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Adamantylazoles: IV* Acid-Catalyzed Adamantylation of Pyrazoles

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Abstract—Pyrazoles with pK_{BH^+} no more than 0.8 and having substituents in 3(5) position with effective van der Waals radii not exceeding 2 Å in a mixture of phosphoric and acetic acids at weight ratio 4 : 1 (H_0 –1,8) react with 1-adamantanol to afford the corresponding 1-(1-adamantyl)- or 1,4-di(1-adamantyl)pyrazoles.

N-Adamantylation of azoles (including pyrazoles) described in the literature occurred in reactions with 1-bromoadamantane either in a high-pressure reactor at 180–200°C or at heating in a microwave oven [2–4]. Adamantylation of azoles may be performed as an acid-catalyzed reaction [1, 5, 6]. The target of this study was investigation of 1-adamantanol (**I**) reaction with pyrazoles in acidic media. It was shown previously by the imidazole example that adamantylation in the acidic medium depended first of all on protolytic equilibria. It was presumable that this rule would be valid also for pyrazoles. However in selection of substrates for the study of adamantylation we met with a limited number of data on basicity constants of pyrazoles, especially those with electron-withdrawing substituents [7]. The published relation between pK_a and pK_{BH^+} is based on few points and provides the values for 3-nitro- and 3,4-dinitropyrazoles with large errors. Besides no published data exist on the basicity and acidity of pyrazolecarboxylic acids. Therefore we tried to fill in this gap using the correlation analysis procedure previously successfully applied to evaluation of basicity for 1,2,4-triazoles [8]. We performed a six-parametric correlation of pyrazoles pK_{BH^+} values with the constants σ_I and σ_c of substituents at C^3, C^4, C^5. The basicity values were taken from review [7], σ_I and σ_c from [9]. The general form of the correlation equation is as follows:

$$pK_{BH^+} = A\sigma_{I(3)} + B\sigma_{c(3)} + C\sigma_{I(4)} + D\sigma_{c(4)} + E\sigma_{I(5)} + F\sigma_{c(5)} + G,$$

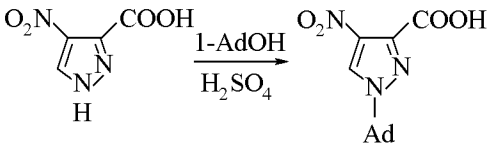
where the figures in the parentheses are the numbers of the corresponding carbon atoms of the ring.

The calculations were carried out with the use of Statgraphics Plus software. The preliminary calculations showed that parameter E did not affect the final correlation form, and thus it was excluded from the final computation.

The analysis proceeding from the data for 35 compounds containing electron-withdrawing substituents in C^{3-5} positions and electron-donating ones and phenyl in $C^{3,4}$ positions resulted in the following equation:

$$\begin{aligned} pK_{BH^+} = {} & -(9.20\pm0.16)\sigma_{I(3)} - (7.01\pm0.40)\sigma_{c(3)} \\ & - (5.84\pm0.12)\sigma_{I(4)} - (4.34\pm0.24)_{c(4)} \\ & - (7.22\pm0.53)_{c(5)} + (2.24\pm0.06) \\ R = {} & 0.9945,\ S = 0.16. \end{aligned} \quad (1)$$

The computation results are presented in Table 1. The basicity constants for pyrazoles that were absent in the literature in this study were calculated by equation (1). The first object of the study was 3-carboxy-4-nitropyrazole (**IIa**) (pK_{BH^+} –4.8) that in 85% sulfuric acid at 22°C in 72 h yielded 1-(1-adamantyl)-3-carboxy-4-nitropyrazole (**IIIa**).



Under the same conditions 5-methyl-3,4-dinitropyrazole (**IIb**) (pK_{BH^+} –8.1) reacted similarly affording 1-(1-adamantyl)-5-methyl-3,4-dinitropyrazole (**IIIb**). Pyrazoles of higher basicity do not react under these conditions. We believed that this fact was due to high degree of heterocycle protonation and tried to

* For communication III see [1].

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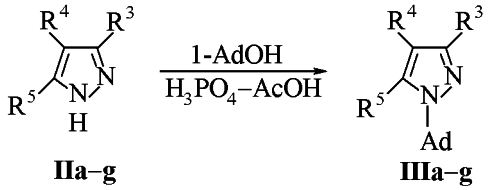
Table 1. Experimental and calculated basicity values pK_{BH^+} of pyrazoles

Substituents	Calculated by equation (1)	Experimental [7]
3-Me	3.08	3.27
3-*t*-Bu	3.52	3.25
4-Me	2.76	3.04
3-Et	3.27	3.25
3,4-Me_2	3.60	3.85
3,5-Me_2	3.92	4.06
3,4,5-Me_3	4.44	4.56
3-Ph	2.09	2.09
4-Ph	2.13	1.64
3-Ph-4-Me	2.61	2.64
3-Ph-5-Me	2.93	2.87
5,4-Me_2-3-Ph	3.45	3.42
4-NO_2	–2.09	–2
4-NO_2-3,5-	–0.41	–0.45
4-NO_2-3-Me	–1.25	–1.23
4-Cl	0.54	0.59
4-Br	0.57	0.63
3-NO_2	–4.60	–4.66
3-Cl	–0.40	–0.49
3-Cl-5-Me	0.43	0.29
3-Br-5-Me	0.48	0.44
3,4-Br_2	–2.03	–1.86
3,4-Br_2-5-Me	–1.20	–0.95
3-Me-4-Cl	1.39	1.4
3-Me-4-Br	1.40	1.43
3-Ph-4-Cl	0.39	0.25
3,5-Me_2-4-Br	2.24	2.26
3-Et-4-Br	1.59	1.5
3,5-Me_2-4-Cl	2.21	2.18
3-Ph-4-Br	0.42	0.29
3,4-Me_2-5-Et	4.44	4.53
3,5-Et_2-4-Me	4.62	4.44
5-Me-3-Ph-4-Br	1.25	1.18
3,4,5-H	2.24	2.47
4-Cl-3-Et	1.56	1.48

use in the reaction less concentrated sulfuric acid. It was shown by an example of 3-nitro-1,2,4-triazole that adamantylation proceeded at sulfuric acid concentration higher than 70% [5]. In order to find out whether pyrazoles adamantylation in sulfuric acid is promising we carried out the reaction with 72% H_2SO_4 (H_O –6.2). It turned out however that in such acid within 7 days at 18–20°C considerably (but not completely) reacted 4-nitropyrazole (**IIc**) (pK_{BH^+} –2.0 [7]), and 3-methyl-4-nitropyrazole (**IId**) (pK_{BH^+} –1.23[7]) gave rise only to traces of 1-(1-adamantyl)-3-methyl-4-nitropyrazole (**IIId**). These data show that sulfuric acid is suitable for pyrazoles adamantylation at pK_{BH^+} of substrates below –2.0.

Further we performed pyrazoles adamantylation in a system phosphoric acid–acetic acid, 4:1 (by weight), that had been used before in nitroimidazoles adamantylation [1]. First of all we determined the acidity function H_0 of the said system. As indicator was used 4-nitropyrazole (**IId**). The protonation degree of the indicator was measured by the chemical shift of CH-protons in the ^1H NMR spectrum. The H_0 value found for the system H_3PO_4–AcOH 4:1 (by weight) was –1.8.

The reaction in the system H_3PO_4–AcOH was carried out at 60°C. It turned out that within 3 h cleanly reacted compound **IId** and 4-bromo-3-carboxypyrazole (**IIe**) (pK_{BH^+} –2.2). The reaction of pyrazoles of higher basicity, 3,5-dimethyl-4-nitropyrazole (**IIf**) (pK_{BH^+} –0.45 [7]), and especially 4-chloropyrazole (**IIg**) (pK_{BH^+} 0.59 [7]) took more time, 4–8 h. In all cases were obtained the corresponding N^1-adamantylpyrazoles.

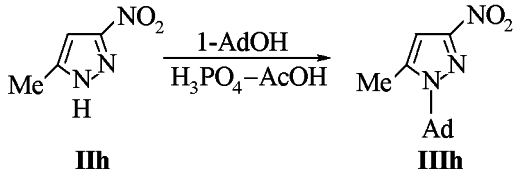


IIa–g **IIIa–g**

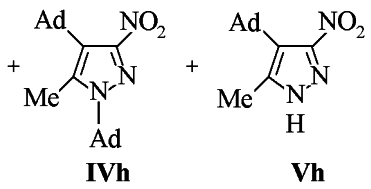
R^3 = COOH, R^4 = NO_2, R^5 = H (**a**); R^3 = R^4 = NO_2, R^5 = Me(**b**); R^3 = R^5 = H, R^4 = NO_2 (**c**); R^3 = Me, R^4 = NO_2, R^5 = H (**d**); R^3 = COOH, R^4 = Br, R^5 = H (**e**); R^3 = R^5 = Me, R^4 = NO_2 (**f**); R^4 = Cl, R^3 = R^5 = H (**g**).

3,5-Dimethylpyrazole (pK_{BH^+} 4.06 [7]) did not react with 1-adamantanol. The data obtained confirm the assumption that adamantylation occurs only with nonionized pyrazole.

The adamantylation of pyrazoles with unoccupied C^4 position is accompanied with formation of



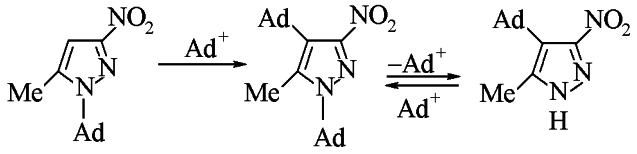
IIh **IIIh**



IVh **Vh**

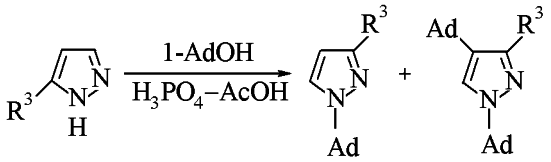
4-adamantyl derivatives. Thus from 3-nitro-5-methylpyrazole (**IIh**) (pK_{BH^+} –3.77) we obtained 1-(1-adamantyl-5-methyl-3-nitropyrazole (**IIIh**), 1,4-di(1-adamantyl)-5-methyl-3-nitropyrazole (**IVh**), and 4-(1-adamantyl)-5-methyl-3-nitropyrazole (**Vh**).

It is presumable that first arises compound **IIIh** which under the reaction conditions is converted into 1,4-diadamantyl derivative. The latter in its turn suffers heterolysis of the N–Ad bond to afford 4-(1-adamantyl)-5-methyl-3-nitropyrazole (**Vh**). In general the processes occurring in adamantylation of compound **IIh** may be described by the following scheme.



IIIl **IVl** **Vl**

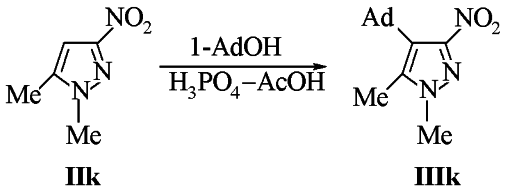
Similarly adamantylation of 3-nitro- (**IIi**) and 3-carboxypyrazole (**IIj**) (pK_{BH^+} –4.66 [7], pK_{BH^+} –0.50 respectively) gives rise to N^1-monoadamantyl and 1,4-diadamantyl derivatives; however no traces were detected of 4-adamantylpyrazoles.



IIi, j **IIIi, j** **IVi, j**

R^3 = NO_2 (**i**), COOH (**j**).

Similar transformations were formerly observed at heating 1- and 4-adamantyl-3,5-dimethylpyrazoles with hydrochloric acid at 190–200°C [2]. The adamantylation into *4* position does not result from intramolecular rearrangement: 1,5-Dimethyl-3-nitropyrazole (**IIk**) under the above conditions readily



IIk **IIIk**

yields 4-(1-adamantyl)-1,5-dimethyl-3-nitropyrazole (**IIIk**).

Compound **Vl** forms through the rupture of N–Ad bond to give 1-adamantyl carbocation. This statement is supported by the fact that on prolonged keeping of a mixture containing adamantylpyrazole **IIIh** and 3-nitro-1,2,4-triazole in the system phosphoric acid–acetic acid arises 1-adamantyl-3-nitro-1,2,4-triazole. Since N-adamantylation in contrast to C-adamantylation is reversible, on long keeping (60 days at 20°C) compound **IIIh** nearly completely is converted into a mixture of pyrazoles **IVh** and **Vh**. In 96% H_2SO_4 at 20°C compound **IVh** is completely transformed into **Vh**: Heterolysis of the N–Ad bond is an easy process, and protonation at the nitrogen atom prevents N-adamantylation of the ring.

The adamantylation is characterized by regioselectivity caused by steric factor: The adamantyl group does not enter into N^1 position when in the neighboring C^5 position are present substituents with van der Waals radii exceeding 2 Å (NO_2, COOH).

3,5-Dicarboxypyrazole (pK_{BH^+} –0.85) and 4-bromo-3,5-dicarboxypyrazole (pK_{BH^+} 2.52), do not react at all. As follows from the quantum-chemical calculations by AM1 method the carboxy groups of these compounds lie virtually in the plane of the ring and hamper the attack of the 1-adamantyl carbocation on the N^1-position. A similar situation is observed in compound **IIh**: the angle between the planes of the ring and the nitro group is 5.2°. However at the attack of the 1-adamantyl carbocation on the C^4-position the nitro group rotates relative to the ring by sufficiently large angle permitting the addition of the adamantyl group to the pyrazole ring.

The structure of compounds obtained was proved by ^1H and ^{13}C NMR spectra. In the ^1H NMR spectra appear the signals of monosubstituted adamantyl, of methyl and carboxy groups, and of the protons of pyrazole ring. The ^{13}C NMR spectral parameters (^{13}C chemical shifts and direct and long-range coupling constants of ^{13}C and protons) provide more important information on the structure of adamantylazoles.

The position of a nitro group in the pyrazole ring both when it is a single substituent or there are the other substituents on carbon atoms can be derived from the chemical shifts of the ring carbons and from the direct and long-range coupling constants of ^{13}C and protons. It was formerly established that in 3,5-disubstituted pyrazoles with nitro group at C^3 atom the difference of the chemical shifts C^3–C^5 amounts from 7 to 24 ppm, and at the nitro group in C^5 position this difference is from –16 to +6 ppm due to dissimilar electronegativity of atoms N^1 and N^2 in the pyrazole ring [10]. The coupling constants ^{13}C, ^1H also confirm the structure. The vicinal coupling constants $^{13}J_{C^5,C^3}$ in compounds with a nitro group in C^3 position equal from 11 to 15 Hz and the

Table 2. ^{1}H NMR spectra of 1-adamantylpyrazoles, δ, ppm

Compd. no.	Chemical shifts, multiplicity, and integral intensity of proton signals
IIIa	8.35 s (1H, H^5); 4.7 br.s (COOH); 2.98 br.s, 2.19 br.s 1.63 br.s (15H, Ad)
IIIb	2.8 s (3H, 5-Me); 2.31 br.s, 1.71 br.s (15H, Ad)
IIIc[a]	8.15 s (1H, H^3); 8.0 s (1H, H^5); 2.1 br.s, 1.8 br.s (15H, Ad)
IIId[a]	8.7 s (1H, H^5); 2.5 (3H, 3-Me); 2.1 br.s, 1.75 br.s (15H, Ad)
IIIe[a]	8.3 s (1H, H^5); 2,1 br.s, 1.7 br.s (15H, Ad)
IIIf	2.81 s (3H, 5-Me); 2.45 s (3H, 3Me); 2.28 br.s, 2.22 br.s, 1.74 br.s (15H, Ad)
IIIg[a]	7.4 s (2H, H^3, H^5); 2.1 br.s, 1.7 br.s (15H, Ad)
IIIh	6.61s (1H, H^4), 2.53 s (3H, 5-Me); 2.29 br.s, 2.23 br.s, 1.78 br.s (15H, Ad)
IIIi	7.43 s (1H, H^5); 6.37 s (1H, H^4); 2.12 br.s, 2.05 br.s, 1.63 br.s (15H, Ad)
IIIj[a]	7.53 s (1H, H^5); 6.8 s (1H, H^4); 2.2 br.s, 1.75 br.s (15H, Ad)
IIIk[a]	3.75 s (3H, 1-Me); 2.4 s (3H, 5-Me); 2.03 br.s, 1.7 br.s (15H, Ad)
IVh	2.26 s (3H, 5-Me); 2.29 br.s, 2.22 br.s, 2.03 br.s, 2.01 br.s, 1.72 br.s (30H, Ad)
IVi	7.32 s (1H, H^5); 2.26 br.s, 2.18 br.s, 2.06 br.s, 2.03 br.s, 1.77 br.s, (30H, Ad)
IVj[a]	7.3 s (1H, H^3); 2.13 br.s 2.0 br.s 1.75 br.s (30H, Ad)
Vh	10.3 br.s ,(1,2,H^1); 2.49 s (3H, 5-Me); 2.09 br.s, 2.06 br.s, 1.71 br.s, (15H, Ad)

[a] The spectra were registered on spectrometer Perkin-Elmer R-12.

Table 3. ^{13}C NMR spectra of 1-adamantylpyrazoles, δ_C, ppm

Compd. no.	C^3	C^4	C^5	Ad	C=O, Me
IIIa				1-Ad: 29.40 d, 35.59 t, 42.15 t, 62.56	3-COOH 159.71 s
IIIb	147.19 br.s	126.66 br.s	140.74 q (6.4)	1-Ad: 30.19 d, 36.01 t, 41.92 t, 66.96 s	5-CH_3 13.78 quint (128.7)
IIIf	144.53 q (6.2)	132.81 br.s	140.34 q (7.5)	1-Ad: 30.51 d, 36.49 t, 42.37 t, 63.73 s	5-CH_3 and-CH_3 14.87 quint (128.4) 14.71 quint (130.5.)
IIIh	153.36 br.s	104.46 d.q (185.0, 6.0)	141.228 d.q (8.0, 8.0)	1-Ad: 29.8 d, 35.9 t, 41.9 t, 63.9 s	5-CH_3 15.17 quint (130.0)
IIIi	155.79 br.s.	102.57 d.d. (186.3, 8.2)	127.93 d.d. (190.2, 8.1)	1-Ad: 29.85 d, 36.18 t, 42.85 t, 61.60 s	
IVh	153.56 br.s.	119.7 s	136.83 quint (6.2)	1-Ad: 30.31 d, 36.94 t, 42.14 t, 63.58 s 4-Ad: 29.02 d, 34.42 s, 36.37 t, 41.21 t	5-CH_3 16.26 quint (128.7)
IVi	153.06 br.s.d (9.8)	127.66 d (6.3)	125.15 d (187.7)	1-Ad: 29.86 d, 36.99 t, 42.75 t, 60.99 s 4-Ad: 28.91 d, 33.21 s, 36.23 t, 41.32 t	
Vh	156.30 br.s	120.71 s	138.48 quint (5.8)	4-Ad: 28.95 d, 34.43 s, 36.87 t, 41.48 t	5-CH_3 14.78 quint (129.5)

coupling constants $^{13}J_{C^3,C^5}$ in compounds with a nitro group in C^5 position are from 4.3 to 7.4 Hz [10]. Similar trends in ^{13}C chemical shifts and coupling constants ^{13}C, ^{1}H were earlier observed for *N*-acetonylnitro-1,2,4-triazoles [11] and *N*–(1-adamantyl)nitro-1,2,4-triazoles [5].

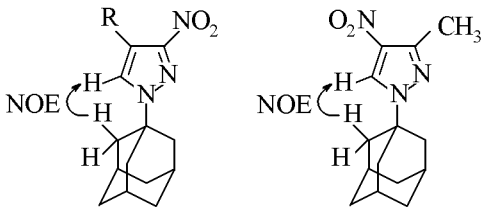
Among compounds under study are no 5-nitropyrazoles. When nitro group was located at C^3 atom the difference in chemical shifts for C^3–C^5 was as expected 7–28 ppm (compounds **IIIh , Vh, IVh, IIIa, IIIc, IVc**), and the coupling constant $^{13}J_{C^3,H^5}$ was 10 Hz (compound **IIIf**). When the position of sub-

Table 4. Reaction time, yields, melting points, and elemental analyses of compounds obtained

Compd. no.	Reaction time, h	Yield, %	mp, °C (solvent)
IIIa	3	82	166–167 (ethanol–water 4 : 1)
IIIb	8	32	145–147 (ethanol)
IIIc	2.5	84	155–157 (ethanol)
IIId	2.5	80	151–152 (ethanol)
IIIe	3	70	238–239 (ethyl acetate)
IIIf	4	60	174–176 (ethanol)
IIIg	8	47	96–98 (ethanol)
IIIh	3	23	159–160 (ethanol)
IIIi	3	40	124–126 (ethanol)
IIIj	4	21	188–190 (ethanol–water 1:1)
IIIk	3	60	96 (ethanol)
IVh	3	23	250–251 (acetone-chloroform 9:1)
IVi	3	21	208–210 (ethanol)
IVj	4	7	229–231 (ethanol–water 1:1)
Vh	3	9	219–220 (ethanol–water 4:1)

Compd. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
IIIa	57.35	5.63	14.29	$C_{14}H_{17}N_3O_4$	57.70	5.88	14.43
IIIb	65.53	7.27	12.92	$C_{14}H_{18}N_4O_4$	68.15	8.24	12.27
IIIc	65.16	7.57	14.96	$C_{13}H_{17}N_3O_2$	65.43	7.68	15.26
IIId	64.58	7.01	16.04	$C_{14}H_{19}N_3O_2$	64.34	7.32	16.07
IIIe	51.44	5.08	8.34	$C_{14}H_{17}BrN_2O_2$	51.70	5.27	8.61
IIIf	65.16	7.57	14.96	$C_{15}H_{21}N_3O_2$	65.43	7.68	15.26
IIIg	65.59	7.49	11.55	$C_{13}H_{17}N_2Cl$	65.95	7.24	11.83
IIIh	64.81	7.55	16.35	$C_{14}H_{19}N_3O_2$	64.34	7.32	16.07
IIIi	64.01	6.82	16.04	$C_{13}H_{17}N_3O_2$	63.14	6.93	16.99
IIIj	67.93	7.67	11.07	$C_{14}H_{18}N_2O_2$	68.27	7.36	11.37
IIIk	65.09	7.58	15.51	$C_{15}H_{21}N_3O_2$	65.43	7.69	15.26
IVh	73.07	7.99	10.63	$C_{24}H_{33}N_3O_2$	72.88	8.41	10.62
IVi	72.03	7.79	10.74	$C_{23}H_{31}N_3O_2$	72.41	8.19	11.01
IVj	75.34	8.05	7.05	$C_{24}H_{32}N_2O_2$	75.75	8.47	7.36
Vh	64.86	6.73	15.76	$C_{14}H_{19}N_3O_2$	64.34	7.32	16.07

stituent in the ring was not unambiguously derived from the ^{13}C chemical shifts, we measured spectra with nuclear Overhauser effect (1D-NOE and ROESY) [12, 132] that confirmed the presence of adjacent methyl and adamantyl groups (**IIIh, b, f**) and of closely located protons of the ring and adamantyl group (**IIIa, i, IVi**) definitely indicating the presence of a methyl group in C^5-position (**IIIh, b, d**) or the lack of a substituent in this position (**IIIa, i, IVi**).



The position of the adamantyl moiety is also indicated by the signal of its quaternary carbon: when the adamantyl is attached to the N^1-position the corresponding chemical shifts are equal to 60–64 ppm (compounds **IIIh, IVh, IIIa, b, i, IVi**), and when it is in C^4-position the chemical shift is 33–55 ppm (compounds **Vh, IVh, i**).

The signals of protons attached to the definite carbons in the ring were assigned by means of two-dimensional H/C correlation registered in HMQC mode (compound **IIIc**).

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometer Perkin-Elmer R-12 (60 MHz), internal reference HMDS. Also ^{1}H and ^{13}C NMR spectra were recorded on spectrometer Bruker DXR-500 at operating frequencies 500.13 and 125.77 MHz respectively from solutions in $CDCl_3$ of concentration 3–5 mol l^{-1} at 30°C. All the spectra were recorded on Bruker DXR-500 instrument in the Fourier-transform mode. The ^{13}C NMR spectra were registered with wide-band and selective decoupling from protons. As internal reference were taken the signals of solvent, deuterochloroform: residual protons with chemical shift 7.27 ppm, 77.5 ppm in the ^{13}C spectra. Two-dimensional spectra were obtained along standard procedures ROESY [10] and HMQR [11]. TLC analyses were performed on Silufol UV-254 plates, development under UV-irradiation and in iodine vapor. The elemental analyses were carried out on CHN-analyzer Hewlett-Packard 185 B.

Pyrazoles adamantylation in sulfuric acid. To 25 ml of 85% sulfuric acid was added 0.01 mol of 1-adamantanol and 0.01 mol of compounds **IIa, b**. The mixture was left standing for 3 days at 20°C, then was poured into 150 ml of water, the separated precipitate was filtered off and washed with water. Yield of compound **IIIa** 60%, of compound **IIIb** 25%.

Procedure for the synthesis of *N*-adamantylpyrazoles in a mixture H_3PO_4–AcOH. To 25 ml of a mixture containing phosphoric and acetic acids in a weight ratio 4 : 1 was added at stirring pyrazole **IIa–k** (0.01 mol) and 1-adamantanol (**I**) (0.01 mol). The mixture was heated to 60°C for 2–8 h (see Table 4), then poured into 150 ml of water, the separated precipitate was filtered off and washed with water.

Separation of the products from 3-nitro-5-methylpyrazole adamantylation. The precipitate was dissolved in 30 ml of a mixture ethanol–water, 4 : 1, and the insoluble part (compound **IVh**) was separated. From the mother liquor compound **IIIh** was isolated by crystallization. The mother liquor was evaporated to 10–15 ml, and compound **Vh** was then isolated.

Preparation of 4-(1-adamantyl)-5-methyl-3-nitropyrazole (Vh). In 25 ml of 96% H_2SO_4 was dissolved 0.01 mol of compound **IVh**. The mixture was left standing at 20°C for 24 h, then it was poured into 150 ml of water, and the separated precipitate of compound **Vh** was filtered off and washed with water. Yield 96%.

Separation of adamantylation products of 3-nitropyrazole (IIi) and 3-carboxypyrazole (IIj). The precipitate was dissolved in 20 ml of a mixture ethanol–water, 4:1 by volume, or ethanol–water 2 : 1 by volume respectively, and compounds **IVi** and **IVj** were filtered off; compounds **IIIi** and **IIIj** were isolated by crystallization from the mother liquor.

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