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SYNTHESIS OF ADAMANTYL-SUBSTITUTED PYRAZOLINES

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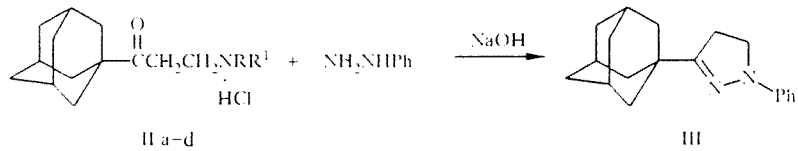
The reaction of a series of N-R-N-R^1-1(β-aminopropionyl)adamantanes with phenylhydrazine formed 3-(adamantyl-1)-1-phenylpyrazoline, the structure of which was confirmed by reverse synthesis from adamantyl-1 vinyl ketone. It is shown that the nitroso derivative of the secondary β-amino ketone is also cyclized into 3-(adamantyl-1)-1-phenylpyrazoline.

It is well known that 1-R-3-aryl-2-pyrazolines manifest antitumor activity [1]. 1-2-Dimethyl-3-arylpyrazolinium perchlorates are used as antidepressants [2], and 1,3-diarylpyrazolines are of interest as fluorescent bleaches [3]. Most widely used in the preparation of pyrazolines are the reaction of tertiary Mannich bases with hydrazides [4, 5] and, as a modification of this method, the reaction of ketones with paraformaldehyde and N-N′-dimethylenediamine dihydrochloride followed by treatment with $HClO_4$ [1]. The synthesis of pyrazolines from hydrochlorides of β-arylamino ketones and phenylhydrazine is carried out in the presence of alkali [3]. Alcohol or acetic acid [6] is used as the solvent in the reaction of β-amino ketones with hydrazides. However, for example, N,N-dimethyl-N-(5-nitrofuorylethylene) amine hydrochloride reacting with arylhydrazines during boiling in alcohol forms only hydrazones, from which pyrazoline could not be obtained [7]. Pyrazolines can also be obtained by reacting vinyl ketones with hydrazides [8].

One of the principal methods of synthesis of N-substituted pyrazolines is cyclization of nitroso derivatives of β-amino ketones [9]. Nitroso derivatives of Mannich bases are obtained by treating a β-amino ketone with $NaNO_2$ in 10% HCl at 5°C [9] or by reacting Mannich bases in a mixture of CH_2Cl_2 and conc. HC; with an aqueous solution of $NaNO_2$ at 0°C [10]. Cyclization of nitro derivatives of β-amino ketones to pyrazolines takes place under the influence of acetic acid in ethanol [9] or CH_2Cl_2 [10] in the presence of a catalyst, zinc dust.

To expand the series of adamantyl-containing heterocycles and study the chemical properties of N-R=N-R^1-1-(β-aminopropionyl)adamantanes (Ia-d), we studied the reaction of their hydrochlorides (IIa-d) with phenylhydrazine in an alcohol medium in the presence of NaOH. However, phenylhydrazones of Mannich bases cannot be obtained under these conditions – cyclization takes place immediately with the formation of 3-(adamantyl-1)-1-phenylpyrazoline (III).



II a–d III

I a R = R^1 = C_2H_5; b R = C_2H_5, R^1 = adamantyl-1; c R = R^1 = CH_2Ph; d NRR^1 = piperidyl

The reaction of β-amino ketones Ia-d with phenylhydrazine in acetic acid has a similar course. Note that in acetic acid, the reaction takes place with a lower yield of product III and is associated with resinification.

To prove the structure of pyrazoline III, the latter was synthesized in 13% yield from adamantyl-1 vinyl ketone and phenylhydrazine. The low yield of compound III is apparently due to the extreme instability of the original ketone.

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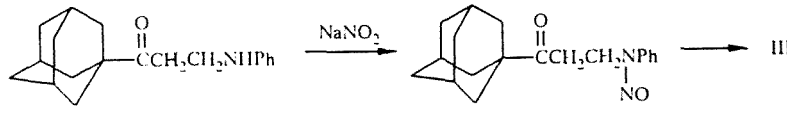
TABLE 1. Properties of the Synthesized Compounds

Compound	Empirical formula	Melting range	R_f*	IR spectrum, ν, cm^{-1}	Yield, %
Ie	$C_{19}H_{25}NO$	85...87	0,356	2910, 2860, 1700, 3400	45
IIa	$C_{17}H_{30}NOCl$	98...100	0,352	2910, 2860, 1690	64
IIb	$C_{24}H_{40}NOCl$	328...330	0,383	2910, 2860, 1700	26
IIc	$C_{27}H_{34}NOCl$	220...222	0,53	2910, 2860, 1700	48
IId	$C_{18}H_{30}NOCl$	173...175	0,433	2910, 2850, 1700	86
III	$C_{19}H_{24}N_2$	127	0,746	2900, 2850, 1600	58*2
IV	$C_{19}H_{24}N_2O_2$	58...59	0,133	2900, 2850, 1680	99

*For compounds Ia-d, the eluent was alcohol, and for compounds Ie, III, and IV, the eluent was 1:6 acetone–CCl_4.

*2Yield based on IIa.

To develop an alternative method of synthesis of 1-R-3-(adamantyl-1)pyrazolines, we carried out the cyclization of the nitroso derivative (IV), obtained from ketone Ie in 80% yield by the action of $NaNO_2$ in acetic acid at 0°C. Compound IV, treated with acetic acid in the presence of zinc dust in boiling ethanol, cyclizes into pyrazoline III in 28% yield.



Ie IV

This method makes it possible to obtain pyrazolines with different substituents in the 1 position; these pyrazolines that cannot be synthesized by reacting Mannich bases with phenylhydrazine.

The starting compounds IIa-d were obtained by Mannich's method from (adamantyl-1)methyl ketone (V), paraformaldehyde, and hydrochlorides of secondary amines. The secondary β-amino ketone Ie was synthesized from ketone Ia by the transamination reaction.

Thus, by reacting N-R-N-R^1-1-(β-aminopropyl)adamantanes with phenylhydrazine, we obtained 1-phenyl-3-(adamantyl-1)pyrazoline. An alternative method of synthesizing 1-R-3-(adamantyl-1)pyrazolines from adamantyl-1 vinyl ketone and the nitroso derivative of a β-amino ketone was proposed.

EXPERIMENTAL

The course of the reaction and the purity of the substances were monitored by means of TLC on Silufol UV-254 plates. The IR spectra were recorded with Specord M-80 and IKS-22 instruments in thin films and KBr pellets.

The fundamental properties of the compounds obtained are listed in Table 1.

(Adamantyl-1)vinyl ketone was prepared in accordance with the method of [11]; melting range, 27-29°C.

N,N-Diethyl-1-(β-aminopropionyl)adamantane Hydrochloride (IIa). A mixture of 5 g (28.4 mmole) of ketone V, 4.36 g (39.8 mmole) of diethylamine hydrochloride, 0.8 g of paraformaldehyde, and 15 ml of isoamyl alcohol is boiled for 1 h. Another 0.8 g of paraform is then added, and the mixture is boiled for 3 h. The mixture is cooled, 50 ml of ethyl ether is added, and the precipitate (white needles) is filtered off.

N-Ethyl-N-(adamantyl-1)-1-(β-aminopropionyl)adamantane Hydrochloride (IIb). A mixture of 3 g (17 mmole) of compound V, 4.7 g (22.1 mmole) of N-(adamantyl-1)-N-ethylamine hydrochloride, 0.8 g of paraform, and 15 ml of isopropyl alcohol is boiled for 1 h. Another 0.8 g of paraform is added, and the mixture is boiled for 3 h. After cooling, the precipitate (colorless plates) is filtered off.

N,N-Dibenzyl-1-(β-aminopropionyl)adamantane Hydrochloride (IIc). It is obtained as a cream-colored powder similarly to the hydrochloride IIb.

1-(β-Piperidinopropionyl)adamantane Hydrochloride (IId). It is obtained as colorless needles similarly to the hydrochloride IIb.

N-Phenyl-1-(β-aminopropionyl)adamantane (Ie). In 5 ml of water is dissolved 0.5 g (1.6 mmole) of β-amino ketone Ia, 0.3 g (3 mmole) of aniline is added to the solution, the latter is boiled for 3 h and cooled, and the precipitate is filtered off and washed with hot hexane. White plates of product Ie are obtained.

N-Nitroso-N-phenyl-1-(β-aminopropionyl)adamantane (IV). To a solution of 0.5 g (1.76 mmole) of β-amino ketone Ie in 5 ml of glacial acetic acid at 0-5°C is added dropwise a solution of 0.57 g (7.1 mmole) of $NaNO_2$ in 5 ml of water. The reaction mixture is stirred for 3 h at 0-5°C and poured onto ice, and the precipitate is filtered off, dried, and recrystallized from alcohol. Product IV is obtained in the form of white cotton.

3-(Adamantyl-1)-1-phenylpyrazoline (III). A. From Mannich bases IIa-d. A mixture of 3.3 mmole of β-amino ketone II hydrochloride, 4 mmole of phenylhydrazine, and 4 mmole of NaOH in 10 ml of 50% ethanol is boiled for 36 h. The precipitate is filtered off, washed with water, and recrystallized from alcohol. Pyrazoline III is obtained in the form of colorless plates.

B. From (adamantyl-1)vinyl ketone. Phenylhydrazine in an amount of 0.68 ml (6.4 mmole) is boiled for 3 h in 10 ml of ethanol. The precipitate formed on cooling is filtered off and recrystallized; yield, 13%.

C. From the nitroso derivative (IV). To a stirred suspension of 0.35 g (5.3 mmole) of zinc dust in 10 ml of ethanol at 60°C are added a hot solution of 0.55 g (1.8 mmole) of the nitroso derivative IV in 10 ml of ethanol and 2 ml of 50% acetic acid. The mixture is boiled for 5 min, the hot solution is filtered off, and the precipitate is washed with hot ethanol. Most of the ethanol is driven out of the filtrate at reduced pressure, and the residue is boiled with 15 ml of 20% NaOH for 1 h. Pyrazoline III is extracted with chloroform, the combined extract is dried with Na_2SO_4, the chloroform is driven off, and the residue is recrystallized from ethanol; yield, 28%.

REFERENCES

1. V. A. Drungilaite, L. V. Chekuolene, and V. I. Shilekyavichene, Tenth Conference on Synthetic and Natural Physiologically Active Compounds, October 2-6, 1990. Erevan (1990), p. 47.
2. A. M. Taha, N. M. Omar, S. M. Bayomi, E. M. Amar, and A. Afifi, J. Pharm. Sci., **63**, 395 (1974).
3. B. H. Chase and J. M. Evans, J. Chem. Soc. C, No. 12, 4825 (1964).
4. Stamper and Aycock, J. Am. Chem. Soc., **76**, 2786 (1954).
5. Organic Reactions [Russian translation], IL, Moscow (1948), Issue 1, p. 527.
6. Judi Lin, P. E. Rivett, and J. F. K. Wishere, Austral. J. Chem., **30**, 629 (1977).
7. R. Andrisano, A. Belotti, and E. Coghi, Ann. Chimica, **54**, 1104 (1964).
8. I. N. Zhmurova, R. I. Yurchenko, and O. M. Voitsekhovskaya, Zh. Org. Khim., **16**, 609 (1980).
9. G. I. Denis, Yu. V. Guryavichene, V. Machionite, and R. R. Bernotas, Zh. Org. Khim., **13**, 199 (1977).
10. Cy Xiping, Wu Yongren, and Yin Chenglie, J. Beijing Nomal. Nat. Sci., No. 3, 70 (1990).
11. F. N. Stepanov, Zh. Org. Khim., **2**, No. 4, 644 (1966).