HETEROCYCLES, Vol. 23, No. 10, 1985

N,*N'*-LINKED BIAZOLES. PART 6. ON THE STRUCTURE OF COMPOUNDS DERIVED FROM THE OXIDATION OF 7-METHYL-4,5,6,7-TETRAHYDROINDAZOLE

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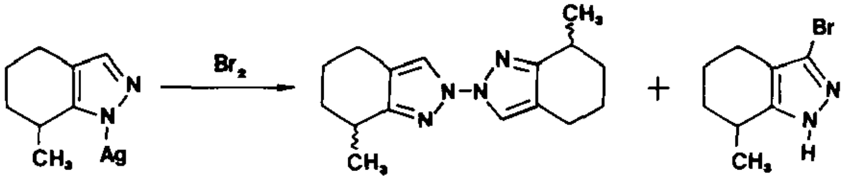
Abstract- The structure of 7,7'-dimethyl-2,2'-bi-4,5,6,7-tetrahydroindazole, the main product from the bromine oxidation of the silver salt of 7-methyl-4,5,6,7-tetrahydroindazole, is corrected in favor of a *C*,*N'*-linked cyclic trimer (mixture of diastereoisomers). Although a *C*,*N'*-linked dimer was also isolated, *N*,*N'*-linked dimers were not found.

The oxidation of the silver salt of 7-methyl-4,5,6,7-tetrahydroindazole (**1**) with bromine (ethyl ether, 0°C) has been reported in 1925 by von Auwers *et al.*[1] to yield mainly the dimer **2**, mp 272-273°C, and minor amounts of 3-bromo-7-methyl-4,5,6,7-tetrahydroindazole (**3**). The N-N bonded structure **2** was supported by elemental analysis, a cryoscopic molecular weight determination, and by its failure to react with acetic anhydride, as a proof for the absence of N-H bonds.



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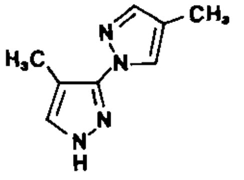
However, other literature results concerning the reaction of bromine with 4-methylpyrazole (free base[2] or silver salt[3]) deal with the formation of C-N bonded compounds, like the dimer **4**,[3] or the linear trimer **5**.[2] Similarly, the bromination of 3(5),4-dimethylpyrazole has been shown by Hüttel *et al.* to produce the cyclic trimer **6**($R=CH_3$).[4] An analogous structure **6**(R=H) has been reported from the condensation of 3-methyl-2-pyrazolin-5-one with phosphorus oxychloride.[5] In none of these structures were N-N bonds present.



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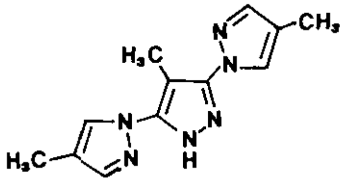

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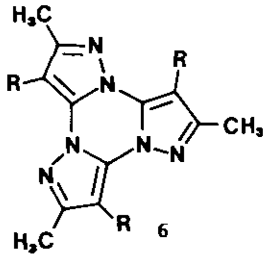

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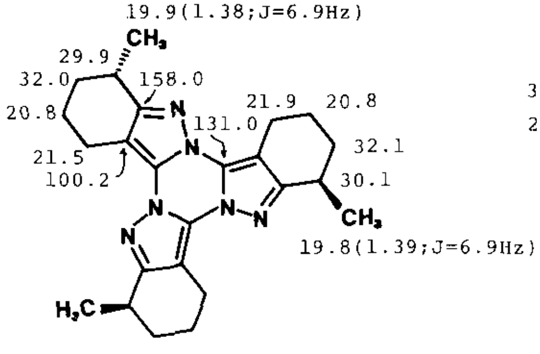
Owing to our interest in 1,1'-bipyrazole and related systems,[6] we repeated the reaction of **1** with bromine, submitting the resulting reaction mixture to flash chromatography. Elution with dichloromethane afforded a solid with identical m.p. to von Auwers' "dimer" **2**. The substance showed no N-H absorption in its ir spectrum (KBr disk). However, microanalytical data and mass spectrometry (molecular peak at m/z 402) suggested that we were dealing with a cyclic trimer instead of a dimer (a linear trimer would require a mass weight of 404). Moreover, tlc analysis showed that the substance was actually a mixture of two components. Careful column chromatography allowed us to isolate a pure compound **7**, mp 290-291°C, and an isomer **8**, mixed with minor amounts of **7**. We were unable to further purify compound **8**. Both isomers showed identical mass spectra, and their ratio was calculated (from ^{1}H nmr) to be 75:25, respectively. On the basis of their nmr spactra, the following structures were assigned (^{13}C and ^{1}H nmr values, in $CDCl_3$, are indicated on the figures, those in parenthesis corresponding to ^{1}H resonances).



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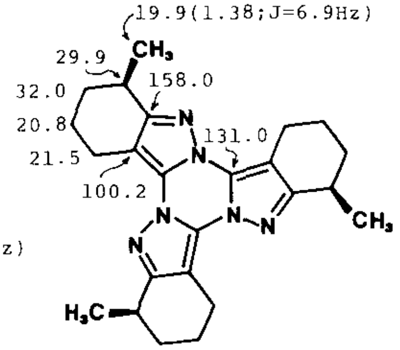

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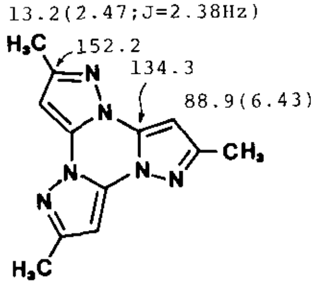
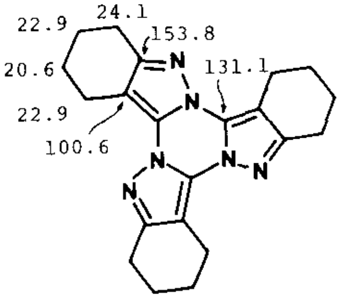
Trimers **6**(R=H)[5] and **9** (prepared by the reaction of 4,5,6,7-tetrahydroindazole with bromine) were used as model compounds for the nmr study. The simple tetrahydroindazoles **10-14** were also prepared and their spectra registered for comparison (Table I).



6(R=H)



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The carbocyclic counterparts of the ^{13}C spectra were assigned by comparison with cyclohexene derivatives.[7] DEPT experiments were carried out to distinguish between all CH, CH_2, and CH_3 signals. The spectra of isomers **7** and **8**, as well as those of their cyclic models **6** and **9** are fully consistent with the structures proposed. In

10a R = H ; R' = H **10b**
11a R = H ; R' = CH_3 **11b**
12a R = CH_3 ; R' = H **12b**
13a R = CH_3 ; R' = CH_3 **13b**
14a R = C_6H_5 ; R' = H **14b**

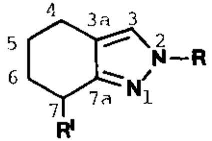


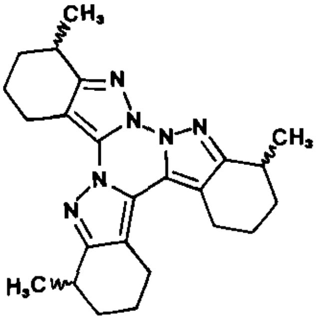
Table I. ^1H and ^{13}C nmr chemical shifts of 4,5,6,7-tetrahydroindazoles (**10-14**).

Compound	^1H Nmr chemical shifts[a]						^{13}C Nmr chemical shifts							
	$CDCl_3$		$(CD_3)_2SO$		C_6D_6		$CDCl_3$							
	Me_7	H_3	Me_7	H_3	Me_7	H_3	C_3	C_{3a}	C_4	C_5	C_6	C_7	C_{7a}	Other signals
10a/10b	-	7.31	-	7.25	-	7.17	131.7	114.8	23.6	20.5	22.1	23.2	143.2	
11a/11b	1.31	7.30	1.19	7.21	1.28	7.22	132.3	114.5	22.3	20.7	32.4	28.2	147.5	Me_7, 20.2
12a	-	7.22	-	7.10	-	7.41	136.2	115.8	23.0	20.6	21.2	22.7	138.1	N-Me, 35.3
13a	1.22	7.22	1.16	7.09	0.86	7.35	135.7	114.8	20.5	18.7	30.8	25.5	141.8	Me_7, 20.0; N-Me, 35.5
14a	-	7.46	-	7.52	-	7.48	138.7	117.7	23.6	20.7	22.8	23.2	138.0	C_6H_5: C_i, 140.3; C_o, 123.0 C_m, 128.9; C_p, 126.4
12b	-	6.89	-	7.28	-	6.49	127.0	115.8	23.5	20.5	23.2*	23.5*	148.8	N-Me, 38.4
13b	1.30	7.02	1.18	7.26	1.47	6.49	126.4	114.9	21.9	20.4	32.3	28.8	153.1	Me_7, 19.2; N-Me, 38.0
14b	-	7.59	-	8.12	-	7.20	123.6	118.2	23.5	20.7	23.5	23.5	151.3	C_6H_5: C_i, 140.6; C_o, 118.6 C_m, 129.2; C_p, 125.5

[a] Other signals($CDCl_3$): (**10a/10b**) 1.7-1.9m(H_5,H_6), 2.54m(H_4), 2.68m(H_7), 9.4broad(N-H); (**11a/11b**) 1.3-2.1m(H_5,H_6), 2.52m(H_4), 2.87m(H_7), 10.4broad(N-H), J_{H-Me}=7.0Hz; (**12a**) 1.5-1.7m(H_5,H_6), 2.51m(H_4), 2.66m(H_7), 3.81(N-Me); (**13a**) 1.6-1.9m(H_5,H_6), 2.49m(H_4), 2.89m(H_7), 3.77(N-Me), J_{H-Me}=6.9Hz; (**14a**) 1.7-1.8m(H_5,H_6), 2.49m(H_4), 2.89m(H_7), 7.2-7.5m(C_6H_5); (**12b**) 1.7-1.8m(H_5,H_6), 2.39m(H_4), 2.53m(H_7), 3.71(N-Me); (**13b**) 1.6-1.9m(H_5,H_6), 2.49m(H_4), 2.89m(H_7), 3.83(N-Me), J_{H-Me}=6.9Hz; (**14b**) 1.7-1.9m(H_5,H_6), 2.60m(H_4), 2.77m(H_7), 7.61m(H_o), 7.38m(H_m), 7.20m(H_p).

* These assignments can be reversed.

particular, their relative simplicity (only three quaternary carbon atoms, and one signal for the 's-triazine' framework) ruled out the alternative mode of cyclization to an unsymmetrical triazine central ring (*i.e.*, structure **15**, with one *N,N'*-, one *C,C'*-, and one *C,N'*-bond).



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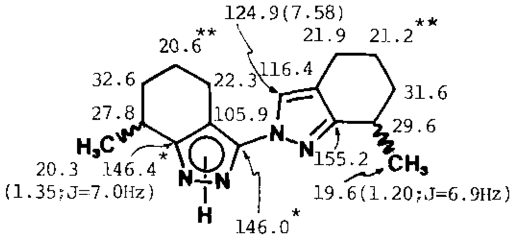

(*,** These assignments can be reversed)

16

Further elution of the column containing the crude reaction mixture with CH_2Cl_2/ ethyl acetate (80:20) afforded a second solid substance, mp 153-154°C, for which we propose the structure **16** on the basis of the following considerations:

i) The compound shows molecular formula $C_{16}H_{22}N_4$ (microanalysis, mass spectrum: m/z 270), *one* aromatic pyrazolic C-H resonance (7.59 ppm in $CDCl_3$), and a broad N-H resonance at *ca*. 8.5 ppm, as expected for a *C,N'*-linked dimer of 7-methyl-4,5,6,7-tetrahydroindazole.

ii) The chemical shift of the $C_{3'}$ resonance (124.9 ppm in $CDCl_3$) clearly demonstrates the nature of the *C,N'* linkage (*i.e.*, C_3 to $N_{2'}$). As shown in Table I, values for C_3 in tetrahydroindazoles are comprised between 123 and 126 ppm in N_2-substituted models, whereas values for N_1-substituted tetrahydroindazoles are always above 130 ppm.

Another way to deduce the position of the *C,N'*-bond could be the study of the solvent effects on the proton nmr spectra of **16**. It is well known[8] that the H_5 proton resonance of 1-substituted pyrazoles is distinguished from the H_3 signal by the higher field shift that it suffers when changing solvent from $CDCl_3$ to C_6D_6. In addition, the shift is to lower field in going to more polar solvents as $(CD_3)_2SO$. Values for models of Table I are in full agreement with this prediction. However, this solvent effect does not apply to **16**. The following chemical shifts for $H_{3'}$ were found: 7.58 ($CDCl_3$), 7.72 [$(CD_3)_2SO$], and 7.95 (C_6D_6). A comparison with 1,5'-bipyrazoles **17** and **18** (Table II) reveals that the solvent effect is present in the *N*-substituted compound, but *not* in the N-H model. The lack of solvent effect in the unsubstituted series has been attributed by Habraken *et al.*[9] to intramolecular hydrogen bonding.

iii) Only one compound was found either in $CDCl_3$ (^1H and ^{13}C nmr) or $(CD_3)_2SO$ (^1H nmr). In C_6D_6, however, one of the methyl proton signals splitted into two well resolved doublets of almost equal intensities. This may be attributed to the presence of both posible diastereoisomers of **16**.

Although the origin of trimers **7** and **8** was not carefully investigated, it seems likely that they are generated from **16**. Considering that asymmetric induction is not present, and that the salt **1** is a racemic, statistical distribution explains why **16** is a 50:50 mixture of *RR*(*SS*) and *RS*(*SR*) diastereoisomers, whereas trimers **7** (*RRS* and *SSR*) and **8** (*RRR* and *SSS*) are in a 75:25 ratio.

Finally, other dimers were not found in the remaining mixture of reaction compounds, since no molecular peaks at m/z 270 appeared in the mass spectra of aliquots taken at regular intervals from the chromatographic column. Only some peaks corresponding to bromine-containing compounds were detected, although we were unable to isolate 3-bromo-7-methyl-4,5,6,7-tetrahydroindazole (**3**), also reported by von Auwers.[1]

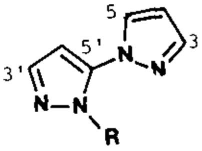

Table II. ^{1}H nmr chemical shifts for H_5 in some 1,5'-bipyrazoles.

Compound	R	$CDCl_3$	$(CD_3)_2SO$	C_6D_6
17	H	8.07[a]	8.22[a]	8.07[b]
18	CH_3	7.58[b]	8.16[b]	6.93[b]

[a]From ref. 9; [b]From ref. 10.

EXPERIMENTAL

Melting points are not corrected. Nmr spectra were registered on a Bruker WP 200 SY instrument. For the recording of ir and mass spectra, Unicam SP 1100 and Hewlett-Packard 5985 instruments were used, respectively. The following compounds were prepared according to known procedures: 2,6,10-trimethyl-tripyrazolo[1,5-*a*:1',5'-*c*:1",5"-*e*]-s-triazine (**6**),[5] 4,5,6,7-tetrahydroindazole (**10**),[11] 7-methyl-4,5,6,7-tetrahydroindazole (**11**),[11] 1-methyl-4,5,6,7-tetrahydroindazole (**12a**),[12] 2-methyl-4,5,6,7-tetrahydroindazole (**12b**),[12] 1,7-dimethyl-4,5,6,7-tetrahydroindazole (**13a**),[13] 2,7-dimethyl-4,5,6,7-tetrahydroindazole (**13b**),[13] 1-phenyl-4,5,6,7-tetrahydroindazole (**14a**),[11] 2-phenyl-4,5,6,7-tetrahydroindazole (**14b**),[11] 1,5'-bipyrazole (**17**),[9,10] and 1-methyl-5-(1-pyrazolyl)pyrazole (**18**).[10] The new compounds **7**, **9**, and **16**, gave elemental analyses corresponding to their molecular formulae for C, H, and N, within a ±0.3% error.

Tri-4,5,6,7-tetrahydroindazolo[2,3-a:2',3'-c:2",3"-e]-s-triazine (**9**). To a solution of 4,5,6,7-tetrahydroindazole (**10**)(0.390 g, 3.10 mmol) in dry chloroform (4 cm^3), a solution of bromine (0.11 ml , 3.10 mmol) in chloroform (3 ml) was slowly added, under stirring. The reaction mixture was refluxed for 1 h and then kept overnight at room temperature. Water (20 ml) and solid $NaHCO_3$ were added, and the organic layer was separated, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was purified by column chromatography (acidic silica gel[14]). Minor impurities were first eluted with toluene, and further elution with toluene/ethyl acetate (80:20) afforded 0.097 g (8.4%) of **9**, mp 274-275°C(dec.), ir(nujol): 1650, 1540, and 1500 cm^{-1}. Mass spectrum: m/z 360(M$^+$, 48.8), 332(36.2), and 41(100).

Reaction of 7-methyl-4,5,6,7-tetrahydroindazole, silver salt (**1**) *with bromine*. To a stirred and cooled (0°C) solution of **1** (2.68 g, 11.0 mmol) in dry ethyl ether (150 ml) was added bromine (0.53 ml , 15.0 mmol). The mixture was stirred for 2.5 h at 0°C, and silver bromide filtered and washed with ether. The combined ethereal solutions were washed sequentially with aqueous sodium bisulfite, water, and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash

chromatography.[15] Elution with dichloromethane afforded 0.411 g (9.3%) of a solid of mp 272-273°C (mixture of diastereoisomers **7** and **8**). Further elution with dichloromethane/ethyl acetate (80:20) gave *2,3'-bi-7-methyl-4,5,6,7-tetrahydroindazole* (**16**), mp 153-154°C (0.670 g, 22.5%), ir(nujol): 3240, 1620, and 1555 cm^{-1}. Mass spectrum: m/z 270(M^+, 100), 255(45.2), and 135(65.3).
The mixture of trimers **7** and **8** was again submitted to flash chromatography (dichloromethane), yielding 0.080 g of pure *(2R*,8R*,14S*)-2,8,14-trimethyl-tri-4,5,6,7-tetrahydroindazolo[2,3-a:2',3'-c:2",3"-e]-s-triazine* (**7**), mp 290-291°C, Ir(nujol): 1650 and 1500 cm^{-1}. Mass spectrum: m/z 402(M^+, 100), 387(4.4), and 360 (36.5). A mixture (0.320 g) of compounds **7** and **8** was also recovered.

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Received, 10th June, 1985