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Prototropic Isomerization of Dihydropyridazinecarboxylic and Dihydropyridazinedicarboxylic Acid Esters

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Abstract—3,5-Disubstituted 1,4-dihydropyridazine-4-carboxylic and 4,6-disubstituted 2,5-dihydropyridazine-3,5-dicarboxylic acid esters undergo isomerization into 2,5-dihydropyridazine-4-carboxylate and 1,4-dihydropyridazine-3,5-dicarboxylate derivatives, respectively, by the action of a catalytic amount of a mineral acid or strong base at 20°C. The transformation may be regarded as prototropic rearrangement, and it includes two consecutive 1,2-hydride shifts. The direction of the isomerization is determined by higher thermodynamic stability of the isomer containing a β-aminoacrylate fragment.

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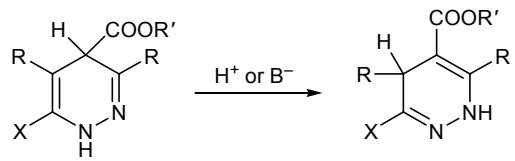
We previously [1, 2] developed a convenient procedure for the preparation of 3,5-disubstituted methyl 1,4-dihydropyridazine-4-carboxylates and 4,6-disubstituted dimethyl 2,5-dihydropyridazine-3,5-dicarboxylates by reaction of 2,3-disubstituted methyl cycloprop-2-ene-1-carboxylates with diazomethane and methyl diazoacetate. The present article reports on prototropic isomerization of analogous dihydropyridazine derivatives, which was not described previously. The revealed isomerization is illustrated by transformations of compounds **Ia**–**IVa** into structural isomers **Ib**–**IVb** (Scheme 1). The isomerization is initiated by addition of a mineral acid or a strong base, and it occurs with a high yield at 20°C.

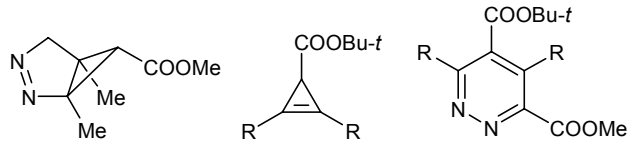
Scheme 1.



Ia–IVa **Ib–IVb**

I, R = Me; **II**, **III**, R = Ph; **IV**, R = Pr; **I**, X = H; **II**–**IV**, X = MeOC(O); **I**, **II**, R′ = Me; **III**, **IV**, R′ = *t*-Bu.

Dihydropyridazine **IIa** was synthesized according to the procedure reported in [1]. The synthesis of the other compounds is described in Experimental. Dihydropyridazine **Ia** was obtained by isomerization of diazabicyclohexene **V** catalyzed by sodium methoxide (cf. [1]). Compounds **IIIa** and **IVa** were prepared by reaction of cyclopropenes **VI** and **VII** with methyl diazoacetate (cf. [2]).

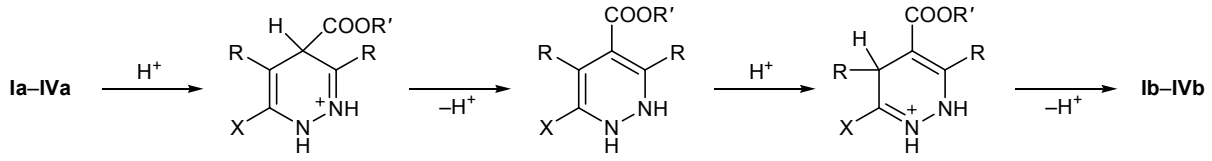


V **VI**, **VII** **VIII**, **IX**

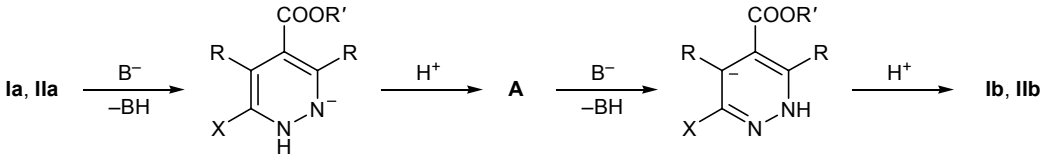
The structure of dihydropyridazines **Ia**, **IIIa**, and **IVa** was proved by ^{1}H and ^{13}C NMR spectroscopy. Their ^{1}H NMR spectra characteristically contained signals from the CH and NH protons, and three signals from sp^2-carbon atoms were observed in the ^{13}C NMR spectra. The structure of compound **Ia** was also confirmed by the expected similarity of its NMR spectra with the spectra of its analogs reported in [1]. The NMR spectra of mixed esters **IIIa** and **IVa** were similar to the spectra of their homologs described in [2]. An additional support for the assumed structure of **IIIa** and **IVa** was obtained by their oxidation with potassium permanganate to the corresponding pyridazinedicarboxylates **VIII** and **IX** (cf. [2]).

The structure of dihydropyridazines **Ib**–**IVb** was also proved by ^{1}H and ^{13}C NMR spectroscopy, in particular by comparing their NMR spectra with those of the corresponding isomers **Ia**–**IVa**. It was especially

Scheme 2.



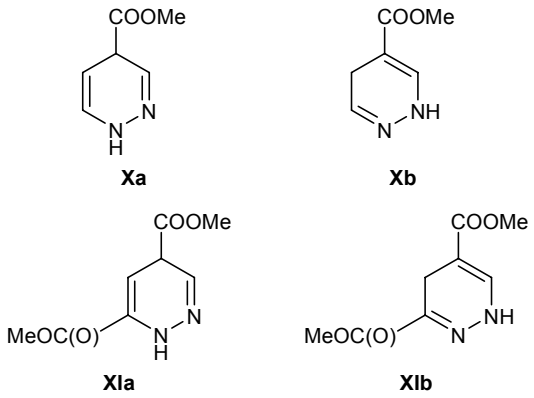
Scheme 3.



easy to distinguish dialkyl derivatives in couples **Ia**/**Ib** and **IVa**/**IVb** by different multiplicities of the CH signal. The latter appeared in the ^{1}H NMR spectra of **Ia** and **IVa** as a singlet at δ 3.71 and 3.78 ppm, respectively, whereas the CH proton in isomers **Ib** and **IVb** resonated as a multiplet at δ 3.33 (d.q) and 4.02 ppm (t), respectively. Dihydropyridazines **IIa** and **IIIa** characteristically displayed in the ^{1}H NMR spectra a downfield two-proton signal at δ 7.80–7.94 ppm from *ortho*-protons in the phenyl substituent at the C=N bond. By contrast, the spectra of dihydropyridazines **IIb** and **IIIb** contained no aromatic proton signals in the region δ > 7.5 ppm.

Thus the transformation of dihydropyridazines **Ia**–**IVa** into isomers **Ib**–**IVb** may be classed with prototropic rearrangements involving two consecutive 1,2-H shifts. The acid-catalyzed isomerization may be illustrated by Scheme 2, and the mechanism of the base-catalyzed process is shown in Scheme 3. In no case we succeeded in detecting intermediate 1,2-dihydropyridazine derivative **A** in the reaction mixture.

The driving force of the described rearrangement is likely to be higher thermodynamic stability of isomers **Ib**–**IVb** due to the presence of a β-aminoacrylate fragment in their molecules. This assumption was confirmed by RM1 quantum-chemical calculations (PC GAMESS [3]) performed for compounds **Ia**, **Ib**, **IIa**, and **IIb** and model structures **Xa**, **Xb**, **XIa**, **XIb**.



In all cases, isomers like **Xb** and **XIb** were more stable than those of type **Xa** and **XIa** by ΔE = 2.1 (**I**), 1.2 (**II**), 5.1 (**X**), and 2.7 kcal/mol (**XI**) (with account taken of zero-point vibration energy). The discovered prototropic isomerization explains why the transformation of 2,3-diazabicyclo[3.1.0]hex-2-ene (**V**) catalyzed by sodium methoxide gave exclusively compound **Ib** [1]. The use of a relatively high concentration of the catalyst (a 0.05 M solution of sodium methoxide in methanol) favored subsequent isomerization of initially formed dihydropyridazine **Ia**. In the present work we showed that isomerization of **V** in the presence of 0.005 M of sodium methoxide resulted in the formation of compound **Ia** as the only product, the conversion of **V** being complete. Prototropic isomerization catalyzed by mineral acid occurs at an appreciably higher rate than in the presence of base catalyst; therefore, even partial transformation of compound **V** in the presence of HCl at a "low" concentration yields only dihydropyridazine **Ib**.

EXPERIMENTAL

The elemental compositions were determined on an HP-185B CHN analyzer. The ^{1}H and ^{13}C NMR spectra were recorded from solutions in chloroform-*d* on a Bruker DPX-300 spectrometer at 300.130 and 75.468 MHz, respectively. Flash chromatography was performed on silica gel L (40–100 μm) using hexane–diethyl ether as eluent. The separation process was monitored by TLC on Silufol UV-254 plates using diethyl ether–hexane (1 : 1) as eluent.

The most stable conformations of compounds **Ia**, **Ib**, **IIa**, **IIb**, **Xa**, **Xb**, **XIa**, and **XIb** were determined by the molecular mechanics method using ChemAxon MarvinBeans program [4]. The structures thus obtained were optimized in the RM1 approximation [5] using PC GAMESS [3].

***tert*-Butyl 2,3-dipropylcycloprop-2-ene-1-carboxylate (VI)** was synthesized according to the procedure described in [6]. bp 110°C (10 mm). ^{1}H NMR spectrum, δ, ppm: 0.97 t (6H, Me, J = 7.2 Hz), 1.43 s (9H, *t*-Bu), 1.51–1.65 m (4H, β-CH_2), 1.94 s (1H, 1-H), 2.39 t (4H, α-CH_2, J = 7.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.9, 20.4, 26.6 (C_3H_7); 23.3 (C^1), 28.1 (C**Me**$_3$), 79.1 (C–O), 106.0 (C^2, C^3), 176.6 (C=O).

***tert*-Butyl 2,3-diphenylcycloprop-2-ene-1-carboxylate (VII)** was synthesized in a similar way. mp 90°C; published data [7]: mp 88.5–89.5°C. ^{1}H NMR spectrum, δ, ppm: 1.46 s (9H, *t*-Bu), 2.74 s (1H, 1-H); 7.35–7.42 m (2H), 7.42–7.53 m (4H), and 7.62–7.72 m (4H) (H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 22.7 (C^1), 28.2 (C**Me**$_3$), 80.1 (C–O), 108.1 (C^2, C^3), 127.4, 128.8 (2C), 129.1, 129.8 (2C), 174.1 (C=O).

Methyl 3,5-dimethyl-1,4-dihydropyridazine-4-carboxylate (Ia). Diazabicyclohexene **V** [1], 300 mg, was dissolved in 3 ml of methanol, 1 ml of 0.02 M solution of sodium methoxide in methanol was added under stirring, the mixture was kept for 1 h at room temperature under nitrogen, and 50 ml of diethyl ether was added. The ether layer was separated, washed with an aqueous solution of sodium chloride, and dried over Na_2SO_4, and the solvent was distilled off under reduced pressure. The residue was 280 mg of an oily material which solidified on cooling with ice. Crystallization from hexane gave 250 mg (85%) of compound **Ia** with mp 29–30°C. ^{1}H NMR spectrum, δ, ppm: 1.72 s (3H, Me), 1.99 s (3H, Me), 3.71 s (4-H), 3.72 s (3H, OMe), 6.23 d (1H, 6-H, J = 3.0 Hz), 6.91 br.s (NH). ^{13}C NMR spectrum, δ_C, ppm: 18.1 and 22.3 (Me), 47.7 (C^4), 52.2 (OMe), 99.6 (C^5), 124.0 and 136.5 (C^3, C^6), 170.5 (C=O). Found, %: C 57.17; H 7.14; N 16.61. $C_8H_{12}N_2O_2$. Calculated, %: C 57.13; H 7.19; N 16.66.

Dimethyl 2,5-dihydro-4,6-diphenylpyridazine-3,5-dicarboxylate (IIa) was synthesized as described in [2]. mp 139°C [2]. ^{1}H NMR spectrum, δ, ppm: 3.69 s (3H, OMe), 3.75 s (3H, OMe), 4.87 s (1H, 5-H), 7.30–7.45 m (8H) and 7.80–7.90 m (2H (Ph), 8.80 br.s (NH). ^{13}C NMR spectrum, δ_C, ppm: 46.5 (C^5), 52.2 and 52.8 (OMe); 111.2 (C^4), 126.8 (2C), 127.7, 127.9 (2C), 128.0, 128.5 (2C), 129.1, 129.4 (2C), 134.8, 135.1, 138.0 (Ph, C^3, C^6); 163.4 and 170.0 (C=O).

5-*tert*-Butyl 3-methyl 2,5-dihydro-4,6-diphenylpyridazine-3,5-dicarboxylate (IIIa). A solution of 0.70 g (2.40 mmol) of compound **VI** and 1.50 g (15.0 mmol) of methyl diazoacetate in 6.0 ml of dimethylformamide was heated for 30 h at 85°C under argon. The mixture was diluted with 50 ml of water and extracted with chloroform, the organic phase was washed with water and dried over Na_2SO_4, the solvent and excess methyl diazoacetate were removed under reduced pressure, and the product was isolated by flash chromatography. Yield 0.85 g (91%), greenish–yellow very viscous oily substance. ^{1}H NMR spectrum, δ, ppm: 1.44 s (9H, *t*-Bu), 3.67 s (3H, OMe), 4.77 s (1H, 5-H), 7.32–7.46 m (8H) and 7.85–7.94 m (2H) (Ph), 8.83 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 27.7 (C**Me**$_3$), 47.8 (C^5), 52.0 (OMe), 82.3 (**C**Me$_3$), 111.8 (C^4), 126.7 (2C), 127.3, 127.5, 127.7 (2C), 128.2 (2C), 128.7, 129.2 (2C), 135.3, 135.4, 138.2 (Ph, C^3, C^6); 163.4 and 168.2 (C=O). Found, %: C 70.55; H 6.22; N 7.17. $C_{23}H_{24}N_2O_4$. Calculated, %: C 70.38; H 6.16; N 7.14.

5-*tert*-Butyl 3-methyl 2,5-dihydro-4,6-dipropylpyridazine-3,5-dicarboxylate (IVa). A solution of 0.70 g (3.12 mmol) of compound **VII** and 1.50 g (15.0 mmol) of methyl diazoacetate in 6.0 ml of dimethylformamide was heated for 30 h at 85°C under argon. The mixture was then treated as described above for **IIIa**. Yield 0.82 g (82%), mp 48°C. ^{1}H NMR spectrum, δ, ppm: 0.91 t and 0.94 t (3H each, Me, J = 7.3 Hz), 1.41 s (9H, *t*-Bu), 1.36–1.65 m (4H, β-CH_2); 2.36–2.44 m (2H), 2.45–2.57 m (1H), and 2.65–2.79 m (1H) (α-CH_2); 3.78 s (1H, 5-H), 3.83 s (1H, OMe), 7.88 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.7 and 13.8 (Me), 19.7 and 21.7 (β-CH_2), 27.8 (C**Me**$_3$), 33.5 and 37.2 (α-CH_2), 48.8 (C^5), 52.0 (OMe), 81.8 (**C**Me$_3$), 117.3 (C^4), 127.3 and 140.6 (C^3, C^6), 163.1 and 167.9 (C=O). Found, %: C 63.05; H 8.73; N 8.62. $C_{17}H_{28}N_2O_4$. Calculated, %: C 62.94; H 8.70; N 8.64.

5-*tert*-Butyl 3-methyl 4,6-diphenylpyridazine-3,5-dicarboxylate (VIII). Potassium permanganate, 0.34 g (2.14 mmol), was added to a solution of 0.70 g (1.78 mmol) of dihydropyridazine **IIIa** in a mixture of 15.0 ml of acetone and 5.0 ml of water, and the mixture was stirred for 6 h at 20°C. The precipitate of MnO_2 was filtered off and washed with acetone (3× 3.0 ml). The filtrate was diluted with 50 ml of distilled water, and the precipitate was filtered off and recrystallized from aqueous methanol (1 : 1). Yield 0.53 g

(76%), mp 93°C. ^{1}H NMR spectrum, δ, ppm: 1.10 s (9H, *t*-Bu), 3.80 s (3H, OMe); 7.32–7.40 m (2H), 7.43–7.54 m (6H), and 7.76–7.83 m (2H) (Ph). ^{13}C NMR spectrum, δ_C, ppm: 27.3 (C**Me**$_3$), 52.9 (OMe), 84.5 (**C**Me$_3$); 128.2 (2C), 128.4 (2C), 128.5 (2C), 129.0 (2C), 129.2, 130.0, 132.6, 133.0, 135.6, 136.5 (Ph, C^4, C^5); 151.5 and 157.8 (C^3, C^6), 163.7 and 165.0 (C=O). Found, %: C 70.79; H 5.67; N 7.13. $C_{23}H_{22}N_2O_4$. Calculated, %: C 70.75; H 5.68; N 7.18.

5-*tert*-Butyl 3-methyl 4,6-dipropylpyridazine-3,5-dicarboxylate (IX). Potassium permanganate, 35 mg (0.22 mmol), was added in one portion to a solution of 60 mg (0.185 mmol) of dihydropyridazine **IVa** in 4.0 ml of acetone, and the mixture was stirred for 5 h at room temperature. The precipitate of MnO_2 was filtered off and washed with acetone (3×2.0 ml). The filtrate was evaporated under reduced pressure, and the uncrystallizable residue was purified by flash chromatography. Yield 47 mg (79%), colorless oily substance. ^{1}H NMR spectrum, δ, ppm: 1.00 t and 1.02 t (3H each, Me, *J* = 6.5 Hz), 1.63 s (9H, *t*-Bu), 1.50–1.68 m and 1.77–1.92 m (2H each, β-CH$_2$), 2.75–2.83 and 2.91–2.99 m (2H each, α-CH$_2$), 4.03 s (3H, OMe). ^{13}C NMR spectrum, δ_C, ppm: 14.0 and 14.3 (Me), 22.8 and 24.1 (β-CH$_2$), 28.0 (C**Me**$_3$), 31.5 and 36.1 (α-CH$_2$), 53.0 (OMe), 84.6 (**C**Me$_3$), 133.9 and 137.7 (C^4, C^5), 151.0 and 159.9 (C^3, C^6), 165.0 and 165.5 (C=O). Found, %: C 63.38; H 8.10; N 8.65. $C_{17}H_{26}N_2O_4$. Calculated, %: C 63.33; H 8.13; N 8.69.

General procedure for the acid-catalyzed isomerization of dihydropyridazines Ia–IVa. A solution of 0.1 ml of concentrated hydrochloric acid in 1 ml of methanol was added at 20°C to a solution of 0.3 mmol of compound **Ia**–**IVa** in 2 ml of methanol. The mixture was kept for 1 h, neutralized with $NaHCO_3$, and diluted with 15 ml of water. The resulting solution was extracted with diethyl ether (2×10 ml), and the extract was dried over $MgSO_4$ and evaporated to isolate isomerization product **Ib**–**IVb**.

Methyl 3,5-dimethyl-2,5-dihydropyridazine-4-carboxylate (Ib) [1]**.** Yield 80%, oily substance. ^{1}H NMR spectrum, δ, ppm: 0.94 d (3H, Me, *J* = 7.1 Hz), 2.23 s (3H, Me), 3.33 d.q (1H, 5-H, *J* = 4.8, 7.1 Hz), 3.68 s (3H, OMe), 6.77 d (1H, 6-H, *J* = 4.8 Hz), 7.80 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 17.7 and 18.1 (Me), 27.3 (C^5), 50.6 (OMe), 94.9 (C^4), 143.6 and 147.1 (C^3, C^6), 167.6 (C=O).

Dimethyl 4,6-diphenyl-1,4-dihydropyridazine-3,5-dicarboxylate (IIb) [2]**.** Yield 94%, mp 153°C. ^{1}H NMR spectrum, δ, ppm: 3.76 s and 3.87 s (3H each, OMe), 4.99 s (1H, 4-H); 7.12–7.18 m (3H), 7.18–7.24 m (2H), 7.30–7.40 m (5H) (Ph); 8.53 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 42.0 (C^4), 52.5 and 52.6 (OMe), 103.2 (C^5); 126.8, 127.4, 127.9 (2C), 129.0 (2C), 129.3, 129.5 (2C), 129.9 (2C), 133.8, 136.5, 137.1 (Ph, C^3, C^6); 164.4 and 171.1 (C=O). Found, %: C 68.55; H 5.27; N 7.82. $C_{20}H_{18}N_2O_4$. Calculated, %: C 68.56; H 5.18; N 8.00.

5-*tert*-Butyl 3-methyl 4,6-diphenyl-1,4-dihydropyridazine-3,5-dicarboxylate (IIIb). Yield 86%, mp 109°C. ^{1}H NMR spectrum, δ, ppm: 1.12 s (9H, *t*-Bu), 3.79 s (3H, OMe), 5.25 s (1H, 4-H), 7.20–7.50 m (10H, Ph), 8.03 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 27.6 (C**Me**$_3$), 37.1 (C^4), 52.6 (OMe); 80.3 (**C**Me-$_3$), 101.3 (C^5); 127.8 (2C), 128.2, 128.5 (2C), 128.6 (2C), 128.7 (2C), 129.1, 129.6, 134.6, 142.6, 145.2 (Ph, C^3, C^6); 164.2 and 165.1 (C=O). Found, %: C 70.43; H 6.12; N 7.19. $C_{23}H_{24}N_2O_4$. Calculated, %: C 70.38; H 6.16; N 7.14.

5-*tert*-Butyl 3-methyl 4,6-dipropyl-1,4-dihydropyridazine-3,5-dicarboxylate (IVb). Yield 81%, mp 62°C. ^{1}H NMR spectrum, δ, ppm: 0.86 t and 0.96 t (3H each, Me, *J* = 7.3 Hz), 1.50 s (9H, *t*-Bu), 1.20–1.31 m (4H, β-CH$_2$); 1.53–1.66 m (2H), 2.53–2.65 m (1H), 2.68–2.81 m (1H) (α-CH$_2$); 3.86 s (3H, OMe), 4.02 t (1H, 5-H, *J* = 7.0 Hz), 8.12 s (NH). ^{13}C NMR spectrum, δ_C, ppm: 13.7 and 14.1 (Me), 18.4 and 21.9 (β-CH$_2$), 28.2 (C**Me**$_3$), 31.0 and 32.4 (α-CH$_2$), 35.2 (C^4), 52.4 (OMe), 80.1 (**C**Me$_3$), 99.9 (C^5), 139.3 and 148.0 (C^3, C^6), 164.7 and 166.0 (C=O). Found, %: C 63.09; H 8.68; N 8.57. $C_{17}H_{28}N_2O_4$. Calculated, %: C 62.94; H 8.70; N 8.64.

Base-catalyzed isomerization of dihydropyridazine (Ia). Dihydropyridazine **Ia**, 100 mg, was dissolved in 3 ml of methanol, 1 ml of a 0.2 M solution of sodium methoxide in methanol was added under stirring, and the mixture was kept for 1 h at 20°C under nitrogen and treated with 30 ml of diethyl ether. The ether solution was washed with an aqueous solution of sodium chloride, dried over Na_2SO_4, and evaporated under reduced pressure, and the residue was subjected to flash chromatography to isolate 83 mg (83%) of dihydropyridazine **Ib** as a colorless oily substance.

Based-catalyzed isomerization of dihydropyridazine (IIa) [2]**.** Dihydropyridazine **IIa**, 50 mg, was dissolved in 0.5 ml of DMSO, 25 mg of a 50% solution of potassium hydroxide in water was added, and the mixture was stirred for 30 min under argon. The mixture was diluted with 15 ml of water, and the

precipitate was filtered off, washed with water, and dried under reduced pressure over anhydrous KOH. Yield of dihydropyridazine **IIb** 27 mg (54%), mp 152–153°C (from aqueous methanol).

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