Synthesis and ^{13}C NMR Study of Some *N*-Substituted 4-Iodo- and 3,4-Diiodopyrazoles

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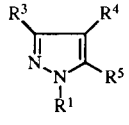
Received July 22, 1994

The synthesis of some novel N-1 substituted 4-iodo- and 3,4-diiodopyrazoles starting from the corresponding NH-pyrazoles is described. On basis of their ^{13}C nmr data and those of already known related congeners the influence of iodo- as well as N-1 substituents on pyrazole ^{13}C chemical shifts and $^{13}C,^{1}H$ spin coupling constants is investigated.

J. Heterocyclic Chem., **32**, 189 (1995).

N-Substituted iodopyrazoles are valuable starting products in the synthesis of biologically active pyrazole derivatives [2], particularly their suitability to serve as educts in cross-coupling reactions with terminal acetylenes should be emphasized [3,4]. In extension of our studies in the field of pyrazole chemistry, we here report on the synthesis and mainly on ^{13}C nmr investigations with 4-iodo (series **b**) and 3,4-diiodopyrazoles (series **c**) carrying different substituents (of alkyl, acyl and sulfonyl type) at the pyrazole N-1 (Scheme 1). Comparison with their des-iodo congeners (series **a**) and two 4,5-diiodo analogues (series **d**) allowed some insight how the iodo substituent(s) (as the well as different N1-substituents) affect ^{13}C chemical shifts and $^{13}C,^{1}H$ spin coupling constants on the pyrazole system.

Scheme 1



No.	R^1		R^3	R^4	R^5
1	H	**a**	H	H	H
2	Me	**b**	H	I	H
3	CH_2Ph	**c**	I	I	H
4	COMe	**d**	H	I	I
5	$COCH_2CH_2Ph$				
6	COPh				
7	COCH=CHPh (E)				
8	SO_2Ph				
9	Tosyl				

Synthesis.

The synthesis of the required novel *N*-substituted iodopyrazoles was achieved by reaction of the appropriate NH-pyrazoles **1b** and **1c** with suitable electrophiles (alkyl, acyl or sulfonyl halogenides) referring to procedures used for the preparation of related compounds. Reaction of 3,4-diiodopyrazole (**1c**) with benzyl chloride afforded a mixture of two regioisomers, namely the 1-benzyl-3,4-diiodo **3c** and the 1-benzyl-4,5-diiodo product **3d**; employing acyl or sulfonyl chlorides as reagents led to the formation of the sterically favored 1,3,4-isomer as the sole product (thermodynamic reaction control), what is in agreement with reports in the literature [5,6].

NMR Spectroscopy.

Recently, an extensive review (containing ~ 1100 compounds) dealing with ^{13}C nmr spectroscopy of pyrazoles has been published by Begtrup, Elguero and co-workers [7]. However, the fact that among the large amount of data presented comparable little information is available on iodopyrazoles and especially on 3,4-diiodo and 4,5-diiodopyrazoles encouraged us for the present study. It should be mentioned that all data given in the following (Tables 1 and 2) result from our own recordings just in order to ensure comparable conditions regarding solvent, temperature, concentration, calibration and digital resolution. In cases when ^{13}C nmr data of (known) compounds included into this investigation have been already published (not necessarily originating from recordings under comparable conditions) this is indicated by an entry in column "Compare Ref" in Table 1 or 2. The ^{1}H nmr data are given in the experimental. The discrimination between pyrazole H-3 and pyrazole H-5 resonances in compounds **2** and **3** rests on NOE-difference experiments irradiating the NCH_3- or NCH_2-resonance (NOE on pyrazole H-5) [8]. This method also enabled us to determine the accurate position of the pyrazole H-5 resonance in case of overlap with signals of phenyl protons (for instance with compound **3c**) as well as to discriminate regioisomers **2c** *versus* **2d** and **3c** *versus* **3d**.

^{13}C Chemical Shifts.

The chemical shift data of the investigated pyrazole derivatives **1-10** are summarized in Table 1. Complete assignments could be achieved on basis of coupling information (from the gated decoupling spectra), considering C-H connectivities (HMQC, long-range INEPT spectra with selective excitation [9]), and by comparison with literature data [7] of closely related species.

It is well known that an iodine atom attached to an aromatic system generates a marked shielding effect for the *ipso* carbon atom, comparing benzene and iodobenzene this "heavy-atom effect" causes a substituent chemical shift

Table 1

^{13}C NMR Chemical Shifts (δ, ppm) of Compounds **1-9** (in deuteriochloroform)

No.	Pyrazole-C C-3	C-4	C-5	Other Carbon Atoms	Compare Ref
1a	133.5	104.6	133.5	-	[7]
1b	138.8	56.4	138.8	-	[7]
1c	[a]	71.4	[a]	-	-
2a	138.5	104.9	129.2	38.0 (Me)	[7]
2b	144.3	55.7	134.2	39.0 (Me)	[7]
2c	105.8	70.3	136.1	41.6 (Me)	-
2d	145.3	71.6	93.6	39.7 (Me)	-
3a	139.0	105.5	128.8	Ph-C: 136.4 (1), 127.2 (2,6), 128.3 (3,5), 127.5 (4); 55.4 (CH_2)	[7]
3b	144.5	56.3	133.5	Ph-C: 135.8 (1), 127.8 (2,6), 128.8 (3,5), 128.2 (4); 56.4 (CH_2)	-
3c	106.3	71.0	135.2	Ph-C: 135.1 (1), 128.1 (2,6), 129.0 (3,5), 128.6 (4); 57.1 (CH_2)	-
3d	146.0	72.5	93.4	Ph-C: 135.8 (1), 127.5 (2,6), 128.7 (3,5), 128.1 (4); 57.7 (CH_2)	-
4a	143.6	109.3	127.7	169.1 (CO), 21.3 (Me)	[7]
4b	148.4	63.3	132.7	168.0 (CO), 21.0 (Me)	-
4c	113.9	78.1	133.8	167.0 (CO), 20.9 (Me)	-
5a	143.8	109.4	128.1	171.3 (CO), Ph-C: 140.3 (1), 128.3 (2,6), 128.4 (3,5), 126.2 (4); 35.5 ($COCH_2$), 30.3 ($PhCH_2$)	-
5b	148.3	63.2	132.8	170.0 (CO), Ph-C: 140.0 (1), 128.3 (2,6), 128.5 (3,5), 126.3 (4); 34.9 ($COCH_2$), 30.2 ($PhCH_2$)	-
5c	113.9	78.0	133.9	169.0 (CO), Ph-C: 139.8 (1), 128.4 (2,6), 128.5 (3,5), 126.4 (4); 34.9 ($COCH_2$), 30.1 ($PhCH_2$)	-
6a	144.0	109.0	130.0	165.8 (CO), Ph-C: 130.0 (1), 131.2 (2,6), 127.7 (3,5), 132.6 (4)	[13]
6b	148.7	63.3	134.9	164.8 (CO), Ph-C: 130.4 (1), 131.4 (2,6), 128.0 (3,5), 133.2 (4)	[4]
6c	114.4	78.0	136.1	163.7 (CO), Ph-C: 130.0 (1), 131.8 (2,6), 128.3 (3,5), 133.6 (4)	-
7a	143.6	109.6	128.6	163.5 (CO), 147.6 (Ph-*C*H=), 115.9 (CO*C*H=), Ph-C: 134.5 (1), 128.7 (2,6), 128.9 (3,5), 130.8 (4)	-
7b	148.1	63.6	133.2	162.1 (CO), 148.6 (Ph-*C*H=), 114.4 (CO*C*H=), Ph-C: 134.1 (1), 128.8 (2,6), 128.9 (3,5), 131.1 (4)	-
7c	113.7	78.1	134.4	161.3 (CO), 149.4 (Ph-*C*H=), 114.3 (CO*C*H=), Ph-C: 134.2 (1), 129.0 (2,6), 129.0 (3,5), 131.4 (4)	-
8a	145.1	108.7	131.0	Ph-C: 136.7 (1), 127.6 (2,6), 129.1 (3,5), 134.3 (4)	[13]
8b	149.7	61.3	134.8	Ph-C: 136.4 (1), 128.2 (2,6), 129.4 (3,5), 134.8 (4)	[13]
8c	115.0	76.4	135.8	Ph-C: 136.0 (1), 128.4 (2,6), 129.6 (3,5), 135.1 (4)	-
9a	145.0	108.6	131.0	Ph-C: 133.9 (1), 127.9 (2,6), 129.9 (3,5), 145.8 (4); 21.5 (Me)	[7]
9b	149.5	60.9	134.7	Ph-C: 133.6 (1), 128.3 (2,6), 130.1 (3,5), 146.3 (4); 21.6 (Me)	[4]
9c	114.7	76.1	135.8	Ph-C: 132.9 (1), 128.4 (2,6), 130.2 (3,5), 146.7 (4); 21.8 (Me)	-

[a] Not unequivocally determined due to low solubility and dynamic behavior.

(SCS) of -34.1 ppm [10]. From the data in Table 1 it can be derived that replacement of hydrogen by iodine in position 4 of the pyrazole system (compounds **a** → compounds **b**) leads to a 46.0-49.2 ppm upfield shift for pyrazole C-4, whereas the signals of pyrazole C-3 as well as those of pyrazole C-5 suffer a downfield shift of ~ 4-6 ppm. Upon switching to series **c** (*i.e.* introduction of a further iodine atom in 3-position of the pyrazole ring) a remarkable deshielding can be observed for pyrazole C-4 (compared to the corresponding resonances in series **b**), for the pyrazole C-3 resonance expectedly a large upfield shift is detected. Similar effects can be observed for the transformation **b** → **d** (marked upfield shift for pyrazole C-5, downfield shift with SCSs of ~ 16 ppm for pyrazole C-4 after introduction of a second iodine atom into position 5).

From the data in Table 1 also the influence of the N-1 substituent on ^{13}C chemical shifts of the pyrazole nucleus can be extracted. In accordance with well known trends [5,7,11], electron-withdrawing N-1 substituents cause a downfield shift for pyrazole carbon atoms C-3 and C-4. For δ (C-5) the effect is comparably small in series **a**, with compounds **b** and **c** such a correlation cannot be postulated.

Iodine substituents on the pyrazole system also affect ^{13}C chemical shifts of carbons belonging to the N-1 substituent (especially those of carbons directly attached to the pyrazole N-1). Increasing iodo substitution leads to a downfield shift for the methyl-C or methylene-C resonance in 1-methyl (**2**) and 1-benzylpyrazoles (**3**) (*e.g.* **3a** 55.4 ppm → **3b** 56.4 ppm → **3c** 57.1 ppm, **3d** 57.7 ppm) and, reversely, to an upfield shift for the CO-signals of acylpyrazoles (**4-7**) (*e.g.* **6a** 165.8 ppm → **6b** 164.8 ppm → **6c** 163.7 ppm).

$^{13}C,^{1}H$ Spin Coupling Constants.

The coupling constants determined for compounds **2-9** are given in Table 2 (absolute values, signs not determined) and mainly origin from a first-order analysis of the gated decoupled ^{13}C nmr spectra (digital resolution 0.2-0.5 Hz/data point). In some cases coupling constants were unambiguously assigned on basis of 2D (δ,J) long-range INEPT experiments with selective DANTE excitation [12] (0.78 Hz digital resolution in f1; for instance discrimination of ^{2}J(C-4,H-3) and ^{2}J(C-4,H-5) as well as determination of ^{3}J(C5,H3) and ^{3}J(C5,CH_X) (Figure 1) - what can be difficult to achieve from the gated decou-

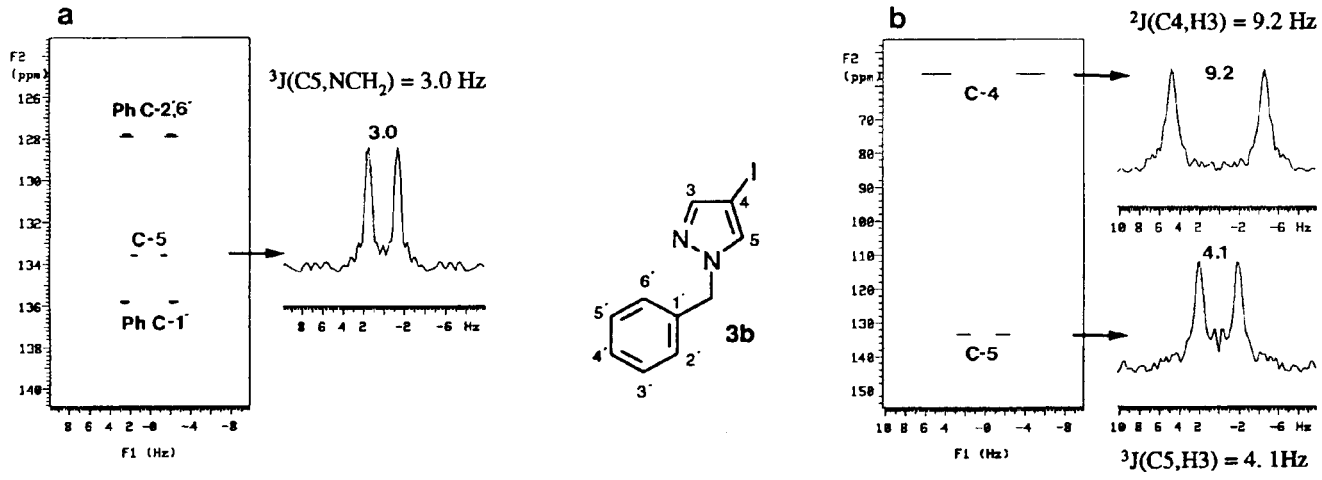


Figure 1. 2D (δ,J) Long-range INEPT spectrum of compound **3b** resulting from selective excitation of NCH_2 (**a**) and pyrazole H-3 (**b**).

Table 2

$^{13}C,^1H$-Spin Coupling Constants (Hz) of Compounds **2-9** (in deuteriochloroform)

	Pyrazole System										Compare
No.	C3,H3	C3,H4	C3,H5	C4,H3	C4,H4	C4,H5	C5,H3	C5,H4	C5,H5	Other Couplings	Ref
2a	184.7	5.7	8.3	10.5	176.5	8.7	4.7	8.7	185.7	$^1J(CH_3)$: 139.5, $^3J(C5,CH_3)$: 2.7	[7]
2b	191.7	-	7.4	9.2	-	7.4	3.9	-	191.4	$^1J(CH_3)$: 140.2, $^3J(C5,CH_3)$: 2.8	-
2c	-	-	9.8	-	-	7.2	-	-	192.9	$^1J(CH_3)$: 140.9, $^3J(C5,CH_3)$: 2.8	-
2d	193.3	-	-	9.4	-	-	5.4	-	-	$^1J(CH_3)$: 141.1, $^3J(C5,CH_3)$: 3.3	-
3a	184.8	5.7	8.3	10.4	176.5	8.6	4.7	8.7	185.7	$^1J(CH_2)$: 139.3, $^3J(C5,CH_2)$: 2.7	[13]
3b	191.9	-	7.4	9.2	-	7.2	4.1	-	191.8	$^1J(CH_2)$: 140.1, $^3J(C5,CH_2)$: 3.0	[13]
3c	-	-	9.8	-	-	7.2	-	-	193.4	$^1J(CH_2)$: 141.0, $^3J(C5,CH_2)$: 3.1	-
3d	194.3	-	-	9.4	-	-	5.3	-	-	$^1J(CH_2)$: 140.5, $^3J(C5,CH_2)$: 3.6	-
4a	187.1	6.2	9.2	10.8	178.6	8.7	4.1	8.9	193.3	$^1J(CH_3)$: 130.6	[7]
4b	194.0	-	8.1	10.0	-	6.9	3.5	-	198.9	$^1J(CH_3)$: 131.0, $^2J(CO,CH_3)$: 6.8	-
4c	-	-	10.5	-	-	7.0	-	-	200.2	$^1J(CH_3)$: 131.2, $^2J(CO,CH_3)$: 7.1	-
5a	187.3	6.0	9.1	10.8	178.8	8.6	4.1	9.3	193.4	$^1J(COCH_2)$: 130.3, $^1J(PhCH_2)$: 128.9	-
5b	194.0	-	8.1	9.9	-	7.1	3.4	-	199.1	$^1J(COCH_2)$: 130.7, $^1J(PhCH_2)$: 128.9	-
5c	-	-	10.5	-	-	7.0	-	-	200.2	$^1J(COCH_2)$: 130.5, $^1J(PhCH_2)$: 129.2	-
6a	187.6	6.1	9.1	10.7	179.1	8.7	4.2	9.3	193.8		[7]
6b	194.3	-	8.1	9.9	-	7.0	3.5	-	199.3		[13]
6c	-	-	10.7	-	-	7.1	-	-	200.3		-
7a	187.2	6.1	9.1	10.7	178.7	8.7	4.0	9.1	193.5	COCH=C: ^1J: 167.8, ^2J: 5.3; PhCH=C: ^1J: 158.2	-
7b	193.9	-	8.1	10.0	-	7.1	3.6	-	199.1	COCH=C: ^1J: 168.0, ^2J: 5.1; PhCH=C: ^1J: 158.2	-
7c	-	-	10.5	-	-	7.1	-	-	200.2	COCH=C: ^1J: 168.6, ^2J: 5.0; PhCH=C: ^1J: 158.3	-
8a	188.8	6.1	9.0	10.9	180.1	8.6	4.4	9.7	195.5		[13]
8b	195.2	-	8.0	10.0	-	7.0	3.8	-	200.8		[13]
8c	-	-	10.1	-	-	7.0	-	-	201.8		-
9a	188.6	6.0	9.0	10.9	179.9	8.7	4.5	9.7	195.2	$^1J(CH_3)$: 127.5	[13]
9b	194.9	-	8.0	10.0	-	7.1	3.9	-	200.5	$^1J(CH_3)$: 127.5	[13]
9c	-	-	10.3	-	-	6.9	-	-	201.6	$^1J(CH_3)$: 127.5	-

pling spectra due to complicated splitting patterns of pyrazole C-5).

Direct Coupling Constants.

With derivatives of type **2-9** the following trends regarding $^1J(^{13}C,^1H)$ of the pyrazole C-atoms can be derived from Table 2. Generally, in accordance with the literature [5,7,13], the relationship $^1J(C5,H5) > ^1J(C3,H3) > ^1J(C4,H4)$ is valid within one species; all direct pyrazole C-H coupling constants increase with increasing electron-withdrawing property of the N1-substituent, $^1J(C5,H5)$ being particularly affected. Introduction of an iodo-substituent into position 4 of the pyrazole ring enhances $^1J(C3,H3)$ by 6.3-7.5 Hz and $^1J(C5,H5)$ by 5.3-6.1 Hz. Switching from 4-iodo (compounds **b**) to 3,4-diiodo congeners (series **c**) results in a further 1.0-1.8 Hz enlargement of $^1J(C5,H5)$.

Iodo substitution on the pyrazole system also affects

$^1J(CH_3)$ and $^1J(CH_2)$ in 1-methyl- (**2**) and 1-benzylpyrazoles (**3**) (*e.g.* **2a**: 139.5 Hz, **2b**: 140.2 Hz, **2c**: 140.9 Hz, **2d**: 141.1 Hz).

Geminal Coupling Constants.

The geminal coupling constants $^2J(C3,H4)$, $^2J(C4,H3)$ and $^2J(C5,H4)$ slightly increase with increasing electron attracting property of the N-1 substituent, for $^2J(C4,H5)$ such a tendency cannot be extracted from the data in Table 2. Switching from series **a** to series **b** (attachment of an iodine substituent on the coupled carbon atom) results in a decrease of the absolute values of $^2J(C4,H3)$ and $^2J(C4,H5)$. The latter coupling is practically not affected upon introduction of a second iodine into position 3 (**b** → **c**).

Vicinal Coupling Constants.

Whereas $^3J(C3,H5)$ exhibits a weak dependence from the nature of the N1-subtituent (*e.g.* series **a**: 8.3 Hz for 1-alkyl substituted compounds, ~ 9 Hz for acyl and sulfonyl congeners), for $^3J(C5,H3)$ no general trend can be deduced on basis of the present data. Again, the most remarkable alteration can be detected upon attachment of iodine on the coupled carbon atom, as $^3J(C3,H5)$ increases with 2.1-2.6 Hz when changing from series **b** to series **c**. If the iodo substituent is linked with the carbon atom in the middle of the coupling path (pyrazole C-4), *i.e.* switching from **a** to **b**, leads to a decrease by ~ 1 Hz for $^3J(C3,H5)$ and by 0.4-0.8 Hz for $^3J(C5,H3)$. Compounds **2** and **3** also exhibit a vicinal coupling between pyrazole C-5 and protons of the NCH_2- or NCH_3-group, respectively (2.7-3.6 Hz). On basis of this splitting an unambiguous distinction between pyrazole C-3 and pyrazole C-5 can be achieved, and thus also 1-alkyl-3,4-diiodo isomers can be unequivocally discriminated from their 1-alkyl-4,5-diiodo congeners.

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra were recorded on a Jasco IRA-1 spectrophotometer or on a Perkin-Elmer FTIR 1605 spectrometer. Mass spectra were obtained on a Hewlett-Packard 5890A/5970B-MSD (glc/ms) or on a Varian MAT 311A instrument (both EI, 70 eV). Most nmr spectra were recorded on a Varian UnityPlus 300 instrument (299.95 MHz for ^1H, 75.43 MHz for ^{13}C), some measurements were carried out on a Bruker AC 80 spectrometer (80.13 MHz for ^1H, 20.15 MHz for ^{13}C). All spectra were recorded from deuteriochloroform solutions at 28°; the solvent signal was used as an internal standard which was related to tetramethylsilane with δ 7.26 ppm (^1H) and δ 77.00 ppm (^{13}C). Column chromatographic separations were performed on Merck Kieselgel 60 (70-230 mesh). Light petroleum refers to the fraction of bp 50-70°. The yields given below are not optimized.

The following compounds were prepared according to reported procedures: **1c** [14], **2a** [15], **2b** [16], **2c** [3], **2d** [3], **3a** [17], **4a** [18], **4b** [18], **6a** [19], **6b** [4], **7a** [20], **8a** [21], **9a** [22], **9b** [4]. Compounds **1a** and **1b** are commercially available.

1-Benzyl-4-iodo-1*H*-pyrazole (**3b**).

To a solution of sodium ethoxide prepared from 230 mg (10 mmoles) of sodium and 15 ml of dry ethanol were added 1.940 g (10 mmoles) of 4-iodopyrazole. After 30 minutes of stirring, 1.266 g (10 mmoles) of benzyl chloride were added and the mixture was refluxed for 4 hours. After cooling, the precipitate was filtered off and the filtrate was evaporated *in vacuo*. The oily residue was triturated with diethyl ether and the obtained solid was recrystallized from ethanol-water to afford 1.700 g (60%) of colorless crystals, mp 58-59° (lit [23] mp 58-59°); ^1H nmr (deuteriochloroform, [23]): δ 7.54 (s, 1H, pyrazole H-3), 7.39 (s, 1H, pyrazole H-5), 7.36-7.32 (m, 3H, Ph H-3,4,5), 7.24-7.20 (m, 2H, Ph H-2,6), 5.28 (s, 2H, CH_2); ms: m/z (%) 285 (11), 284 (M^+, 100), 283 (74), 91 (46), 65 (13).

1-Benzyl-3,4-diiodo-1*H*-pyrazole (**3c**) and 1-Benzyl-4,5-diiodo-1*H*-pyrazole (**3d**).

Sodium (23 mg, 1 mmole) in 2 ml of dry ethanol, benzyl chloride (127 mg, 1 mmole) and 3,4-diiodopyrazole (320 mg, 1 mmole) were reacted as described for the preparation of compound **3b**. After workup, 303 mg (74%) of an oily residue was obtained consisting of compounds **3c** and **3d** in an 85:15 ratio (according to ^1H-nmr and glc/ms). Column chromatography (eluent: dichloromethane) afforded 70 mg (17%) of pure **3c** (faster eluted component) and fractions containing **3c** and **3d** (totally 150 mg, 37%).

Compound **3c** was obtained as colorless crystals of mp 63-66°; ^1H nmr (deuteriochloroform): δ 7.37-7.20 (m, 5H, Ph-H), 7.23 (s, 1H, pyrazole H-5 [24]), 5.30 (s, 2H, CH_2); ms: m/z (%) 411 (12), 410 (M^+, 100), 409 (50), 156 (16), 91 (58), 65 (11).

Anal. Calcd. for $C_{10}H_8I_2N_2$: C, 29.27; H, 1.95; N, 6.83. Found: C, 29.57; H, 1.70; N, 6.62.

Compound **3d** (analytical sample containing some percent of isomer **3c**): ^1H nmr (deuteriochloroform): δ 7.64 (s, 1H, pyrazole H-3), 7.40-7.23 (m, 5H, Ph-H), 5.50 (s, 2H, CH_2); ms: m/z (%) 411 (12), 410 (M^+, 100), 409 (32), 156 (24), 91 (54), 65 (12).

Anal. Calcd. for $C_{10}H_8I_2N_2$: C, 29.27; H, 1.95; N, 6.83. Found: C, 29.53; H, 1.71; N, 6.53.

1-Acetyl-4-iodo-1*H*-pyrazole (**4b**) [18].

This compound had ^1H nmr (deuteriochloroform): δ 8.29 (s, 1H, pyrazole H-5), 7.65 (s, 1H, pyrazole H-3), 2.65 (s, 3H, $COCH_3$).

1-Acetyl-3,4-diiodo-1*H*-pyrazole (**4c**).

To a solution of 320 mg (1 mmole) of **1c** and 101 mg (1 mmole) of triethylamine in 5 ml of dry benzene were added 79 mg (1 mmole) of acetyl chloride and the resulting mixture was stirred at room temperature for 24 hours. Then the precipitate was filtered off, the filtrate was evaporated *in vacuo* and the remaining solid (340 mg) was recrystallized from light petroleum to yield 246 mg (68%) of pure **4c**, mp 83-85°; ^1H nmr (deuteriochloroform): δ (ppm) 8.17 (s, 1H, pyrazole H-3), 2.68 (s, 3H, $COCH_3$); ir (potassium bromide): cm^{-1} 1732 (C=O); ms: m/z (%) 362 (M^+, 32), 320 (100).

Anal. Calcd. for $C_5H_4I_2N_2O$: C, 16.59; H, 1.11; N, 7.74.

Found: C, 16.70; H, 0.91; N, 7.55.

1-(1-Oxo-3-phenylpropyl)-1*H*-pyrazole (**5a**).

To a solution of 681 mg (10 mmoles) of **1a** and 1.012 g (10 mmoles) of triethylamine in 20 ml of dry benzene was added dropwise 1.686 g (10 mmoles) of 3-phenylpropionyl chloride and the resulting mixture was stirred at room temperature for 6 hours. Then the solution was filtered and the filtrate was evaporated *in vacuo* to give 1.817 g (91%) of pure **5a** (according to ^1H nmr) as a nearly colorless oil. For elemental analysis a sample was subjected to Kugelrohr-distillation (10 mbar, 215°) to afford a colorless oil; ^1H nmr (deuteriochloroform): δ 8.27 (dd, $J_{4,5}$ = 2.8 Hz, $J_{3,5}$ = 0.6 Hz, 1H, pyrazole H-5), 7.70 (m, 1H, pyrazole H-3), 7.33-7.23 (m, 5H, Ph-H), 6.42 (dd, $J_{3,4}$ = 1.5 Hz, $J_{4,5}$ = 2.8 Hz, 1H, pyrazole H-4), 3.50 (m, 2H, $COCH_2$), 3.14 (m, 2H, $PhCH_2$); ir (CH_2Cl_2): cm^{-1} 1735 (C=O); ms: m/z (%) 200 (M^+, 10), 105 (20), 104 (100), 103 (13), 91 (32), 77 (15), 69 (56), 51 (10).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.74; H, 5.87; N, 13.88.

4-Iodo-1-(1-oxo-3-phenylpropyl)-1*H*-pyrazole (**5b**).

To a solution of 1.940 g (10 mmoles) of **1b** and 1.113 g (11 mmoles) of triethlyamine in 15 ml of dry toluene were added dropwise 1.855 g (11 mmoles) of 3-phenylpropionyl chloride and the resulting mixture was refluxed for 3 hours. After cooling, the solution was filtered, the filtrate was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from light petroleum to yield 2.120 g (65%) of colorless crystals, mp 64-66°; ^1H nmr (deuteriochloroform): δ 8.32 (s, 1H, pyrazole H-5), 7.67 (s, 1H, pyrazole H-3), 7.32-7.22 (m, 5H, Ph-H), 3.45 (m, 2H, $COCH_2$), 3.12 (m, 2H, $PhCH_2$); ir (potassium bromide): cm^{-1} 1743 (C=O); ms: m/z (%) 326 (M^+, 43), 195 (60), 131 (15), 105 (25), 104 (100), 103 (11), 91 (32), 77 (11).

Anal. Calcd. for $C_{12}H_{11}IN_2O$: C, 44.19; H, 3.40; N, 8.59. Found: C, 44.42; H, 3.39; N, 8.57.

3,4-Diiodo-1-(1-oxo-3-phenylpropyl)-1*H*-pyrazole (**5c**).

Compound **5c** was obtained from 3.199 g (10 mmoles) of **1c** and 1.855 g (11 mmoles) of 3-phenylpropionyl chloride according to the procedure given for the preparation of **5b**. Recrystallization from light petroleum-diisopropyl ether afforded 2.954 g (66%) of colorless crystals, mp 94-96°; ^1H nmr (deuteriochloroform): δ 8.15 (s, 1H, pyrazole H-5), 7.25 (m, 5H, Ph-H), 3.54-3.34 (m, 2H, $COCH_2$), 3.17-2.96 (m, 2H, $PhCH_2$); ir (potassium bromide): cm^{-1} 1734 (C=O); ms: m/z (%) 452 (M^+, 13), 321 (63), 320 (31), 131 (18), 105 (31), 104 (100), 103 (10), 91 (41), 77 (13).

Anal. Calcd. for $C_{12}H_{10}I_2N_2O$: C, 31.88; H, 2.23; N, 6.20. Found: C, 31.98; H, 1.97; N, 5.98.

1-Benzoyl-3,4-diiodo-1*H*-pyrazole (**6c**).

Compound **6c** was obtained from 3.199 g (10 mmoles) of **1c** and 1.546 g (11 mmoles) of benzoyl chloride according to the procedure given for the preparation of **5b**. Recrystallization from light petroleum-diisopropyl ether afforded 3.744 g (88%) of colorless crystals, mp 107-109°; ^1H nmr (deuteriochloroform): δ 8.34 (s, 1H, pyrazole H-5), 8.13 (m, 2H, Ph H-2,6), 7.63 (m, 1H, Ph H-4), 7.50 (m, 2H, Ph H-3,5); ir (potassium bromide): cm^{-1} 1698 (C=O); ms: m/z (%) 424 (M^+, 41), 297 (12), 105 (100), 77 (39), 51 (14).

Anal. Calcd. for $C_{10}H_6I_2N_2O$: C, 28.33; H, 1.43; N, 6.61. Found: C, 28.25; H, 1.45; N, 6.62.

(*E*)-1-(1-Oxo-3-phenyl-2-propenyl)-1*H*-pyrazole (**7a**) [20].

This compound had ^1H nmr (deuteriochloroform): [20] δ 8.38 (dd, $J_{4,5}$ = 2.9 Hz, $J_{3,5}$ = 0.6 Hz, 1H, pyrazole H-5), 8.01 (A-part of an AB-system, J = 16.1 Hz, 1H, Ph-CH=), 7.91 (B-part of an AB-system, J = 16.1 Hz, COCH=), 7.77 (m, 1H, pyrazole H-3), 7.67 (m, 2H, Ph H-2,6), 7.41 (m, 3H, Ph H-3,4,5), 6.47 (dd, $J_{3,4}$ = 1.5 Hz, $J_{4,5}$ = 2.9 Hz, 1H, pyrazole H-4); ms: m/z (%) 198 (M^+, 26), 170 (60), 169 (35), 132 (10), 131 (100), 103 (73), 102 (29), 77 (50), 51 (22).

(*E*)-4-Iodo-1-(1-oxo-3-phenyl-2-propenyl)-1*H*-pyrazole (**7b**).

Compound **7b** was prepared from 1.940 g (10 mmoles) of **1b** and 1.833 g (11 mmoles) of *trans*-cinnamoyl chloride according to the procedure given for the preparation of **5b**. Recrystallization from diisopropyl ether-light petroleum afforded 2.366 g (73%) of colorless needles, mp 130-135°; ^1H nmr (deuteriochloroform): δ 8.45 (d, $J_{3,5}$ = 0.5 Hz, 1H, pyrazole H-5), 8.03 (A-part of an AB-system, J = 16.0 Hz, 1H, Ph-CH=), 7.82 (B-part of an AB-system, J = 16.0 Hz, COCH=), 7.74 (d, $J_{3,5}$ = 0.5 Hz, 1H, pyrazole H-3), 7.70-7.62 (m, 2H, Ph H-2,6), 7.46-7.38 (m, 3H, Ph H-3,4,5); ir (potassium bromide): cm^{-1} 1709 (C=O); ms: m/z (%) 324 (M^+, 49), 297 (12), 296 (96), 295 (10), 132 (10), 131 (100), 103 (48), 102 (13), 77 (30), 51 (11).

Anal. Calcd. for $C_{12}H_9IN_2O$: C, 44.47; H, 2.80; N, 8.64. Found: C, 44.42; H, 2.64; N, 8.61.

(*E*)-3,4-Diiodo-1-(1-oxo-3-phenyl-2-propenyl)-1*H*-pyrazole (**7c**).

Compound **7c** was prepared from 3.199 g (10 mmoles) of **1c** and 1.833 g (11 mmoles) of *trans*-cinnamoyl chloride according to the procedure given for the preparation of **5b**. Recrystallization from diisopropyl ether-light petroleum afforded 3.510 g (78%) of colorless needles, mp 141-143°; ^1H nmr (deuteriochloroform): δ 8.28 (s, 1H, pyrazole H-5), 8.02 (A-part of an AB-system, J = 15.9 Hz, 1H, Ph-CH=), 7.75 (B-part of an AB-system, J = 15.9 Hz, COCH=), 7.68 (m, 2H, Ph H-2,6), 7.43 (m, 3H, Ph H-3,4,5); ir (potassium bromide): cm^{-1} 1708 (C=O); ms: m/z (%) 450 (M^+, 15), 422 (32), 132 (10), 131 (100), 103 (41), 102 (10), 77 (24).

Anal. Calcd. for $C_{12}H_8I_2N_2O$: C, 32.03; H, 1.79; N, 6.22. Found: C, 31.93; H, 1.60; N, 6.00.

1-Benzenesulfonyl-4-iodo-1*H*-pyrazole (**8b**).

A solution of **1b** (1.940 g, 10 mmoles) and benzenesulfonyl chloride (1.766 g, 10 mmoles) in 12 ml of dry pyridine was heated to reflux for 2 hours. After cooling, the mixture was poured into water (100 ml) and the precipitate was filtered off, washed with water and recrystallized from ethanol to yield 2.740 g (82%) of colorless crystals, mp 108-109°; ^1H nmr (deuteriochloroform): δ 8.15 (s, 1H, pyrazole H-5), 8.08-7.95 (m, 2H, Ph H-2,6), 7.69 (s, 1H, pyrazole H-3), 7.66-7.52 (m, 3H, Ph H-3,4,5); ms: m/z (%) 334 (M^+, 30), 270 (24), 141 (17), 77 (100), 51 (30).

Anal. Calcd. for $C_9H_7IN_2O_2S$: C, 32.35; H, 2.11; N, 8.38. Found: C, 32.40; H, 2.10; N, 8.41.

1-Benzenesulfonyl-3,4-diiodo-1*H*-pyrazole (**8c**).

Compound **8c** was prepared from 3.199 g (10 mmoles) of **1c** and 1.766 g (10 mmoles) of benzenesulfonyl chloride according to the procedure given for the preparation of **8b**. Recrystallization

from diisopropyl ether-ethanol afforded 3.312 g (72%) of colorless crystals, mp 142-143°; ^{1}H nmr (deuteriochloroform): δ 8.09-7.97 (m, 2H, Ph H-2,6), 8.00 (s, 1H, pyrazole H-5), 7.73-7.55 (m, 3H, Ph H-3,4,5); ms: m/z (%) 460 (M^+, 56), 396 (62), 164 (25), 142 (39), 141 (37), 77 (100), 51 (28).

Anal. Calcd. for $C_9H_6I_2N_2O_2S$: C, 23.50; H, 1.31; N, 6.09. Found: C, 23.72; H, 1.22; N, 6.09.

3,4-Diiodo-1-(4-toluenesulfonyl)-1*H*-pyrazole (**9c**).

Compound **9c** was prepared from 3.199 g (10 mmoles) of **1c** and 1.907 g (10 mmoles) of 4-toluenesulfonyl chloride according to the procedure given for the preparation of **8b**. Recrystallization from diisopropyl ether-ethanol yielded 3.792 g (80%) of colorless crystals, mp 130-131°; ^{1}H nmr (deuteriochloroform): δ 7.98 (s, 1H, pyrazole H-5), 7.98-7.85 (m, 2H, benzene H-2,6), 7.41-7.30 (m, 2H, benzene H-3,5), 2.45 (s, 3H, Me); ms: m/z (%) 474 (M^+, 41), 410 (68), 164 (22), 156 (35), 155 (48), 91 (100), 65 (30).

Anal. Calcd. for $C_{10}H_8I_2N_2O_2S$: C, 25.34; H, 1.70; N, 5.91. Found: C, 25.32; H, 1.43; N, 5.86.

Acknowledgements.

The authors thank Mr. E. Möllner for performing the glc/ms analyses and for recording some ir spectra.

REFERENCES AND NOTES

[1] Part of the planned Diploma Thesis of I. Pöcher, University of Vienna.

[2] B.-R. Tolf, R. Dahlbom, H. Theorell and A. Akeson, *Acta Chem. Scand. B*, **36**, 101 (1982).

[3] S. F. Vasilevskii, M. S. Shvartsberg and I. L. Kotlyarevskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1764 (1971); *Chem. Abstr.*, **75**, 151724p (1971).

[4] G. Heinisch, W. Holzer and C. Obala, *Monatsh. Chem.*, **119**, 253 (1988).

[5] J. Elguero, Comprehensive Heterocyclic Chemistry, Vol **5**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, p 167.

[6] A. N. Kost and I. I. Grandberg, *Adv. Heterocyclic Chem.*, **6**, 347 (1966).

[7] M. Begtrup, G. Boyer, P. Cabildo, C. Cativiela, R. M. Claramunt, J. Elguero, J. I. Garcia, C. Toiron and P. Vedso, *Magn. Reson. Chem.*, **31**, 107 (1993).

[8] W. Holzer, *Tetrahedron*, **47**, 1393 (1991).

[9] H. Kessler, M. Gehrke and C. Griesinger, *Angew. Chem.*, **100**, 507 (1988); *Angew. Chem., Int. Ed. Eng.*, **27**, 490 (1988); and references cited therein.

[10] H.-O. Kalinowski, S. Berger and S. Braun, ^{13}C-NMR Spektroskopie, Georg Thieme Verlag, Stuttgart-New York, 1984, p 287.

[11] M. Begtrup, J. Elguero, R. Faure, P. Camps, C. Estopa, D. Ilavsky, A. Fruchier, C. Marzin and J. de Mendoza, *Magn. Reson. Chem.*, **26**, 134 (1988).

[12] T. Jippo, O. Kamo and K. Nagayama, *J. Magn. Reson.*, **66**, 344 (1986).

[13] G. Heinisch and W. Holzer, *Heterocycles*, **27**, 2443 (1988).

[14] D. Giles, E. W. Parnell and J. D. Renwick, *J. Chem. Soc. C*, 1179 (1966).

[15] R. Hüttel and M. E. Schön, *Liebigs Ann. Chem.*, **625**, 55 (1959).

[16] R. Hüttel, O. Schäfer and P. Jochum, *Liebigs Ann. Chem.*, **593**, 200 (1955).

[17] R. G. Jones, *J. Am. Chem. Soc.*, **71**, 3994 (1949).

[18] R. Hüttel and J. Kratzer, *Chem. Ber.*, **92**, 2014 (1959).

[19] L. Knorr, *Chem. Ber.*, **28**, 714 (1895).

[20] J. Besida, R. F. C. Brown, S. Colmanet and D. N. Leach, *Aust. J. Chem.*, **35**, 1373 (1982).

[21] I. L. Finar and G. H. Lord, *J. Chem. Soc.*, 3314 (1957).

[22] M. Bertrand, J. Elguero, R. Jaquier and J. Le Gras, *Compt. Rend., Ser. C*, **262**, 782 (1966).

[23] M. Begtrup, *Acta Chem. Scand.*, **27**, 2051 (1973).

[24] This singlet signal (which is overlapped by Ph-H signals in the ^{1}H nmr spectrum) emerges in an NOE-difference experiment irradiating the NCH_2-resonance.