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Isomerization of Substituted Tricyclic 4,5-Dihydropyrazoles

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Summary. The acid and base catalyzed isomerization of some tricyclic 2-pyrazolines with N-Carbamoyl-, N-thiocarbamoyl- and N-phenyl substituents was investigated. Starting from *cis* or *trans* 3-H, 3a-H diastereomers, equilibrium mixtures of *cis* and *trans* diastereomers were prepared which were separated and subsequently studied by ^{1}H NMR and ^{13}C NMR spectroscopy. A mechanism for the isomerization of the pyrazolines is suggested, supported by a deuterium exchange at C-3a.

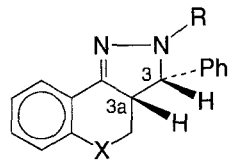
Keywords. Isomerization; N-Substituted 2*H*-benz[*g*]indazoles; ^{1}H and ^{13}C NMR spectroscopy.

Isomerisierung von einigen substituierten 4,5-Dihydropyrazolen

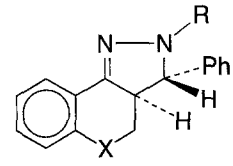
Zusammenfassung. Die Isomerisierung einiger tricyclischer 2-Pyrazoline mit N-Carbamoyl-, N-Thiocarbamoyl- und N-Phenyl-substituenten unter saurer und basischer Katalyse wurde untersucht. Ausgehend von den *cis* oder *trans* 3-H,3a-H-Diastereomeren wurden *cis*- und *trans* Gleichgewichtsgemische gewonnen, die getrennt und durch ^{1}H- und ^{13}C-NMR-Spektroskopie untersucht wurden. Ein Mechanismus für die Isomerisierung von Pyrazolinen wird vorgeschlagen, der durch den Deuteriumaustausch in Position 3a-C unterstützt wird.

Introduction

Previously we have reported the preparation of some benz[*g*]indazoles and their hetero analogues formed in the reaction of arylidene ketones and hydrazine derivatives [1, 2]. The isomeric composition of the products was found to depend on the nucleophilic reagent and the reaction conditions. Using phenylhydrazine in acidic medium a mixture of the *cis* and *trans* diastereomers was obtained whereas in pyridine only the latter was formed [3]. The outcome of the reaction with methylhydrazine and thiosemicarbazide in turn was independent of solvent and catalyst, giving in the first case only the *trans* diastereoisomer, whereas in the latter case only the *cis* diastereoisomer was formed (Fig. 1) [1, 2]. In this paper, we report studies on the interconversion of these *cis* and *trans* diastereoisomers which also can be used to obtain diastereoisomers (**3b**–**5b**) not directly accessible from the unsaturated ketones. Our model compounds were the tricyclic pyrazolines **1a**–**5a**, **1b**–**5b**, and **6b** [2, 3, 8]. Since we have found earlier that the *S*-alkyl derivatives of the *cis* dias-



cis H-3/H-3a



trans H-3/H-3a

	X	R	isomeric ratio (%)		X	R	isomeric ratio (%)
1a	CH_2	$CONH_2$	94	**1b**	CH_2	$CONH_2$	6
2a	CH_2	Ph	68	**2b**	CH_2	Ph	32
3a	CH_2	$CSNH_2$	100	**3b**	CH_2	$CSNH_2$	0
4a	$(CH_2)_2$	$CONH_2$	67	**4b**	$(CH_2)_2$	$CONH_2$	33
5a	$(CH_2)_2$	$CSNH_2$	100	**5b**	$(CH_2)_2$	$CSNH_2$	0
				6b	CH_2	CH_3	100

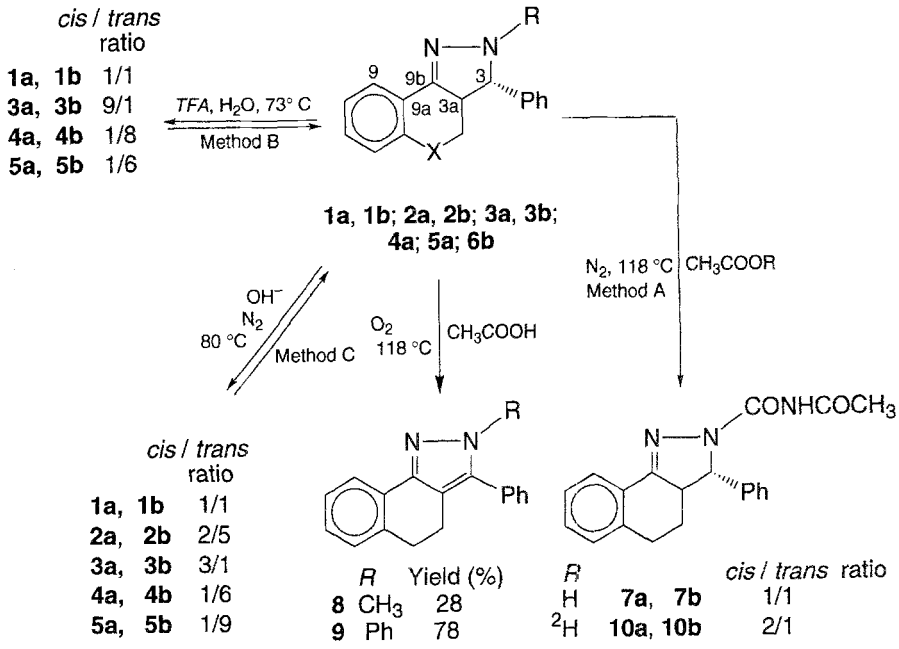
Fig. 1. Starting tricyclic pyrazolines of the isomerization reactions

tereomer (**3a**) shows antimicrobial activity *in vitro* [9], we extended our investigations to the *S*-alkyl derivatives of the *trans* diastereomer (**3b**) as well.

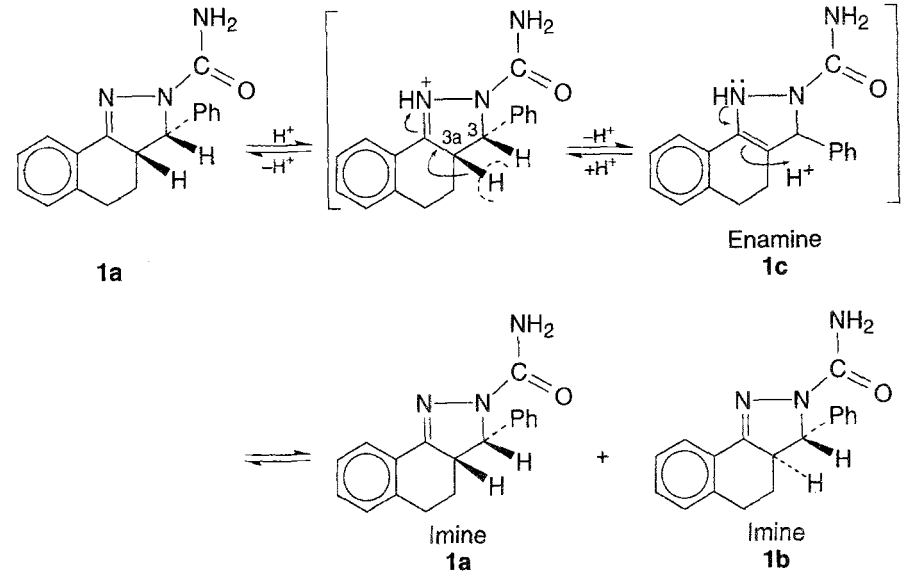
Results and Discussion

Isomerizations were carried out in acetic acid (Method A), in trifluroacetic acid containing 2% water (method B), and in ethanolic potassium hydroxide solution (Method C). They were monitored by ^1H NMR spectroscopy. Epimerizations were carried out starting from **1a** or **1b**, **2a**, or **2b**, **3a**, or **3b**, **4a**, **5a**, and **6b** as pure diastereoisomers. Equilibrium reactions were characterized by the composition of the equilibrium mixture based on the integral values of the H-3 signals. Starting from either the *cis* or the *trans* isomers of **1**, **2**, and **3**, the same ratio was obtained proving a real equilibrium. Products **1a**, **b**, **3a**, **b**, and **7a**, **b** were separated by column chromatography; the structures were verified by IR and NMR spectroscopy (Tables 1–3). For the differentiation of *cis* and *trans* isomers, homonuclear NOE difference spectra were used [2, 3]. The chemical shifts of H-3, H-3a, C-3, and C-3a are of diagnostic value indicating the relative configuration and also serving as a basis for quantitative analysis.

The 2-methyl derivative **6b** and the 2-phenyl derivatives **2a** or **2b** gave pyrazoles **8** and **9**, respectively, in boiling acetic acid (Scheme 1). Although aromatization caused by oxygen from the air could be suppressed by working under nitrogen, no isomerization of **6b** could be detected in acetic acid at 80 °C. Base catalyzed isomerization also yielded equilibrium mixtures, but without considerable aromatization and decompostion. The latter method proved to be the best to produce the diastereoisomers not available through direct synthesis from unsaturated ketones. The *trans* diastereoisomer **6b** failed to react under both acidic and basic conditions; even sodium methoxide caused no isomerization. The mechanism of the isomerization was also considered (Scheme 2). In analogy to Ref. [4], **1a** is protonated at N-1; then it yields a 3-pyrazoline of enamine type under proton catalysis (Scheme 2; **1c**). After the tautomerization of this intermediate, isomers of 'imine' type appear (**1a** and **1b**). Stereochemically, the decisive step is the protonation of **1c** affording **1a** and **1b**.



Scheme 1



Scheme 2

An analogous type of enamine (3-pyrazoline) prepared by *Elguero et al.* [5] was protonated at C-4 [6] (corresponding to C-3a in benz[*g*]indazoles).

To prove the mechanism of the isomerization, **1a** was treated with hot CH_3COOD yielding a mixture of **7a, b** and **10a, b**. According to ^1H NMR analysis of the mixture, a deuterium atom was incorporated at position 3a. Contrary to our

Table 1. ^{1}H NMR data (chemical shifts (δ/ppm) and coupling constants (Hz)) of compounds **1a**, **b**, **3b**, and **7a**, **b** in $CDCl_3$

	1a	**1b**	**3b**	**7a**	**7b**
H-3	5.63	4.87	5.33	5.61	4.93
H-3a	3.64	3.19	3.17	3.58	3.19
H-4_{ax}	1.04	1.98	2.01	1.03	1.93
H-4_{eq}	1.78	2.23	2.23	1.75	2.27
H-5_{ax}	2.90	–	–	2.92	–
	–	2.90	2.90	–	2.89
H-5_{eq}	2.82	–	–	2.79	–
H-9	8.01	7.95	7.89	8.07	7.96
H-2′,6′	7.09	[a]	[a]	6.98	[a]
NH_2	5.40	5.70	6.30	[a]	[a]
$COCH_3$	–	–	–	2.44	2.40
$J_{3,3a}$	11.3	10.5	8.4	11.0	9.3

[a] not observed (very broad) or overlapped

observations, *Ferres* experienced deuterium incorporation only at the *cis*-diastereoisomer formed at under similar conditions [4], whereas in our case deuterium incorporation amounted to more than 90% with **7a**-*cis* and 60% with **7b**-*trans*. Meanwhile, it has been found that formation of *cis* and *trans* isomers deuterated at C-4 (which corresponds to our C-3a) and a nondeuterated *trans* isomer occurs performing a similar equilibration in CH_3COOD [7]. These observations propose a somewhat different mechanism for our compounds: an isomerization *via* tautomerism, *i.e.* a route *via* ring cleavage can be excluded. The results of the isomerization experiments are consistent with our previous experiments preparing bicyclic 2-pyrazolines from α,β-unsaturated ketones and hydrazine derivatives [1]. In the reaction of 2-arylidene-cycloalkanones and semicarbazide, the ratio of *cis* and *trans* isomers formed was found to depend on the size of the ring: increasing the ring size of the starting ketone resulted in predominant formation of the *trans* diastereoisomers. This can be explained by the nonbonding interactions present in the *cis* diastereoisomers with larger rings. In the case of the eight-membered ring, no *cis* isomer was formed at all. This steric effect plays also an important role in the isomerization of **4** and **5** where the *trans* isomers prevailed. In the ring closures from cyclic α,β-unsaturated ketones and semicarbazide, thiosemicarbazide, or phenyl hydrazine, the *cis* diastereoisomer is predominantly formed in a kinetically controlled reaction [1, 2]. This could then be isomerized to the thermodynamically more stable *trans* isomer.

Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were carried out at Central Research Laboratory, University Medical School, Pécs. IR spectra were recorded

Table 2. ^{13}C NMR data (chemical shifts (δ/ppm)) of compounds **1a, b, 3b,** and **7a, b** in $CDCl_3$

	1a	**1b**	**3b**	**7a**	**7b**
C-3	62.9	66.2	70.3	63.1	67.3
C-3a	48.1	56.2	56.7	48.5	55.5
C-4	23.6	27.8	28.1	23.9	27.7
C-5	28.8	29.2	29.2	29.3	29.0
C-5a	139.1	139.2	139.8	139.4	139.1
C-6	129.0	129.1	129.2	130.4	130.1
C-7	129.7	130.2	130.9	128.9	128.9
C-8	126.4	126.7	126.7	126.6	126.5
C-9	124.2	124.7	125.0	124.9	124.6
C-9a	127.3	127.2	127.2	127.3	127.2
C-9b	151.6	153.6	156.8	155.4	154.9
C-1′	138.4	142.3	143.1	136.6	141.6
C-2′,6′	125.7	128.8	128.8	125.7	128.6
C-3′,5′	128.3	125.6	125.8	128.3	125.5
C-4′	127.0	127.4	127.2	127.0	127.2
C=O	154.6	157.3	175.1	155.4	154.9
Ac	–	–	–	168.3	170.0
CH_3	–	–	–	21.8	22.0

on a Specord 75IR spectrometer using KBr pellets. ^1H NMR spectra were run on Bruker AC 250, JEOL FX 100, and Perkin-Elmer R-12A spectrometers with *TMS* as internal standard at ambiant temperature. ^{13}C NMR spectra were obtained at 62.7 and 25.0 MHz on Bruker AC 250 and JEOL FX 100 spectrometers. The synthesis of the starting tricyclic pyrazolines (**1a–5a** and **6b**) has been reported earlier [1–3, 8]. The preparation and the structure verification at **4b**, **5b** has been published elsewhere [8]. The equilibration time of isomerization reactions (in hours) and the yield (in percentage) are given in square brackets. Isomerizations were monitored by ^1H NMR spectroscopy. We could not examine the isomerization reactions in acetic acid at 80 °C because they were very slow even at 118 °C (in boiling acetic acid).

General Procedure for the Acid catalyzed Isomerization of Pyrazolines **1a** [85%, 30 h], **2a, b** [78% *from* **2a**, 75% *from* **2b**, 15 h], *and* **6b** [28%, 35 h] *(Method A)*

0.01 moles of 2-pyrazoline (pure *cis* or *trans* diastereoisomer) were dissolved in 50 ml of acetic acid and refluxed. 1.1 ml samples were withdrawn, evaporated, treated with 10 ml of toluene, and once more evaporated. The crude product was analyzed by ^1H NMR spectroscopy. Having reached equilibrium, the whole reaction mixture was worked up as described above. The residue was recrystallized from methanol, and the diastereoisomers were separated by column chromatography.

General Procedure for the Acid Catalyzed Isomerization of Pyrazolines **1a** [82%, 25 h], **3a** [97%, 45 h], **4a** [88%, 40 h], *and* **5a** [81%, 60 h] *in Trifluoroacetic Acid (Method B)*

0.0072 moles of pyrazoline were dissolved in a mixture of trifluoroacetic acid (30 ml) and water (0.6 ml). 0.7 ml samples were withdrawn and worked up as in method A.

Table 3. Physical constants, analytical and IR data of compounds **1b**, **3b**, **7a**, **7b**, **8**, and **9**

	Yield (%)	mp (°C)	Molecular Formula	Calculated C%	H%	N%	Found C%	H%	N%
1b[a]	44[b]	198(d)[c]	$C_{18}H_{17}N_3O$	74.20	5.88	14.42	74.13	5.72	14.59
3b[d]	10[e]	182(d)[c]	$C_{18}H_{17}N_3S$	70.33	5.51	13.67	70.15	5.31	13.61
7a[f]	35[g]	148–150[c]	$C_{20}H_{19}N_3O_2$	72.05	5.74	12.60	72.19	5.71	12.59
7b[h]	35[g]	97–98[c]	$C_{20}H_{19}N_3O_2$	72.05	5.74	12.60	72.22	5.60	12.44
8	28[g]	139–142[c]	$C_{18}H_{16}N_2$	83.05	6.19	10.76	83.32	6.21	10.63
9	78[g]	139–142[c]	$C_{23}H_{18}N_2$	85.68	5.63	8.69	85.54	5.68	8.45

[a] IR (cm^{-1}): 3480, 3345, 3275, 3200 (NH), 1680 (C=O); [b] method C; [c] from methanol; [d] IR (cm^{-1}): 3360, 3330, 3260 (NH), 1360 (thioamide); [e] method B; [f] IR (cm^{-1}): 3300 (NH), 1660 (C=O); [g] method A; [h] IR (cm^{-1}): 3520, 3500 (NH), 1670, 1655 (C=O)

General Procedure for the Base Catalyzed Isomerization of Pyrazolines **1a, b** [90% *from* **1a**, 87% *from* **1b**, 3 h], **2a, b** [80% *from* **2a**, 83% *from* **2b**, 40 h], **3a, b** [88% *from* **3a**, 85% *from* **3b**, 1 h], **4a** [86%, 4 h], **5a** [83%, 1.5 h], *and* **6b** [90%, 24 h] *(Method C)*

0.0014 moles of pyrazoline were dissolved in 0.72% ethanolic sodium hydroxide (110 ml). The samples withdrawn were evaporated, the solid residue was treated with water, the precipitate filtered off, washed with water until neutral, and dried. **6b** failed to react under these conditions and did not show any isomerization even in 6% ethanolic sodium methoxide.

Separation of Diastereoisomers **1a, b, 3a, b, 7a, b**

The mixture of the *cis* and *trans* diastereoisomers was separated on silica gel (Kieselgel 60, 0.063–0.2 mm, Merck, $L = 40$ cm, $\varnothing = 5$ cm), the *trans* diastereoisomer being eluted first. Eluents: benzene-ethyl acetate-*i*-propanol (55:1:1 v/v) for **1a, b** (yields: 45%, 44%), benzene-ethylacetate (50:1 v/v) for **3a, b** (yields: 87%, 10%), benzene-ethylacetate (10:1 v/v) for **7a, b** (yields: 35%, 35%). TLC analysis (Kieselgel 60 F_{254}, Merck, benzene-ethylacetate (1:1 v/v): **1a**: $R_f = 0.20$; **1b**: $R_f = 0.35$; **3a**: $R_f = 0.77$; **3b**: $R_f = 0.81$; **7a**: $R_f = 0.50$; **7b**: $R_f = 0.65$).

Isomerization of **1a** *in Deuteroacetic Acid:*

1a (3.00 g, 0.0103 mol) was boiled in CH_3COOD containing 20% D_2O (50 ml) for 51 h yielding the stereoisomers **7a**, **10a**, and **7b**, **10b** (*cis/trans* ratio: 2:1; deuterium incorporation: more than 90% at **7a** and 60% at **7b**). The *cis-trans* diastereoisomers were separated by chromatography as mentioned before.

4,5-Dihydro-2-methyl-3-phenyl-2H-benz[g]indazole (**8**)

Compound **8** was prepared according to Method A. 2.62 g (0.01 mol) of **6b** were boiled in acetic acid in the presence of oxygen for 35 h. The solvent was evaporated and the solid resiude was recrystallized from methanol. ^1H NMR ($CDCl_3$): 2.70 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.88 (s, 3H, NCH_3), 7.15–7.55 (m, 8H, Ar-H), 7.88 (d, 1H, H-9) ppm; ^{13}C NMR ($CDCl_3$): 19.5 (s, C-4), 29.8 (s, C-5), 37.4 (NCH_3), 130.3 (s, C-3), 115.4 (s, C-3a), 122.2 (s, C-9), 147.3 (s, C-9b) ppm; other aromatic CH signals: 126.8, 127.3, 128.3 (2C), 128.8 (2C), 129.3 (2C) ppm; quaternary carbons: 130.0, 136.6 and 139.6 ppm.

4,5-Dihydro-2,3-diphenyl-2H-benz[g]indazole (**9**)

Compound **9** was prepared according to Method A. 3.24 g (0.01 mol) of **2a** or **2b** were boiled in acetic acid in the presence of oxygen for 15 h. The solvent was evaporated and the solid residue was recrystallized from methanol. ^{1}H NMR ($CDCl_3$): 2.83 (m, 2H, CH_2), 2.98 (m, 2H, CH_2), 7.05–7.40 (m, 13H, Ar-H), 7.99 (m, 1H, H-9) ppm; ^{13}C NMR ($CDCl_3$): 19.6 (s, C-4), 29.7 (s, C-5), 134.0 (s, C-3), 117.2 (C-3a), 122.7 (C-9), 148.9 (C-9b) ppm; other aromatic CH signals: 125.1 (2C), 126.2, 127.0, 127.8, 128.0, 128.4, 128.5 (2C), 128.8 (2C), 129.3 (2C) ppm; quaternary carbons: 129.6, 136.9, 138.6 and 140.3 ppm.

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