

^{15}N , ^{13}C , AND ^1H NMR SPECTRA OF AZO AND HYDRAZO COMPOUNDS DERIVED FROM 1,3,3-TRIMETHYL-2-METHYLIDENE-2,3-DIHYDRO-INDOLE (FISCHER BASE)

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Dedicated to Professor Vojeslav Sterba on the occasion of his 75th birthday.

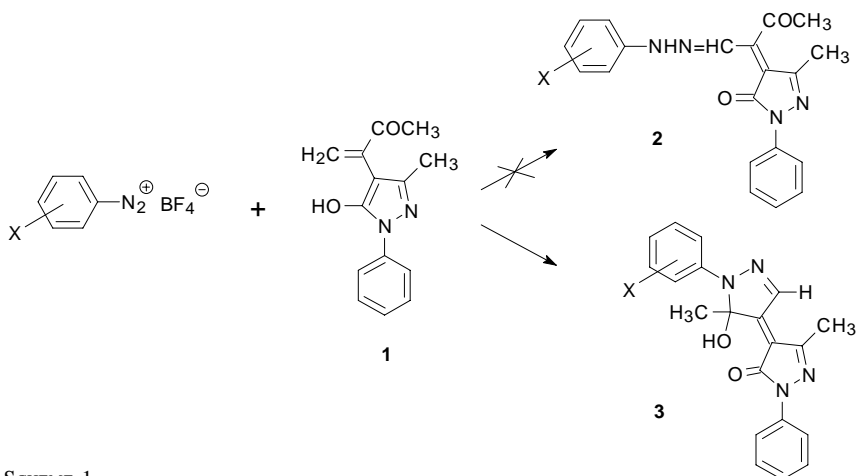
The ^{15}N , ^{13}C , and ^1H NMR spectra were measured for azo and hydrazo compounds derived from 1,3,3-trimethyl-2-methylidene-2,3-dihydroindole (Fischer base), which is a passive component with a terminal methylidene group. Products prepared by coupling in hydrochloric acid exist in the corresponding hydrazone form as the *E*-isomers. Neutralization gives a mixture of two isomeric azo compounds which differ in the arrangement at the C(2)=C(10) double bond. This mixture was alkylated with methyl iodide to obtain the =N–N(CH₃)– hydrazone derivatives. The geometric isomers were resolved based on the NOESY approach and the stereospecific behaviour of the $^2J(^{15}\text{N}, ^{13}\text{C})$ coupling constants was studied for the ^{15}N -labelled compounds.

Key words: ^1H , ^{13}C , and ^{15}N NMR spectroscopy; NOESY; ^{15}N – ^{13}C Coupling constants; Azo dyes.

Azo dyes $\text{R}^1\text{–N=N–R}^2$ are conventionally prepared by coupling of diazonium salts with components containing hydroxy or amino groups^{1–5}. The coupling to an activated methylene group of the X–CH₂–Y type is also feasible^{1–5}. Compounds where the coupling occurs at a terminal methylidene group represent a special group of compounds of this type. Mustroph and Bach⁶ reported that the reaction of diazonium salts with 4-(1-acetylothenyl)-3-methyl-1-phenylpyrazol-5(4*H*)-one (**1**) gives rise to a single product of azo coupling to the terminal methylidene group existing in the hydrazone form **2** (Scheme 1).

It is conceivable that compound **2** provides several tautomers, some of them with a hydrogen bond giving rise to a seven-membered or eight-membered ring, which would be interesting to study with respect to the hydrogen bonding. On the basis of the ^{15}N , ^{13}C , and ^1H NMR spectra⁷, however, we obtained evidence that the hydrazone compounds **2** are not the actual reaction products. Instead, a cyclization reaction with the COCH₃ group takes place giving rise to derivatives of 5'-hydroxy-3,5'-dimethyl-1,4'-diphenyl-4,4'-bi(4,5-dihydropyrazol-4-ylidene)-5-one (**3**) (Scheme 1).

The aim of the present work was to prepare azo and hydrazo compounds derived from the Fischer base **4** (Scheme 2), which is another passive coupling component with a terminal methylene group, and to measure and elucidate their ^{15}N , ^{13}C , and ^1H NMR spectra.



SCHEME 1

EXPERIMENTAL

Substances **5a**, **5b–7a**, **7b** in Scheme 2 were synthesized following refs^{8–11}. The ^{15}N isotopomers of **5a–7a** were prepared likewise using $\text{Na}^{15}\text{NO}_2$ (95% ^{15}N) and ^{15}N -aniline (20% ^{15}N).

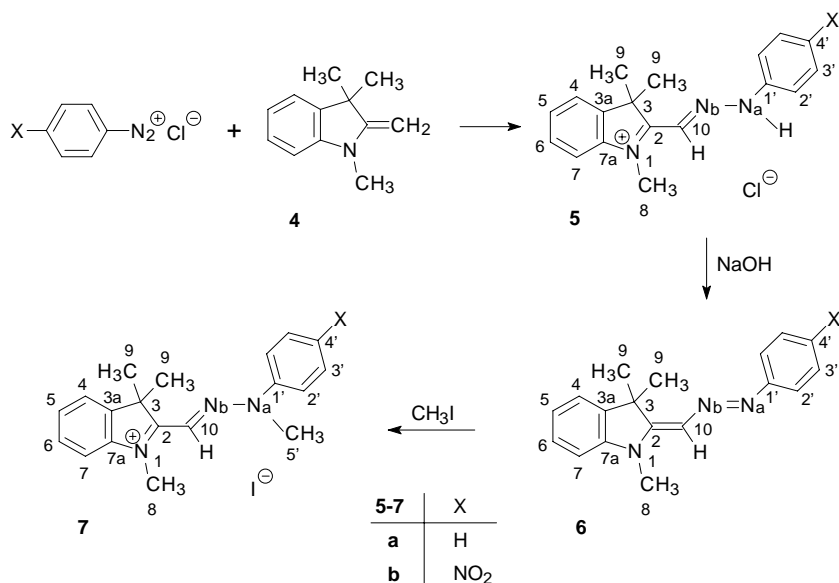
The ^1H , ^{13}C , and ^{15}N NMR spectra were measured at room temperature on a Bruker AMX-360 instrument at 360.13, 90.56, and 36.50 MHz, respectively. The ^1H and ^{13}C chemical shifts are given relative to internal tetramethylsilane (δ 0.0), the ^{15}N chemical shifts, relative to external nitromethane in a coaxial capillary (δ 0.0). Positive values of chemical shifts refer to downfield shifts relative to the standards. Solutions in $(\text{CD}_3)_2\text{SO}$ or CDCl_3 were measured in 5-mm NMR tubes using a 5-mm tuneable broadband probe.

RESULTS AND DISCUSSION

The ^1H , ^{13}C , and ^{15}N chemical shifts and $^nJ(^{15}\text{N}, ^{13}\text{C})$ and $^nJ(^{15}\text{N}, ^1\text{H})$ coupling constants of compounds **5–7** are given in Tables I–IV. The ^1H and ^{13}C chemical shifts were assigned on the basis of 1D and 2D (H,H-COSY, NOESY, H,C-COSY, H,H,C-RELAY) NMR spectra^{12–14}.

In contrast to the products of azo coupling to 4-(1-acetylenyl)-3-methyl-1-phenylpyrazol-5(4*H*)-one⁷, interaction with the group in the side chain can be ruled out in the coupling to the Fischer base. Reaction of 4-X-substituted benzenediazonium salts ($X = \text{H}, \text{NO}_2$) with the Fischer base in diluted hydrochloric acid (Scheme 2) provides single reaction products **5**, existing in the hydrazone form.

NOESY (Nuclear Overhauser effect and Exchange Spectroscopy) is employed to demonstrate that the protons concerned are sterically in a close vicinity¹²⁻¹⁴. Evidence was obtained that the protons of the NCH₃ and C(10)H groups in compounds **5a**, **5b** are in a close vicinity, which determines the prevalent orientation of the C(10)H proton with respect to the methyl groups in position 3. The steric interactions of protons in the C(CH₃)₂/C(4)H and NCH₃/C(7)H groups were employed to make an unambiguous assignment of the proton chemical shifts for the benzene ring of the heterocycle and, in the subsequent step, an unambiguous assignment of the ¹³C chemical shifts by means of H,C-COSY spectra.



SCHEME 2

Neutralization of substances **5** with concentrated aqueous sodium hydroxide in pyridine gave compounds **6**, which encompass two components as the NMR spectra indicate. The ¹³C NMR spectra give evidence^{15,16} that the products exist in the azo forms. Hence, the molecules **6** contain two conjugate double bonds which are not involved in the ring and can give four geometric isomers, *i.e.* *Z/Z*, *Z/E*, *E/Z*, and *E/E*. The ¹³C chemical shifts of the phenyl group correspond to the values in *trans* azobenzene^{15,16}. The two components present in substances **6** thus differ in the arrangement at the C(2)=C(10) double bond. NOESY measurement by the TPPI technique¹⁴ is very convenient for this purpose because steric interactions can be discriminated from the exchange effect. The TPPI-NOESY spectra¹⁴ gave unambiguous evidence, based on the positive off-diagonal signals, that both components present in substances **6** undergo mutual exchange. The existence of negative off-diagonal signals in the NOESY spec-

trum of the majority component gave evidence, like for substance **5**, of steric interaction of the NCH₃/C(10)H groups (which suggests the *E*-arrangement of the substituents at the C(2)=C(10) double bond), C(CH₃)₂/C(4)H or NCH₃/C(7)H groups. The NOESY results for the minority component in substance **6** are not convincing (see later).

Reaction of the two components of substances **6** with methyl iodide again gave invariably a single substance of the type **7**. The NOESY spectra show not only interactions observed for substances **5** and **6**, but also a steric interaction of protons of the methyl group originating from the methyl iodide, which is bonded at the N_a nitrogen,

TABLE I
¹H, ¹³C, and ¹⁵N NMR characteristics^a of compounds **5a** and **5b**

H/C/N	5a			5b	
	δ(¹ H)	δ(¹³ C)	ⁿ J(¹⁵ N _b , ¹³ C)	δ(¹ H)	δ(¹³ C)
1	–	–206.4 ^b	–	–	<i>f</i>
2	–	176.87	10.6	–	177.55
3	–	51.41		–	52.02
3a	–	142.28		–	142.89
4	7.83	122.85		7.88	123.05
5	7.62 ^c	128.85 ^c		7.63	129.09 ^c
6	7.54 ^c	127.89 ^c		7.63	128.91 ^c
7	7.83	113.84		7.92	114.68
7a	–	142.28		–	142.25
8	3.94	33.22		4.04	33.99
9	1.78	26.62	1.1	1.81	26.23
10	8.56 ^d	122.64	4.8	8.66	126.81
–N _a H–	14.73	–184.1 ^e		14.75	<i>f</i>
		–184.4 ^b			
=N _b –	–	1.3 ^e		–	<i>f</i>
		1.0 ^b			
1'	–	141.97	5.8	–	147.59
2'	7.51	115.83	2.4	7.64	115.61
3'	7.51	130.02		7.38	126.21
4'	7.27	125.59		–	143.25

^a In hexadeuteriodimethyl sulfoxide; ^b δ(¹⁵N), measured at natural abundance of the ¹⁵N isotope after addition of 15 mg of Cr(acac)₃; ^c assignment may be reverse; ^d ²J(¹⁵N_b, ¹H) = 2.3 Hz, ³J(¹⁵N_a, ¹H) = 4.6 Hz; ^e δ(¹⁵N), ¹⁵N-labelled compound; ^f not measured.

and C(2')H of the phenyl group. This result is consistent with the literature¹¹ where *N*-methylaniline was identified after reductive splitting of compound **7a**.

Another independent way to determine the geometric arrangement of substituents at the N=C double bond consists in the use of the stereospecific behaviour of the coupling constants ${}^2J({}^{15}\text{N}, {}^{13}\text{C})$. The values are known to be markedly higher for the *cis* orienta-

TABLE II
 ${}^1\text{H}$, ${}^{13}\text{C}$, and ${}^{15}\text{N}$ NMR characteristics^a of compounds **6a** and **6b** (the values for the minority isomer are given in parentheses)

H/C/N	6a^b			6b^c	
	$\delta({}^1\text{H})$	$\delta({}^{13}\text{C})$	${}^nJ({}^{15}\text{N}_b, {}^{13}\text{C})$	$\delta({}^1\text{H})$	$\delta({}^{13}\text{C})$
1	–	–268.2 ^d	–	–	<i>h</i>
2	–	166.19 (162.71)	8.2 (4.4)	–	169.48 (166.33)
3	–	47.91 (46.56)	(1.8)	–	48.87 (47.61)
3a	–	139.74		–	140.25 (138.38)
4	7.27	121.79		7.34	123.08
5	7.03	121.54		7.11	122.12
6	7.25	127.59		7.32	128.01 (128.27)
7	6.82	107.26 (107.62)		6.95 (7.01)	108.37 (108.77)
7a	–	144.11 (145.33)		–	143.63 (144.83)
8	3.31 (3.93)	29.46 (34.22)	(3.5)	3.42 (3.98)	30.04 (34.77)
9	1.76 (1.46)	28.94 (28.29)		1.77 (1.51)	28.93 (27.76)
10	7.33 ^e (7.26)	121.41	1.8	7.53 (7.41)	123.08
–N _a H–	–13.1	48.2 ^{f,g} (49.8) ^{f,g}		–	<i>h</i>
		49.4 ^d			
=N _b –	–	99.4 ^{e,g} (98.7) ^{e,g}		–	<i>h</i>
		99.5 ^d			
1'	–	153.85 (153.85)	5.1	–	158.39 (158.39)
2'	7.67 (7.70)	121.19	4.1	7.71 (7.65)	121.14 (121.25)
3'	7.41 (7.45)	128.79		8.27 (8.27)	124.88
4'	7.28	127.16		–	145.43

^a In deuteriochloroform; ^b majority to minority isomer ratio 7 : 1; ^c majority to minority isomer ratio 10 : 1; ^d $\delta({}^{15}\text{N})$, measured at natural abundance of the ${}^{15}\text{N}$ isotope after addition of 15 mg of Cr(acac)₃; ^e ${}^2J({}^{15}\text{N}_b, {}^1\text{H}) = 1.8$ Hz; ^f $\delta({}^{15}\text{N})$, ${}^{15}\text{N}$ -labelled compound; ^g ${}^1J({}^{15}\text{N}, {}^{15}\text{N}) = 14.1$ Hz; ^h not measured.

tion of the lone pair at the nitrogen and the corresponding carbon^{13,14}, as follows from Fig. 1 in which data published for model compounds are used.

Thus, the coupling constants for the planar arrangement of the substituents differ considerably and are relatively little affected by the nature of the substituents. In azo or

TABLE III
¹H, ¹³C, and ¹⁵N NMR characteristics^a of compounds **6a** (the values for the minority isomer are given in parentheses)

H/C/N	6a		
	$\delta(^1\text{H})$	$\delta(^{13}\text{C})$	$^nJ(^{15}\text{N}_b, ^{13}\text{C})$
2	–	166.07 (162.69)	8.3 (4.2)
3	–	47.62 (46.42)	(1.4)
3a	–	139.36	
4	7.39	121.86	
5	7.05	121.61	
6	7.31	127.93	
7	7.09	108.31	
7a	–	144.12 (145.15)	
8	3.39 (3.92)	29.65 (34.23)	(3.4)
9	7.42 ^c	121.23 (121.11)	1.5 (4.2)
10	1.74 (1.46)	28.92 (28.07)	
–N _a H–	–14.32	52.5 ^{d,e} (55.8) ^{d,e}	
=N _b –	–	100.3 ^{d,e} (101.1) ^{d,e}	
1'	–	153.87	5.3
2'	7.64 (7.62)	120.79	4.2
3'	7.47	129.16	
4'	7.28	127.11	

^a In hexadeuteriodimethyl sulfoxide; ^b majority to minority isomer ratio 11 : 1; ^c $^2J(^{15}\text{N}_b, ^1\text{H}) = 1.8$ Hz; ^d $\delta(^{15}\text{N})$, ¹⁵N-labelled compound; ^e $^1J(^{15}\text{N}, ^{15}\bullet\text{N}) = 14.1$ Hz.

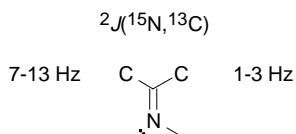


FIG. 1
Structure of model compounds with values of coupling constant published

hydrazo compounds which, according to the X-ray data, exist as virtually planar molecules, the range of the coupling constants for carbons in the *trans* position with respect to the electron pair can be specified even narrower, to less than 1.5 Hz (ref.¹⁸). The coupling constants ${}^2J(^{15}\text{N}, ^{13}\text{C})$ observed for compounds **5a** and **7a** and for the majority component in substance **6a** lie within the expected range (8.2–11.9 Hz) and thus present an independent proof of the existence of the *E*-isomers.

For the minority component of substance **6a**, the situation is more complex. As mentioned above, the NOESY results are not very convincing. The minority component

TABLE IV
 ${}^1\text{H}$, ${}^{13}\text{C}$, and ${}^{15}\text{N}$ NMR characteristics^a of compounds **7a** and **7b**

H/C/N	7a			7b	
	$\delta(^1\text{H})$	$\delta(^{13}\text{C})$	${}^nJ(^{15}\text{N}_b, ^{13}\text{C})$	$\delta(^1\text{H})$	$\delta(^{13}\text{C})$
1	–	–202.3 ^b		–	^e
2	–	177.63	11.9	–	178.09
3	–	51.57		–	52.02
3a	–	142.17		–	142.71
4	7.85	122.81		7.91	122.79
5	7.64 ^c	128.79 ^c		7.66	128.92
6	7.59 ^c	128.17 ^c		7.69	128.92
7	7.88	114.06		7.95	114.69
7a	–	142.17		–	141.99
8	3.94	34.06		3.89	34.54
9	1.79	26.15		1.83	25.77
10	7.96	120.37	5.5	8.15	123.43
–N _a CH ₃	4.16	37.61		4.24	36.57
		–199.7 ^d			^e
		–199.8 ^b			
=N _b –	–	2.6 ^d		–	^e
		2.6 ^b			
1'	–	145.68	6.9	–	149.99
2'	7.72	118.49	2.3	7.91	118.27
3'	7.61	129.73		8.44	125.32
4'	7.27	126.41		–	143.96

^a In hexadeuteriodimethyl sulfoxide; ^b $\delta(^{15}\text{N})$, measured at natural ${}^{15}\text{N}$ abundance after addition of 15 mg of Cr(acac); ^c assignment may be reverse; ^d $\delta(^{15}\text{N})$, ${}^{15}\text{N}$ -labelled compound, ${}^1J(^{15}\text{N}_a, ^{15}\text{N}_b) = 11.4$ Hz; ^e not measured.

fraction makes roughly 10% with respect to the majority component, and so it is rather difficult to observe reliably the NOESY signals. Nevertheless, a hint of existence of the corresponding off-diagonal signals due to steric interaction of the $\text{NCH}_3/\text{C}(10)\text{H}$ groups in the minority component was also apparent. Such signals, however, should not exist in the expected *Z*-isomer. The corresponding ${}^2J(^{15}\text{N}_b, {}^{13}\text{C}(2))$ coupling constant is 4.2–4.4 Hz (Tables II and III); hence, it lies beyond the expected range for the planar arrangement of molecules of substances **6**. If the weighted average method is used, the value of the coupling constant ${}^2J(^{15}\text{N}, {}^{13}\text{C})$ would correspond to the arrangement where the planes of the five-membered ring with respect to the plane determined by the $\text{C}(10)\text{H}$ group and the azo bond are roughly perpendicular. A similar behaviour has been observed for the coupling constants ${}^2J(^{15}\text{N}, {}^{13}\text{C})$ of substituted azobenzenes¹⁸. The arrangement of the substituents would make it possible for the methyl groups to get to vicinity of the $\text{C}(10)\text{H}$ proton, and this fact can account for the occurrence of weak signals in the NOESY spectrum. This explanation is feasible owing to the fact that in such conjugated systems the bond order need not be an integer and the bond can be delocalized. The signals of the methyl groups in the minority component are broadened ($w_{1/2} = 7\text{--}10$ Hz) in ${}^1\text{H}$ NMR, indicating a relatively slowly (on the NMR scale) establishing equilibrium. The effects of solvent (CDCl_3 or $(\text{CD}_3)_2\text{SO}$) and heating by 30°C on the appearance of the ${}^1\text{H}$ NMR spectra are rather small. The behaviour of substances **6** is not exceptional because the presence of two components in comparable proportions having very similar coupling constants have been observed for products of condensation of the Fischer base with nitroso compounds¹⁹.

Combination of NOESY spectral measurement and determination of the ${}^2J(^{15}\text{N}, {}^{13}\text{C})$ coupling constant values provides more detailed information regarding the geometric arrangement of molecules in solutions. The ${}^{15}\text{N}$ chemical shifts give evidence that compounds **5** and **7** exist nearly completely in the hydrazo forms, whereas the two components of substances **6** are azo compounds^{15,16}. In addition to the ${}^2J(^{15}\text{N}, {}^{13}\text{C})$ coupling constant measurement, the selective ${}^{15}\text{N}$ labelling allowed the chemical shifts to be rapidly assigned quite unambiguously. This was necessary particularly for compound **7a** where the difference between the ${}^{15}\text{N}$ chemical shifts of the N-CH_3 and $\text{N}_a\text{-CH}_3$ groups is only 2.5 ppm.

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