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SYNTHESIS OF SOME HETEROCYCLIC DERIVATIVES OF ADAMANTANE

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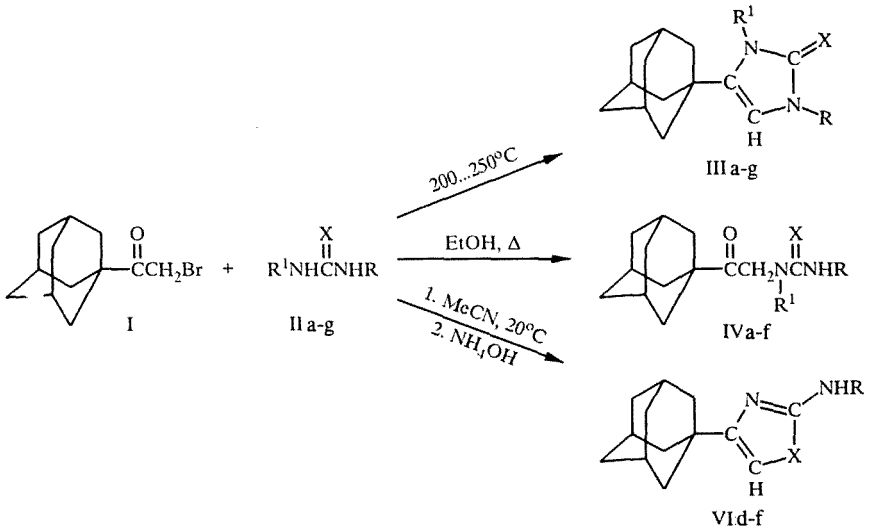
The reaction of bromomethyl(1-adamantyl)ketone with urea, thiourea, ammonium formate, and thiosemicarbazide gave a series of new imidazolin-2-ones, imidazolin-2-thiones and 2-aminothiazoles in the adamantane series.

It is known that aliphatic α-haloketones react with urea [1-3], thiourea [4-6], formamide [7, 8], and thiosemicarbazide [9, 10] with the formation of the corresponding 4-alkylimidazolinones, 2-aminothiazoles, imidazoles, oxazoles, and thiazolidines, of interest as biologically-active materials, and also as starting materials for the synthesis of other pharmaceuticals. Thus, 4-alkylimidazolinones are intermediates for the synthesis of betaines [1] showing high biological activity and 2-aminothiazoles, used for obtaining drug materials such as sulfathiazole [11, 12].

In order to synthesize hterocyclic compounds containing the adamantane cycle, we studied the interaction of bromomethyl(1-adamantyl)ketone (I) with ureas IIa-c, thiourea IId-g, ammonium formate, and thiosemicarbazide.

It was established that the reaction of bromide I with ureas IIa-c and thioureas IId-g in ethylene glycol at a temperature of 200-250°C in the presence of K_2CO_3 formed the 4-adamantylimidazolin-2-ones (IIIa-c) and -2-thiones (IIId-g), respectively.

Further, carying out the reaction in ethanol in the presence of Na_2CO_3 results in nucleophilic substitution and the formation of adamantyl-substituted ureas (IVa-c) and thioureas (IVd-g). Subsequent heating in ethylene glycol results in transformation into products IIIa-c and IIId-g.



II—IV, VI a X = O, R = H, b X = O, R = Ph, c X = O, R = Ac, d X = S, R = H, e X = S, R = Ph, f X = S, R = Ac, g X = S, R = Ph; II—IIIa-f R^1 = H, g R^1 = Ph

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The structures of compounds IIIa-g were confirmed by IR spectral data and elemental analysis.

In the IR spectra of the adamantylimidazolinones IIIa-c absorption bands were oserved in the 3400 (NH) and 1690 (C=O) cm^{-1} regions. The IR spectra of the adamantylimidazolinthiones IIId-f show absorption bands in the 3395-3450 (NH), 1508-1510 (N−C=S), and 1175-1189 (N=S) cm^{-1} regions.

The cyclocondensation reactions proceed in low yields (9-28%). Increasing the time of reaction and the temperature leads only to tarring of the starting bromomethyl(1-adamantyl)ketone.

Attempts to increase the yields of compounds IIIa-g in the reaction with urea initially gave (adamantanoyl-1-methylen)piperidine as described in [6], not the desired result.

The reaction of bromide I with thioureas IId-f under Hansch reaction conditions [6] led to the formation of the hydrobromides of 2-amino-4-adamantylthiazoles (Vd-f), which were converted to the free bases (VId-f) by treatment with $N\bar{H}_4OH$.

The product Vd was identical with 2-amino-4-adamantylthiazole prepared earlier [13]. The hydrobromides V, in addition to absorption bands characteristic of the amino groups (3400 cm^{-1}), also had absorption bands for the thiazole ring in the 1600-1640 and 1515-1540 cm^{-1} regions.

It is known that the reaction of bromide I with formamide gives the corresponding substituted imidazole [7], but our attempt at oxazole synthesis from this bromide by boiling in formamide with concentrated sulfuric acid according to [8] did not lead to the expected 4-adamantyloxazole (VII). The latter was obtained by heating I with ammonium formate in concentrated formic acid. For compound VII the IR spectrum was characterized by absorption bands at 3200 (NH) and 1605 (C=N) cm^{-1}.

VII

The reaction of α-haloketones with thiosemicarbazide proceeds unambiguously and depends upon the conditions of the reaction [9]. Thus, boiling in alcohol leads to thiazolidines [10], but in 2N hydrochloric acid, the thiosemicarbazone of the haloketone is formed [14], which is transformed into thiadiazoline upon heating in absolute alcohol [9] in concentrated hydrochloric acid [15, 16].

Heating bromoketone I in alcohol with thiosemicarbazide forms the thiosemicarbazone of bromomethyl(1-adamantyl)ketone (VIII), also obtained from the same reagents in 2N hydrochloric acid. Heating VIII in absolute alcohol and concentrated hydrochloric acid did not result in the formation of the cyclic product.

EXPERIMENTAL

Control of the course of the reactions and purity of the products was carried out by TLC on Silufol UV-254 plates. The IR spectra were recorded with Specord M-80 and IKS-22 instruments as thin films and in KBr pellets.

The characteristics of the synthesized compounds are presented in Table 1. Elemental analysis results corresponded with the calculated values.

4-(1-Adamantyl)-1-R-3-R′-imidazolyl-2-ones (IIIa-c) and -2-thiones (IIId-g). A mixture of 1.9 mmoles of bromide I, 13.3 mmoles of urea IIa-c or thiourea IId-g, 3.8 mmoles of K_2CO_3, and 3-5 ml of ethylene glycol was kept at 200-250°C for 70 min (for the case of IIa), 8 h (for IIb, d, e, and g), or 6 h (IIc, f). The reaction mixture was then cooled, diluted with water, and the product IIIa-g was filtered off, dried, and washed with ether, chloroform (IIIc) or toluene (IIIf).

1-[(Adamantyl-1)methylene]-1-R′-3-R-urea (IVa-c) and -thiourea (IVd-f). A mixture of 5.8 mmoles of bromide I, 8.7 mmoles of urea IIa, and 1.4 mmoles of Na_2CO_3 was boiled in 15 ml of alcohol for 8 h. The reaction mixture was then poured into water and the product IVa was filtered off, dried, washed with hexane, and recrystallized from alcohol. Analogously, boiling for 3 h in the presence of 1.9 mmoles of Na_2CO_3 a mixture of 0.78 mmole of bromide I and 1.5 mmoles of urea IIb, c or 1.2 mmoles of thiourea IIe, f in 5 ml of alcohol (or 10 ml in the case of IIb) gave products IVb, c and IVe, f, respectively, and 1.9 mmoles of bromide I with 2.85 mmoles of thiourea IId gave compound IVd.

Hydrobromide of 2-R-4-(1-Adamantyl)thiazole (Vd-f). To a solution of 2.85 mmmoles of thiourea IId-f in 5 ml of acetonitrile was added 1.9 mmoles of bromoketone I, the resulting mixture was kept for 10 min at room temperature (20 min for the case of IIf), and diluted with ethyl acetate. The product Id-f was filtered off and washed with ethyl acetate.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical Formula	mp, °C	R_f, Eluent	IR Spectrum, ν, cm^{-1}	Yield, %
IIIa	$C_{13}H_{18}N_2O$	295...297	0,358, Chloroform	2900, 2850, 1680,3150	28
IIIb	$C_{19}H_{22}N_2O$	185...187	0,254, Chloroform	2900, 2850, 1690, 3400	9
IIIc	$C_{15}H_{20}N_2O_2$	298...299	0,218, Alcohol	2900, 2840, 1690, 3400	98
IIId	$C_{13}H_{18}N_2S$	270...272	0,245, Chloroform	2900, 2850, 3450, 1508, 1180	65
IIIe	$C_{19}H_{22}N_2S$	153...155	0,118, Chloroform	2900, 2850, 3395, 1510, 1175	75
IIIf	$C_{15}H_{20}N_2OS$	192...193	0,178, Chloroform	2900, 2850, 3395, 1540, 1175	96
IIIg	$C_{25}H_{26}N_2S$	145...147	0,552, Acetone	2900, 2850, 3350, 1510, 1180	13
IVa	$C_{13}H_{20}N_2O_2$	168...169	0,339, Chloroform	2900, 2850, 1700, 3450, 1505, 1180	28
IVb	$C_{19}H_{24}N_2O$	55...56	0,250, Alcohol	2900, 2850, 1710, 3400	21
IVc	$C_{15}H_{22}N_2O_3$	222...224	0,616, Alcohol	2900, 2850, 1710, 3400	22
IVd	$C_{13}H_{20}N_2OS$	211...213	0,531, Alcohol	2900, 2850, 1700, 3350	82
IVe	$C_{19}H_{24}N_2OS$	286...287	0,758, Alcohol	2890, 2840, 1650, 3200	21
IVf	$C_{15}H_{22}N_2O_2S$	277...278	0,483, Alcohol	2890, 2840, 1700, 3390	19
Vd	$C_{13}H_{19}BrN_2S$	218...219*	0,367, Chloroform	2900, 2850, 3250, 1640, 1520	98
Ve	$C_{19}H_{23}BrN_2S$	304...305	0,627, Chloroform	2900, 2850, 3250, 1640, 1540	85
Vf	$C_{15}H_{21}BrN_2O$	258...259	0,383 Chloroform	2900, 2850, 3400, 1700, 1600, 1515	35
VId	$C_{13}H_{18}N_2S$	98...99	0,517, Alcohol	—	~100
VIe	$C_{19}H_{22}N_2S$	178...180	0,817, Alcohol	—	~100
VIf	$C_{15}H_{20}N_2OS$	283...285	0,766, Alcohol	—	~100
VII	$C_{13}H_{17}NO$	140...142	0,918, Alcohol	2900, 2850,1450	25
VIII	$C_{13}H_{20}BrN_3S$	230...232	0,741, Alcohol	2900, 2850, 3200, 1605, 1180	16

*mp 220°C [13].

4-(1-Adamantyl)oxazole (VII, $C_{13}H_{17}NO$). A mixture of 0.5 g (1.9 mmoles) of bromoketone I and 0.44 g (6.8 mmoles) of ammonium formate in 10 ml of concentrated formic acid was heated for 18 h, cooled to room temperature, neutralized with weak base solution, and extracted with ether. The ethereal extract was dried over Na_2SO_4. Distillation of the ether gave VII, which was recrystallized from alcohol.

Thiosemicarbazone of Bromomethyl(1-adamantyl)ketone (VIII, $C_{13}H_{20}N_3SBr$). A mixture of 0.5 g (1.9 mmoles) of bromoketone I and 0.18 g (1.9 mmoles) of thiosemicarbazide in 10 ml of alcohol was boiled for 2 h. The resulting precipitate of VIII was filtered off, washed with hot hexane, and recrystallized from alcohol.

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