2.3]hexane-5-carbonitrile (**VII**) whose configurational assignment was proved [6]: in the *E*-isomers (a) the signals of C^3 and C^5 are shifted downfield, and the signal of $C^{4,6}$ upfield with respect to the corresponding resonances in the *Z*-isomers (b). Below are given the chemical shifts of carbon atoms (δ, ppm) in the four-membered rings for diastereomers of spirohexane compounds **Ia, Ib–IIIa, IIIb, VIIa, VIIb**.

	C^3	$C^{4,6}$	C^5
Ia/Ib	33.2/32.5	32.3/33.1	17,2/16.6
IIa/IIb	32.9/32.3	32.4/33.2	17.4/16.8
IIIa/IIIb	35.0/34.4	31.2/31.5	17.0/16.6
VIIa/VIIb	57.6/56.2	35.6/35.9	15.0/13.5

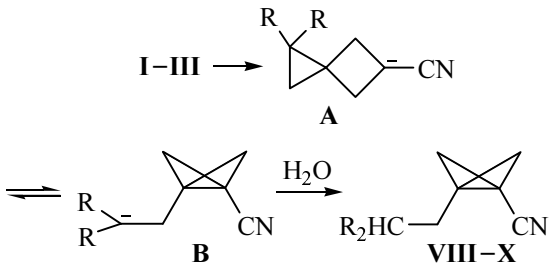
Note that the above configurational assignment fully agrees with already mentioned conclusion on the *Z*-configuration of compound **IIIb**.

The isomerization of spirohexanes **I–III** at room temperature was a fast process, and the corresponding substituted bicyclobutanes **VIII–X** were obtained in a high yield. The structure of the latter compounds was conclusively confirmed by their ^{1}H and ^{13}C NMR spectra. As particular features of the spectral parameters proving the presence in their structure of a 1-cyanobicyclobutane fragment should be mentioned the broadened singlets of the nonequivalent methylene protons of the ring separated by ~ 0.7 ppm, and the upfield shift of C^1 atom located in the negative region of the δ scale, cf. [6, 7].

The observed prototropic isomerization **(I–III) → (VIII–X)** is especially interesting since it is irreversibly shifted to the bicyclobutane compounds **VIII–X** contrary to the greater strain energy of the bicyclobutane skeleton (63.9 kcal mol^{-1} [8]) as compared to that of the spirohexane (56.7 kcal mol^{-1}).*

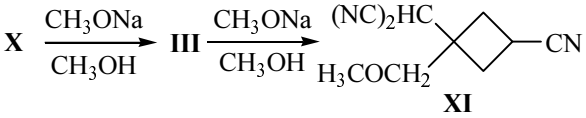
* Inasmuch as the data for spiro[2.3]hexane are lacking we give the strain energy value of 1-oxaspiro[2.3]hexane [9] that is presumably similarly strained.

However since the reaction was carried out in an aprotic medium at the use of a strong base, the direction of isomerization should be governed here by an equilibrium between the carbanion intermediates **A** and **B**.



R = CO_2CH_3 (**VIII**), $CO_2C_2H_5$ (**IX**), CN (**X**).

The relative stability of the latter depends mostly on the degree of the charge delocalization that is greater in the **B** ion. Finally, the target isomerization products **VIII–X** arise only on diluting the reaction mixture with water. The above reasoning on the mechanism of the observed isomerization is indirectly confirmed by the formation of cyclobutane **XI** resulting from treating bicyclobutane **X** with sodium methylate.



Unlike the situation in the aprotic medium, the equilibrium between compounds **X** and **III** in methanol holds a position favoring the latter. Further compound **III** being an activated cyclopropane [1] and hence unstable under these conditions suffers a nucleophilic ring opening effected by sodium methylate to afford cyclobutane **XI**. The ready conversion **(III) → (XI)** was proved by a direct experiment. Compound **XI** was obtained as a mixture of two diastereomers. The structure of compound **XI** was proved by comparing its ^{1}H and ^{13}C NMR spectra with the data of model 1,1,3-trisubstituted cyclobutanes [8].

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker DPX-300 at 300.13 and 75.47 MHz respectrively from solutions in $CDCl_3$. Elemental analyses were performed on a CHN-analyzer HP-185 B. Analytical TLC was carried out on Silufol UV-254 plates. The separation and purification of compounds was

performed by column chromatography on silica gel L 40/100 (Chemapol). 3-Methylenecyclobutane-1-carbonitrile (**IV**) [10], bromomalononitrile [5], dimethyl(ethyl) diazomalonates [11], potassium *tert*-butylate [12], and butyllithium [13] were prepared by published procedures.

Dimethyl *E*- and *Z*- 5-cyanospiro[2.3]hexane-1,1-dicarboxylate (Ia) and (Ib). Into a flask was charged 0.93 g (10 mmol) of nitrile **I**, 1.58 g (10 mmol) of dimethyl diazomalonate, 50 mg of anhydrous copper sulfate, and 10 ml of octane. The air from the system was replaced by a flow of argon. The mixture was stirred at heating to 120°C till the end of nitrogen liberation (~30 min). On cooling the reaction mixture was diluted with 10 ml of ether for homogenizing, and the solution obtained was subjected to column chromatography on silica gel using as eluent a mixture of light petroleum ether and ethyl ether, 1:1. The collected fraction contained a mixture of diastereomers **Ia** and **Ib** in a ratio ~1:1 (according to ^{1}H NMR data) as a viscous oily fluid. Yield 0.91 g (41%). ^{1}H NMR spectrum, δ, ppm: 1.63 s (2H, H^2, **Ib**), 1.69 s (2H, H^2, **Ia**), 2.42–2,57 m (4H) and 2.65–2.82 m (4 H), H^{4,6}, **Ia + Ib,** 3.25 m (1H, H^5, **Ia**), 3.45 m (1H, H^5, **Ib**), 3.70 s (6H, OCH_3, **Ia**), 3.72 s (6H, OCH_3, **Ib**). ^{13}C NMR spectra, δ, ppm: **(Ia) -** 17.2 (C^5), 25.9 (C^2), 32.3 (2 C, C^{4,6}), 33.2 (C^3), 35.6 (C^1), 52.2 (2C, OCH_3), 121.8 (CN), 167.7 (2C, C=O); **(Ib) -** 16.6 (C^5), 32.5 (C^3), 33.1 (2C, C^{4,6}), 35.4 (C^1), 52.2 (2C, OCH_3), 121.0 (CN), 167.7 (2C, C=O). Found, %: C 59.28; H 5.73; N 6.12. $C_{11}H_{13}NO_4$. Calculated, %: C 59.19; H 5.87; N 6.27.

Diethyl *E*- and *Z*- 5-cyanospiro[2.3]hexane-1,1-dicarboxylates (IIa) and (IIb) were prepared by procedure similar for the above described for compounds **Ia** and **Ib**. On separating the reaction mixture by column chromatography on silica gel we obtained oily substance composed of a mixture of diastereomers **IIa** and **IIb** in a ratio ~1:1 (according to ^{1}H NMR data). Yield ~40%. ^{1}H NMR spectrum, δ, ppm: 1.36 t (6H, CH_3, *J* 7 Hz, **IIa**), 1.47 t (6H, CH_3, *J* 7 Hz, **IIb**), 1.62 s (2H, H^2, **IIb**), 1.68 s (2H, H^2, **IIa**), 2.43–2.58 m (4 H) and 2.72–2.89 m (4H), H^{4,6}, **IIa + IIb,** 3.25 m (1H, H^5, **IIb**), 3.51 m (1H, H^5, **IIa**), 4.33 q (4 H, OCH_2, *J* 7 Hz, **IIa**), 4.48 q (4H, OCH_2, *J* 7 Hz, **IIb**). ^{13}C NMR spectra, δ, ppm: **(IIa) -** 14.0 (2C, CH_3), 17.4 (C^5), 25.9 (C^2), 32.4 (2C, C^{4,6}), 32.9 (C^3), 35.8 (C^1), 61.3 (2C, OCH_2), 122.1 (CN), 167.5 (2C, C=O); **(IIb) -** 14.0 (2C, CH_3), 16.8 (C^5), 26.0 (C^2), 32.3 (C^3), 33.2 (2C, C^{4,6}), 35.7 (C^1), 61.3 (2C, OCH_2), 121.3 (CN), 167.5 (2C, C=O). Found, %: C 61.92; H 7.01; N 5.31. $C_{13}H_{17}NO_4$. Calculated, %: C 62.14; H 6.82, N 5.57.

***E*-3-Bromo-3-(2,2-dicyanoethyl)cyclobutane-1-carbonitrile (Va).** Into a quartz vessel was charged 0.93 g (10 mmol) of nitrile **I** and 1.45 g (10 mmol) of bromomalononitrile in 10 ml of CH_2Cl_2. To remove oxygen a weak argon flow was passed through the solution for 15 min, and then the UV irradiation was switched on (from a medium pressure mercury lamp). The irradiation was continued till complete consumption of the bromomalononitrile (TLC monitoring). The reaction continued for ~6 h. On removing the solvent the residue was recrystallized from CH_2Cl_2. Yield 1.40 g (59%), mp 128°C. ^{1}H NMR spectrum, δ, ppm: 4.24 d [1H, $CH(CN)_2$, *J* 7 Hz], 3.66 quint (1H, H^1, *J* 9 Hz), 2.89–3.21 m (4H, H^{2,4}), 2.67 d (2H, CH_2, *J* 7 Hz). ^{13}C NMR spectrum, δ, ppm: 18.6 (C^1), 20.7 [$C(CN)_2$], 43.8 (C^{2,4}), 44.1 (C^3), 58.7 (CH_2), 111.4 (2 C, CN), 119.5 (CN). Found, %: C 45.60; H 3.50; N 17.73. $C_9H_7N_3$. Calculated, %: C 45.40; H 3.39; N 17.65.

***E*- and *Z*-Spiro[2.3]hexane-1,1,5-tricarbonitriles (IIIa) and (IIIb).** *a*. A solution of 1.67 g (7 mmol) of bromide **Va** and 1.0 g (10 mmol) of triethylamine in 10 ml of CH_2Cl_2 was heated at reflux for 1 h. On cooling the separated precipitate was filtered off and washed with dichloromethane (10 ml). The organic layer was washed with 3% hydrochloric acid, with water, and dried on sodium sulfate. On removing the solvent we obtained 0.91 g (83 %) of ***Z*-spiro[2.3]hexane-1,1,5-tricarbonitrile (IIIb),** mp 122°C. ^{1}H NMR spectrum, δ, ppm: 1.92 s (2 H, H^2), 2.68–2.82 m (2H) and 2.91–3.07 m (2H), H^{4,6}, 3.35–3.50 m (1H, H^5). ^{13}C NMR spectrum, δ, ppm: 9.0 (C^1), 16.6 (C^5), 28.5 (C^2), 31.5 (2 C, C^{4,6}), 34.4 (C^3), 112.7 (2 C, CN), 120.0 (CN). Found, %: C 68.75; H 4.59; N 26.91. $C_9H_7N_3$. Calculated, %: C 68.78; H 4.49; N 26.73.

b. Likewise using instead of bromide **Va** the mixture of bromides **Va, Vb** recoved from the mother liquor after recrystallization of bromide **Va** (see above) we obtained a mixture of *E*- and ***Z*-spiro[2.3]hexane-1,1,5-tricarbonitriles (IIIa)** and **(IIIb).** From the ^{13}C NMR spectrum of this mixture by subtracting the signals of **IIIb** component was revealed the ^{13}C NMR spectrum of isomer **IIIa**, δ, ppm: 9.3 (C^1), 17.0 (C^5), 27.8 (C^2), 31.2 (2 C, C^{4,6}), 35.0 (C^3), 113.0 (2 C, CN), 120.3 (CN).

Spiro[2.3]hexane-5-carbonitrile (VI). To 100 ml of diazomethane ether solution prepared from 10.3 g (0.1 mol) of nitrosomethyl urea was added at cooling to 0°C first 1.40 g (15 mmol) of nitrile **IV** and then a dispersion of 0.225 g (1 mmol) of palladium acetate. The mixture was stirred at 0°C till the end of gas evolution

(~1 h), and then thereto was added again the same amount of diazomethane and $Pd(OAc)_2$, the cooling was removed, and the stirring was continued for ~2 h till complete consumption of initial nitrile **IV** (monitoring by ^1H NMR spectroscopy). The solution obtained was filtered,the ether was distilled off, and the residue was distilled in a vacuum. Yield 1.30 g (81%), bp. 72–74°C (10 mm Hg). ^1H NMR spectrum, δ, ppm: 0.53 br.s (4 H, $H^{1,2}$), 2.39–2.48 m (2H) and 2.57–2.66 m (2 H), $H^{4,6}$, 3.25 quint (1 H, H^5). ^{13}C NMR spectrum, δ, ppm: 11.0 and 12.0 (C^1 and C^2), 17.6 (C^3), 17.7 (C^5), 35.1 (2 C, $C^{4,6}$), 122.7 (CN). Found, %: C 78.51; H 8.41. C_7H_9N. Calculated, %: C 78.46; H 8.47.

Izomerization of spirohexanes Ia, Ib and IIa, IIb. To a solution of 4 mmol of diisopropylamine in 10 ml of anhydrous ethyl ether at–78°C was added by a syringe 6.8 ml (4 mmol) of 0.58 M butyllithium solution in pentane. Then the stirring was started, and the mixture was warmed to –20°C. To the mixture at this temperature 3 mmol of spirohexane **Ia, Ib** or **IIa, IIb** was added. In 15 min the reaction mixture was diluted with water solution of ammonium chloride. The ether layer was separated, the water layer was extracted with ether (3...15 ml). The combined organic solution was washed with water and dried on magnesium sulfate. On removing the solvent the reaction product was purified by column chromato-graphy on silica gel.

3-(2,2-Dimethoxycarbonylethyl)bicyclo[1.1.0]-butane-1-carbonitrile (VIII). Yield 75 %, uncrystallizable oily substance. ^1H NMR spectrum, δ, ppm: 1.32 br.s (2H, *endo*-$H^{2,4}$), 2.06 br.s (2 H, *exo*-$H^{2,4}$), 2.60 d (2H, CH_2, *J* 7 Hz), 3.68 t (1H, CH, *J* 7 Hz), 3.78 s (6H, OCH_3). ^{13}C, d, ppm: -2.9 (C^1), 23.4 (C^3), 27.3 (CH_2), 39.3 (2 C, $C^{2,4}$), 50.5 (CH), 52.7 (OCH_3), 118.9 (CN), 168.5 (C=O). Found, %: C 59.39; H 5.77; N 6.31. $C_{11}H_{13}NO_4$ Calculated, %: C 59.19; H 5.87; N 6.27.

3-(2,2-Diethoxycarbonylethyl)bicyclo[1.1.0]-butane-1-carbonitrile (IX). Yield 71%, oily substance. ^1H NMR spectrum, δ, ppm: 1.30 t (6 H, CH_3, *J* 8 Hz), 1.33 br.s (2H, *endo*-$H^{2,4}$), 2.10 br.s (2H, *exo*-$H^{2,4}$), 2.61 d (2H, CH_2, *J* 7 Hz), 3.64 t (1H, CH, *J* 7 Hz), 4.26 q (4 H, OCH_2, *J* 8 Hz). ^{13}C NMR spectrum, δ, ppm: –2.9 (C^1), 13.9 (2 C, CH_3), 23.5 (C^3), 27.2 (CH_2), 39.5 (2C, $C^{2,4}$), 50.9 (CH), 61.7 (2C, OCH_2), 119.0 (CN), 168.1 (2C, C=O). Found, %: C 62.02; H 7.01; N 5.39. $C_{13}H_{17}NO_4$. Calculated, %: C 62.14; H 6.82; N 5.57.

3-(2,2-Dicyanoethyl)bicyclo[1.1.0]butane-1-carbonitrile (X). To a solution of 0.47 g (3 mmol) of trinitrile **IIIb** in 5 ml of THF while stirring in an argon atmosphere at external cooling (–20°C) was added in one portion 0.45 g (4 mmol) of freshly sublimed potassium *tert*-butylate. In 10 min the cooling was removed, and the stirring was continued for 1 h more, and then the reaction was terminated. The reaction mixture was diluted with 30 ml of ether, and 10 ml of ammonium chloride saturated solution was added thereto. The organic layer was washed with water and dried on magnesium sulfate. On removing the solvent and recrystallization of the residue we obtained 0.34 g (72%) of compound **X**, mp 83°C (CH_2Cl_2). ^1H NMR spectrum, δ, ppm: 1.62 br.s (2H, *endo*-$H^{2,4}$), 2.30 br.s (2H, *exo*-$H^{2,4}$), 2.73 d (2H, CH_2, *J* 7 Hz), 4.14 t (1H, CH, *J* 7 Hz). ^{13}C NMR spectrum, δ, ppm: -2.4 (C^1), 20.6 (C^3), 23.1 (CH), 30.8 (CH_2), 40.0 (2 C, $C^{2,4}$), 111.5 (2 C, CN), 117.7 (CN). Found, %: C 68.74; H 4.68; N 26.88. $C_9H_7N_3$. Calculated, %: C 68.78; H 4.49; N 26.73.

3-Dicyanomethyl-3-methoxymethylcyclobutane-1-carbonitrile (XI). *a*. A solution of 157 mg (1 mmol) of bicyclobutane **X** in 10 ml (5 mmol) of 0.5 M methanol solution of sodium methylate was heated at reflux for 3 h. The solution obtained was concentrated in a vacuum, diluted with water, and thoroughly extracted with ether. The extracte was washed with a saturated solution of NH_4Cl and with water, and dried on magnesium sulfate. On removing the solvent we obtained 163 mg (86%) of analytically pure compound **XI** (oily substance) composed of a mixture of two diastereomers (**a** and **b**)* in a ratio 1.5 : 1 (according to ^1H NMR spectrum). ^1H NMR spectra, δ, ppm: (**a**), 2.57-2.78 m (4H, $H^{2,4}$), 3.29-3.42 m (1 H, H^1), 3.43 s (3 H, OCH_3), 3.70 s (2 H, OCH_2), 4.15 s [1 H, $CH(CN)_2$]; (**b**), 2.42-2.57 m (4 H, $H^{2,4}$); 3.10–3.26 m (1H, H^1), 3.42 s (3H, OCH_3), 3.56 s (2H, OCH_2), 4.16 s [1 H, $CH(CN)_2$]. ^{13}C NMR spectra, δ, ppm: (**a**), 15.9 (C^1), 28.8 (CH), 30.9 (2 C, $C^{2,4}$), 42.3 (C^3), 59.3 (OCH_3), 74.8 (OCH_2), 111.0 (2C, CN), 121.2 (CN); (**b**), 15.9 (C^1), 29.6 (CH), 31.2 (2C, $C^{2,4}$), 41.4 (C^3), 59.3 (OCH_3), 73.0 (OCH_2), 110.7 (2C, CN), 120.0 (CN). Found, %: C 63.32; H 5.74; N 22.33. $C_{10}H_{11}N_3O$. Calculated, %: C 63.48; H 5.86; N 22.21.

b. Likewise from 79 mg (0.5 mmol) of spirohexane **IIIb** was obtained 71 mg (75%) of compound **XIa, XIb** in diastereomers ratio ~ 2 : 1.

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* The configurations of diastereomers **XIa, b** were not assigned.

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