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Adamantylation of Indazole and Its C-Nitro Derivatives

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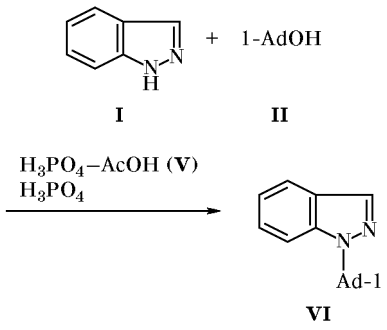
Abstract—Adamantylation of indazole and its C-nitro derivatives with 1-hydroxyadamantane in mineral acids yields exclusively the corresponding 1-(1-adamantyl)indazoles via attack by 1-adamantyl cation on the protonated substrate. The oxidative alkylation with 1-iodoadamantane leads to formation of 1- and 2-(1-adamantyl)indazoles, the 2-isomer prevailing.

One of the most widely used methods for alkylation of indazole (**I**) and its derivatives is based on the reaction with alkyl halides. These reactions lead to either predominant or exclusive formation of 2-alkylindazoles [1–10]. As a rule, alkylation in the presence of alkali or alkali metal alkoxides [1, 3–11] yields mixtures of isomeric 1- and 2-substituted indazoles, the former prevailing. Isomer mixture was also formed in the reaction of indazole with 1-bromoadamantane at 190–200°C [12]. Alkylation of indazole in the presence of acids was poorly studied. Lopes *et al.* [13] reported on the reaction of 1-hydroxymethylindazoles with indazoles without a solvent in the presence of Lewis acids ($ZnCl_2$, $NiCl_2$), which afforded mixtures of 1- and 2-(1-indazolylmethyl)indazoles. We can conclude that in the general case the alkylation of indazole and its derivatives with alkyl halides is not regioselective. The predominant formation of one or another isomer is governed either by the state of tautomeric equilibrium of the substrate [9, 10] or by electron density distribution therein.

In the present work we examined acid-catalyzed adamantylation of indazoles with 1-hydroxyadamantane (**II**) and oxidative alkylation of the same substrates with 1-iodoadamantane (**III**) in the presence of iodine(V) oxide (**IV**). We previously showed that 1,2,4-triazoles [14] and tetrazoles [15, 16] undergo adamantylation in the protonated form and that the reaction readily occurs in concentrated sulfuric acid. By contrast, diazoles react only as free bases; therefore, the reactions are possible only in those acids whose $\log I = pK_{BH^+} - H_0$ value does not exceed 2 [17, 18]. The adamantylation of indazole (**I**, pK_{BH^+} 1.2 [19]) with 1-hydroxyadamantane (**II**) was carried out at 55–60°C in the system phosphoric acid–acetic acid (**V**, 4 : 1 by weight, H_0 –1.8). As a result, 1-(1-adamantyl)indazole (**VI**) was obtained in 83% yield (Scheme 1). In spite of the existing views on the conditions for adamantylation of diazoles [17], adamantylindazole **VI** is also formed in phosphoric acid (H_0 –5.2), though the $\log I$ value is 6.4.

Scheme 1.



We also performed acid-catalyzed adamantylation of 5-nitroindazole (**VII**), 3-nitroindazole (**VIII**), 5,7-dinitroindazole (**IX**), and 3,5,7-trinitroindazole (**X**) in 93% sulfuric acid and obtained 1-(1-adamantyl)-5-nitroindazole (**XI**), 1-(1-adamantyl)-3-nitroindazole (**XII**), and 1-(1-adamantyl)-5,7-dinitroindazole (**XIII**) in 51, 37, and 63% yield, respectively (Scheme 2, Table 1). No 2-(1-adamantyl)-substituted isomers were detected, i.e., the acid-catalyzed adamantylation of nitroindazoles was regioselective. 3,5,7-Trinitroindazole failed to react with 1-hydroxyadamantane under these conditions. Compounds **XII** and **XIII** were also synthesized in 78 and 70% yield, respectively, by heating the same initial reactants in boiling chloroform containing traces of sulfuric acid.

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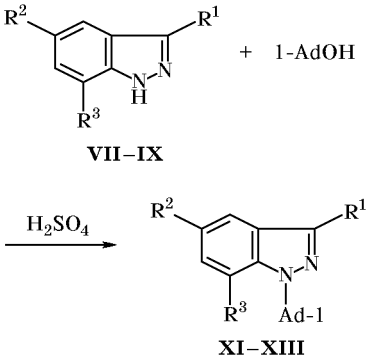
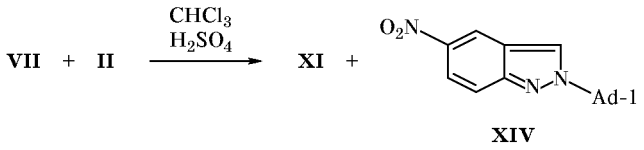
Scheme 2.



VII, **IX**, **XI**, **XIII**, R^1 = H; **VIII**, **XII**, R^1 = NO_2; **VIII**, **XII**, R^2 = H; **VII**, **IX**, **XI**, **XIII**, R^2 = NO_2; **VII**, **VIII**, **XI**, **XII**, R^3 = H; **IX**, **XIII**, R^3 = NO_2.

On the other hand, the reaction of 5-nitroindazole (**VII**) with 1-hydroxyadamantane (**II**) in chloroform in the presence of traces of sulfuric acid gave a mixture of isomeric 1- and 2-(1-adamantyl)-5-nitroindazoles **XI** (8%) and **XIV** (40%) (Scheme 3).

Scheme 3.

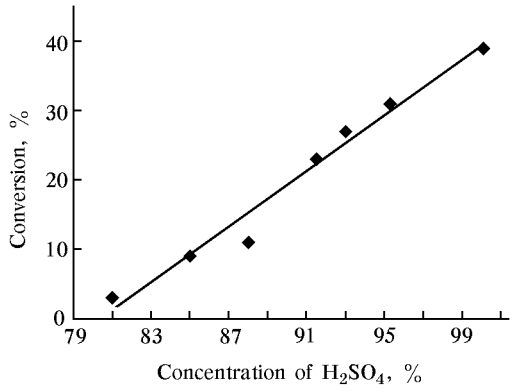


Unlike 2-(1-adamantyl)-1,2,4-triazoles [14], no isomerization of **XIV** into 1-(1-adamantyl) isomer **XI** was observed.

The results of adamantylation of indazole and its C-nitro derivatives in concentrated mineral acids whose ionization ratio logarithm ($\log I$) ranges from 4 to 8 are hardly consistent with the assumption [17, 18] that diazoles are involved in this reaction as free bases. Using 5-nitroindazole (**VII**) as an example, we examined in detail the relation between the yield of the adamantylation product and sulfuric acid concentration. A series of experiments was carried out with variation of sulfuric acid concentration from 81.0 to 100.1%, other conditions (temperature, reactant concentrations, and isolation procedure) being equal. In all experiments the reaction time was 5 h. The yield of *N*-adamantylindazole **XI** was determined by GLC. Figure shows that the reaction begins at a sulfuric acid concentration of 80% and that its rate increases as the sulfuric acid concentration rises. The pK_{BH^+} value of 5-nitroindazole (**VII**) is –0.96 [20], and in the examined concentration range $\log I$ increases from 7 to 11. Therefore, the fraction of non-ionized 5-nitroindazole (**VII**) in the mixture is negligible. Hence we believe that the reactive species is protonated indazole **VII** and that the reaction rate increases due to increase in the concentration of 1-adamantyl cations in the reaction mixture. Alternatively, one could presume that the rate of adamantylation of the non-protonated form of indazoles is very high, so that even small fraction of free base (10^{-7}–10^{-11}) is sufficient to ensure the observed reaction rate. However, study of the adamantylation of unsubstituted indazole (**I**) and pyrazoles in phosphoric–acetic acid mixture showed [17, 18] that the rates of reactions with non-protonated compounds are comparable and are not very high, which contradicts the latter assumption.

Assuming that, unlike pyrazoles, 5-nitroindazole (**VII**) undergoes adamantylation in the protonated form, such reaction is likely to be possible due to charge delocalization with participation of π-electron system of the benzene ring. On the other hand, the process may involve formation of a π-complex between adamantyl cation and benzene ring of the indazole molecule with subsequent transformation of the complex into the final product.

We also examined reactions of indazoles with 1-iodoadamantane in the presence of oxidants. According to our previous data [21], in such a way adamantylation of more basic pyrazoles, $pK_{BH^+} \le 2.26$, can be effected. By reactions of indazoles **I**, **VII**, and **VIII** with 1-iodoadamantane (**III**) in dioxane in the presence of iodine(V) oxide (**IV**) we obtained the corresponding 1-(1-adamantyl)indazoles **VI** and **XI**, as well as 2-(1-adamantyl)indazole (**XV**) and 2-(1-adamantyl)-5-nitroindazole (**XIV**), the latter prevailing. In the reaction with 3-nitroindazole (**VIII**) 2-(1-adamantyl)-3-nitroindazole (**XVI**) was the only product. The predominant formation of 2-substituted isomers



Plot of the conversion of 5-nitroindazole (**VII**) versus concentration of sulfuric acid.

Table 1. Adamantylation of indazole (**I**) and its C-nitro derivatives **VII**–**IX**

Comp. no.	Reaction medium	Temperature, °C	Reaction time	Product (yield, %)
I	H_3PO_4–AcOH	55–60	12 h	**VI** (83)
I	100% H_3PO_4	55–60	20 h	**VI** (68)
I	Dioxane–I_2O_5	90–95	8 h	**VI** (2) **XV** (5), **II** (57), **XVIII** (4), **XVII** (6)
VII	93% H_2SO_4	15–16	2 days	**XI** (51)
VII	$CHCl_3$–H_2SO_4	61	70 h	**XI (8),** **XIV** (40), **II** (21)
VII	Dioxane–I_2O_5	90–95	5 h	**XI** (traces), **XIV** (3), **II** (58), **XVIII** (2)
VIII	93% H_2SO_4	17–20	3 days	**XII** (37)
VIII	$CHCl_3$–H_2SO_4	61	0.5 h	**XII** (78),
VIII	Dioxane–I_2O_5	90–95	4 h	**XVI** (11), **II (56)**, **XVIII** (3)
IX	93% H_2SO_4	15–17	2 days	**XIII** (63)
IX	$CHCl_3$–H_2SO_4	61	28 h	**XIII** (70)

Table 2. ^{1}H and ^{13}C NMR spectra of *N*-adamantylindazoles **VI**, **XI**, **XII**, **XIII**, and **XIV**–**XVI** in DMSO-d_6

Compound no.	^{1}H NMR spectrum, δ, ppm	^{13}C NMR spectrum, δ_C, ppm
VI	8.0 m, 7.9 m, 7.75 m, 7.3 m, 7.1 m (5H); 2.5 m, 2.4 m, 2.25 m, 1.8 m (15H)	143.26, 137.17, 131.26, 125.08, 121.00, 119.78, 112.40 (indazole); 60.06, 41.77, 39.84, 29.36 (Ad)
XI	8.80 s (1H), 8.36 s (1H), 8.14 t (2H), 2.39 br.s, 2.25 br.s, 1.81 br.q (15H)	141.08, 139.27, 134. 93, 124.36, 119.92, 119.09, 113.20 (indazole); 62.12, 41.52, 35.54, 29.27 (Ad)
XII	8.21 d.d (2H), 7.56 quint (2H), 2.42 br.s, 2.28 br.s, 1.87 br.d., 1.77 br.d (15H)	145.69, 139.36, 127.63, 125.80, 120.78, 117.47, 114.64 (indazole); 63.36, 41.12, 35.33, 29.28 (Ad),
XIII	9.25 s (1H), 9.19 s (1H), 8.82 s (1H), 2.34 br.s, 2.29 br.s, 1.81 br.q (15H)	159.82, 140.02, 136.39, 128.34, 127.02, 123.72, 118.44 (indazole); 62.56, 42.39, 35.48, 29.21 (Ad)
XIV[a, b]	8.6 s (1H); 7.95 m, 7.6 m (3H); 2.3 m, 1.8 m (15H)	–
XV[a, b]	8.2 s (1H); 7.55 m, 7.0 m (4H); 2.3 m, 1.8 m (15H)	–
XVI[b]	7.85 m, 7.4 m (4H); 2.48 m, 2.2 m, 1.75 m (15H)	–

[a] The ^{1}H NMR spectrum was recorded in acetone-d_6.

[b] The NMR spectra were obtained on a Perkin–Elmer R-12 instrument.

may be explained in terms of attack by adamantyl cation on the pyridine-like nitrogen atom of non-protonated 1*H*-indazole; i.e., the isomer ratio of the products is determined by the state of tautomeric equilibrium of the substrate.

The reaction of indazole (**I**) with 1-iodoadamantane (**III**) gave also 3-iodoindazole (**XVII**). From the preparative viewpoint, the oxidative alkylation procedure is not efficient, for the yield of *N*-adamantylindazoles does not exceed 10–12%. The major product is 1-hydroxyadmantane (**II**), and a small amount of 1,1′-diadamantyl ether (**XVIII**) [22] is formed. The latter is likely to result from O-alkylation of 1-hydroxyadamantane (**II**) with adamantyl cation.

The structure of the products was established on the basis of their ^{1}H and ^{13}C NMR spectra (Table 2). The presence of an N–Ad bond was judged by the chemical shifts of tertiary carbon atoms in the ^{13}C NMR spectrum (δ_C 60–63 ppm for adamantylazoles [17]). The position of the adamantyl substituent in molecules **VI** and **XI**–**XIII** was determined using the 1D NOE Difference technique [23]. The structure

Table 3. Melting points and elemental analyses of adamantylazoles **VI**, **XI**–**XIII**, and **XIV**–**XVI**

Compound no.	mp, °C	Found, %			Formula	Calculated, %		
		C	H	N		C	H	N
V	173–175	81.20	8.42	10.58	$C_{17}H_{20}N_2$	80.95	7.94	11.11
XI	170–172	68.67	6.16	14.05	$C_{17}H_{19}N_3O_2$	68.67	6.40	14.14
XII	154–156	69.06	5.97	13.91	$C_{17}H_{19}N_3O_2$	68.67	6.40	14.14
XIII	278–280	59.47	5.47	15.98	$C_{17}H_{18}N_4O_4$	59.56	5.26	16.37
XIV	155–157	68.58	6.54	13.75	$C_{17}H_{19}N_3O_2$	68.67	6.40	14.14
XV	133–134	80.76	8.03	10.89	$C_{17}H_{20}N_2$	80.95	7.94	11.11
XVI	173–175	68.37	6.57	13.82	$C_{17}H_{19}N_3O_2$	68.67	6.40	14.14

of 2-(1-adamantyl)indazoles was proved by the elimination method, after comparing the analytical data and NMR spectra of **VI** and **XV**, **XI** and **XIV**, and **XII** and **XVI**.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer at 300.13 MHz for ^1H and 75.47 MHz for ^{13}C using DMSO-d_6 as solvent (concentration 1–5 M; 30–50°C). The ^{13}C NMR spectra were recorded with broad-band decoupling from protons. The solvent signals (δ 2.50 ppm and δ_C 39.5 ppm) were used as reference. The ^1H NMR spectra of some compounds (Table 2) were measured on a Perkin–Elmer R-12 instrument (60 MHz) in acetone-d_6 containing HMDS as internal reference. The elemental compositions were determined on a semiautomatic Hewlett–Packard 185 C,H,N-microanalyzer. Chromatographic separations were performed using a 46 × 1-cm column charged with silica gel 100/400 μm; eluent chloroform or (for compound **XVII**) chloroform–ethyl acetate, 80 : 20 (by volume). GLC analysis was performed on an LKhM-80 chromatograph; stationary phase 5% of SE-30 on Chromaton N-AW-DMCS (0.1–0.125 mm); oven temperature programming from 100 to 300°C; injector temperature 270°C; detector temperature 270°C.

Dioxane was treated with tin(II) chloride to remove peroxide impurities, dried over sodium hydroxide, and distilled. The concentration of sulfuric acid was determined by titration with an accuracy of ±0.1%.

1-(1-Adamantyl)indazole (VI). *a.* To a solution of 0.15 g (1 mmol) of 1-hydroxyadamantane (**II**) in 10 ml of a 4 : 1 (by weight) mixture of 100% phosphoric acid and glacial acetic acid we added 0.24 g (2 mmol) of indazole (**I**). The mixture was heated for 12 h at 55–60°C, cooled, and poured into 30 ml of an ice–water mixture. The precipitate was filtered off, washed with 50 ml of a 5% aqueous solution of sodium hydroxide and 10 ml of water, and dried.

b. To a solution of 0.15 g (1 mmol) of 1-hydroxyadamantane (**II**) in 10 ml of 100% phosphoric acid we added 0.24 g (2 mmol) of indazole (**I**). The mixture was heated for 20 h at 55–60°C, and the product was isolated as described above in *a*.

1-(1-Adamantyl)nitroindazoles XI–**XIII.** *a.* To a solution of 0.15 g (1 mmol) of 1-hydroxyadamantane (**II**) in 10 ml of 93% sulfuric acid we added 1.05 mmol of *C*-nitro indazole. The mixture was kept under the conditions specified in Table 1 and poured into 30 ml of an ice–water mixture. The precipitate was filtered off, washed with 10 ml of a 5% solution of sodium hydroxide and 20 ml of water, dried, and recrystallized from 2-propanol.

b. 1-Hydroxyadamantane (**II**), 0.15 g (1 mmol), and nitroindazole, 1 mmol, were dissolved in succession in 5 ml of chloroform containing 2 drops of 93% sulfuric acid, and the mixture was refluxed in such a way that the condensate passed through a paper bag containing magnesium sulfate (drying agent). The reaction time is specified in Table 1. The mixture was then cooled and evaporated, and the dry residue was washed with 10 ml of a 5% solution of sodium hydroxide amd 20 ml of water, dried, and recrystallized from 2-propanol.

Reaction of 5-nitroindazole (VII) with 1-hydroxyadamantane (II) in sulfuric acid of different concentrations. To a solution of 0.15 g (1 mmol) of 1-hydroxyadamantane (**II**) in 10 ml of sulfuric acid of appropriate concentration we added 0.16 g (1 mmol) of 5-nitroindazole (**VII**). After 5 h, the mixture was poured into 30 ml of an ice–water mixture and neutralized to pH 7 with a 5% solution of sodium hydroxide. The precipitate was filtered off,

washed with 20 ml of water, and dried. The product composition was determined by GLC.

Oxidative adamantylation of indazole (I), 5-nitroindazole (VII), and 3-nitroindazole (VIII) (*general procedure***).** To a solution of 0.26 g (1 mmol) of 1-iodoadamantane (**III**) in 3 ml of anhydrous peroxide-free dioxane we added in succession 1.5 mmol of indazole **I**, **VII**, or **VIII** and 0.5 g (1.5 mmol) of iodine(V) oxide (**IV**). The mixture was stirred at 90–95°C until initial 1-iodoadamantane (**III**) disappeared (TLC). It was then cooled and filtered, and the precipitate of iodine(V) oxide (**IV**) was washed with 3 ml of dioxane. The filtrate was combined with the washings and evaporated, the residue was dissolved in 20 ml of chloroform, and the solution was treated with 50 ml of 10% aqueous sodium sulfite. The organic phase was separated and evaporated, and the residue was washed with 50 ml of a 5% solution of sodium hydroxide and dried at 40–45°C. The yields were determined by GLC. The products were isolated by column chromatography, followed by recrystallization from 2-propanol (Table 3).

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