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INVESTIGATION OF THE REACTION OF 1-ADAMANTYL BROMOMETHYL KETONE WITH AZOLES

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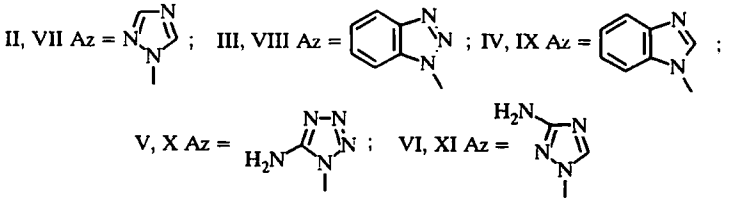
The reactions of 1-adamantyl bromomethyl ketone with 1,2,4-triazole, benzotriazole, benzimidazole, 5-aminotetrazole, and 3(5)-amino-1,2,4-triazole were investigated, and the respective N-alkylation products were obtained. The optimum conditions were determined for alkylation in the presence of sodium hydride in hexamethylphosphorotriamide.

Recently [1-3] papers have appeared on the reaction of halogeno- or hydroxyadamantanes with azoles (imidazole, tetrazole, pyrazole, benzotriazole, etc.), leading to the respective N-adamantylazoles, individual examples of which exhibit antiviral activity comparable with that of rimantadine. Reactions involving 1-adamantyl bromomethyl ketone (I), leading to adamantyl-substituted heterocycles such as thiophene [4], 2-mercaptoimidazole [5], thiazole [6], 2-NHR-thiazole [7], indole [8], imidazo[2,1-*b*]thiazole, imidazo[1,2-*a*]pyridine, indolizine [9], etc., have been represented fairly well in the literature. There have been comparatively few papers on the reactions of the ketone I with azoles. Thus, the synthesis of 1-(1-adamantanoylmethyl)imidazole from this compound and imidazole has been described [10], and the alkylation of uracil, adenine, 8-azaadenine, and theophylline has also been studied [11]. It should be noted 1-(1-adamantanoylmethyl)azoles are of interest not only as potential biologically active compounds but also as subjects for synthetic investigations.

Ad = 1-adamantyl, Az = azole



We have investigated for the first time the reaction of bromomethyl 1-adamantyl ketone (I) with a series of heterocyclic azoles: 1,2,4-Triazole (II), benzotriazole (III), benzimidazole (IV), 5-aminotetrazole (V), and 3(5)-amino-1,2,4-triazole (VI). It was shown that the reaction in dimethylformamide, tetrahydrofuran, and acetone in the presence of such bases as sodium hydroxide, potassium carbonate, sodium bicarbonate, and triethylamine leads to a mixture of products, and this greatly complicates the separation, purification, and identification of the individual components. The yields of the target products, separated by column chromatography, are only 10-15%. With a

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TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	Yield, %
		C	H	N			
VII	$C_{14}H_{19}N_3O$	68.49 / 68.34	7.79 / 7.81	17.05 / 17.73	113-114	0.47*	80
VIII	$C_{18}H_{21}N_3O$	72.99 / 73.19	7.27 / 7.17	14.12 / 14.23	245-247 (dec.)	0.68*	78
IX	$C_{19}H_{22}N_2O$	77.13 / 77.52	7.03 / 7.53	9.91 / 9.52	123-125	0.55*	81
X	$C_{13}H_{19}N_5O$	59.63 / 59.75	7.27 / 7.33	27.02 / 26.80	170-173 (dec.)	0.16*[2]	82
XI	$C_{14}H_{20}N_4O$	64.84 / 64.59	7.45 / 7.74	21.53 / 21.52	195-197 (dec.)	0.12*[2]	83

* 1:1 Hexane–acetone.

*[2] 1:3 Hexane–acetone.

TABLE 2. The IR and PMR Spectra of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}				PMR spectrum, δ, ppm			
	C=C	C=N	C=O	CH_2 in Ad	CH_2 in Ad, 12H, m	CH in Ad, 3H, s	$COCH_2$ 2H, s	H in heterocycle
VII	1465 1500	1610	1700	2850 2900	1.65-1.70	1.90	5.15	7.95 (1H, s, 3-H) 8.15 (1H, s, 5-H)
VIII	1450 1500	1600	1700	2850 2900	1.65-1.70	1.95	5.5	7.40-8.40 (4H, m, 4-, 5-, 6-, 7-H)
IX	1480 1510	1620	1690	2840 2900	1.65-1.70	1.90	5.45	7.20-7.65 (4H, m, 4-, 5-, 6-, 7-H) 8.1 (1H, s, 2-H)
X*	1450 1530	1570	1680	2850 2900	1.70-1.75	1.95	5.2	
XI*	1465 1530	1650	1680	2850 2900	1.65-1.70	1.90	5.2	7.5 (1H, s, 5-H)

* The presence of the NH_2 group in compounds X and XI is confirmed by a band at 3380 or 3390 cm^{-1} respectively in the IR spectra and also by a broad singlet for two protons at 6.00 or 6.50 ppm in the PMR spectra.

two-, three-, and fourfold excess of the azole without additional proton acceptors the target products cannot be obtained even with heating. The best results (yields of alkylated azoles 80-85%) are obtained with sodium hydride, which has strongly basic characteristics and is at the same time a weak nucleophilic, and with hexamethylphosphorotriamide as solvent. Under these conditions we synthesized 1-(1-adamantanoylmethyl)-1,2,4-triazole (VII), 1-(1-adamantanoylmethyl)benzotriazole (VIII), 1-(1-adamantanoylmethyl)-5-aminotetrazole (X), and 1-(1-adamantanoylmethyl)-3-amino-1,2,4-triazole (XI).

The structure of the obtained compounds was confirmed by IR and PMR spectroscopy (Table 2), and their purity was determined by TLC.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS-487C instrument at 80 MHz with HMDS as internal standard. The IR spectra were recorded on an IKS-29 instrument in KBr tablets. The reactions and the individuality of the substances were monitored by TLC on Silufol UV-254 plates (solvent systems 1:1 and 1:3 hexane–acetone).

1-(1-Adamantanoylmethyl)azoles (VII-XI) (General Procedure). To a solution of 10 mmol of the azole II-VI in 15 ml of hexamethylphosphorotriamide, cooled to 0°C, with stirring we slowly added 0.264 g (11 mmol) of sodium hydride which had been previously washed with hexane. The reaction mixture was kept at room temperature for 5 h and was then cooled to 0°C. A solution of 2.57 g (10 mmol) of the ketone in 10 ml of hexamethylphosphorotriamide was added dropwise. The mixture was stirred for 12 h, diluted with 25 ml of water, and extracted with ether (3 × 20 ml). The extract was washed with water and dried with sodium sulfate. The ether was distilled, and the residue was recrystallized from benzene.

The characteristics of the synthesized compounds are presented in Tables 1,2.

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