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2-(ADAMANTAN-1-YL)IMIDAZO[1,2-*a*]-PYRIDINES AND THEIR DERIVATIVES

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A series of 1-adamantylimidazo[1,2-a]pyridines has been synthesized. The negative influence of electron-acceptor substituents in the pyridine ring on the alkylation of substituted 2-aminopyridines with bromomethyl (adamantan-1-yl) ketone has been demonstrated. Bromination of adamantylimidazo-[1,2-a]pyridines on boiling in liquid bromine or in the presence of a Lewis acid resulted in insertion of a bromine atom in the imidazole ring without affecting the adamantane nucleus. The compounds studied take part in the Ritter reaction despite the absence of an easily removed groups in the adamantane nucleus.

Keywords: 2-(adamantan-1-yl)imidazo[1,2-*a*]pyridines, bromination, nitrosation, the Ritter reaction.

In [1] we described an improved method, in comparison with that described elsewhere [2], for the preparation of 2-(adamantan-1-yl)imidazo[1,2-*a*]pyridine (**1a**) and a number of its conversions. Since imidazopyridines and many derivatives of adamantane possess notable physiological activity, an important role in which is played by substitutions in the molecules, we have carried out work on the synthesis of various functional derivatives of compound **1a**.

The formation of imidazopyridines is known to be a two-step process [3]. It was shown earlier that the first step in the reaction – the alkylation of 2-aminopyridine with bromomethyl (adamantan-1-yl) ketone was successfully carried out with a high yield of 1-[3-adamantan-1-yl)-2-oxoethyl]-2-aminopyridinium bromide (**2a**) by boiling the reagents for 1 h in ethanol [2] or ethyl acetate [1].

We have established that the introduction of an electron-acceptor substituent into the pyridine ring considerably hinders the reaction. When 2-aminopyridine, 2-amino-3-methylpyridine, or 2-amino-4-methylpyridine are heated with bromomethyl (adamantan-1-yl) ketone in ethyl acetate for 1 h, the yields of compounds **2a-c** varied within the limits of 80-95% (compare [1, 4] and the Experimental], whereas with 2-amino-5-chloro- and 2-amino-6-bromopyridine the corresponding alkylation products – compounds **2d,e** – were obtained in yields of only 50%. The yields of compounds **2d,e** were effectively unchanged after heating the reactants for 3 h. In the case of 2-amino-5-bromo-3-trifluoromethylpyridine the formation of only a negligible amount of compound **2f** was observed after 1 h and the yield reached 42% only after 5 h.

The second stage – cyclization – occurred effectively in acetic acid, but not in aqueous sodium bicarbonate solution, as was previously described [2]. We succeeded in obtaining adamantanylimidazopyridine **1a** in a yield of 84% on heating compound **2a** in acetic acid for just 1 h (in [2] the yield was 28%). We obtained compounds **1b-f** in acetic acid (Table 1). We note that an electron-accepting substituent in the pyridine ring appeared to have a negative effect in the cyclization stage. A longer reaction time was required for compounds **1d,e,f** than for compound **1a** (see Experimental).

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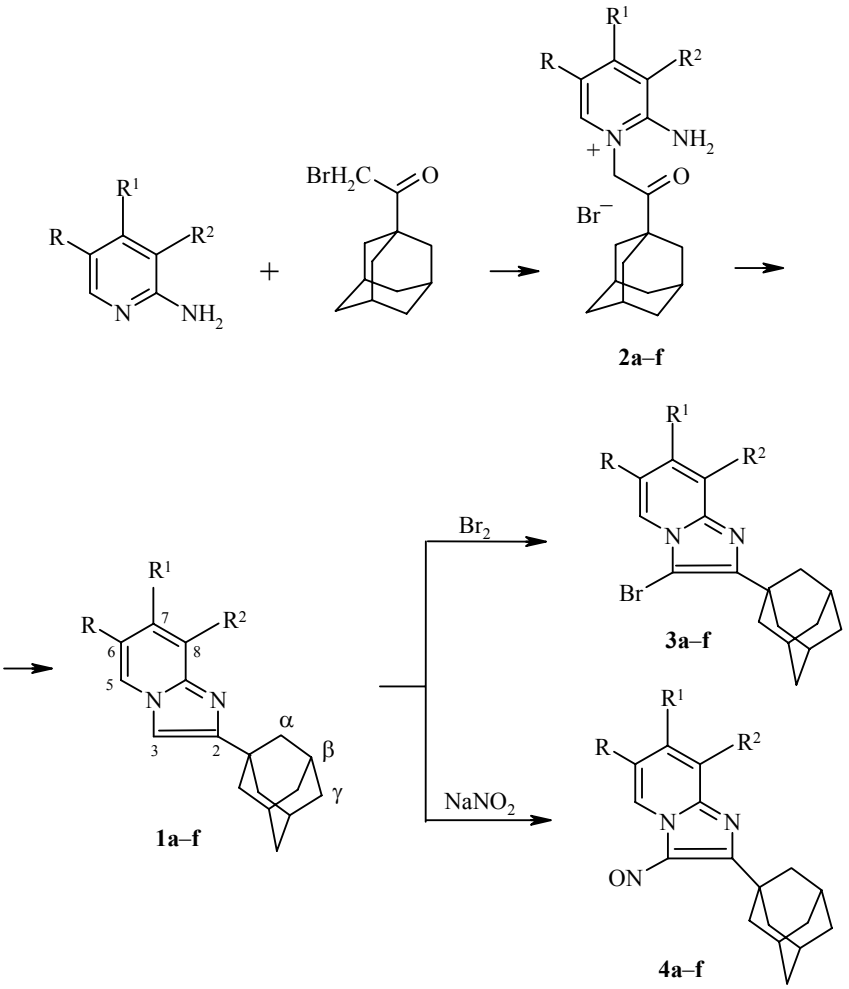
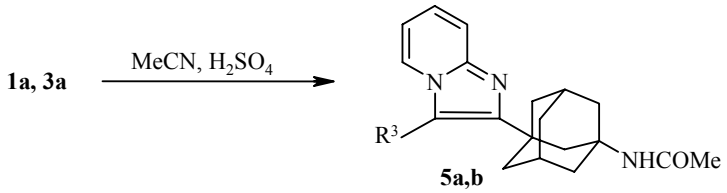


a-**c** R = H, **d** R = Cl, **e** R = Br; **a**, **c**-**e** R^1 = H, **b** R^1 = Me; **a**, **b**, **d**, **e** R^2 = H, **c** R^2 = Me, **f** R^2 = Cl

Compounds **1a-f** were shown to have properties characteristic of imidazopyridines [3]. For example they were converted to the corresponding 3-bromoimidazopyridines (**3a-e**) on treatment with elemental bromine and into the corresponding 3-nitrosoimidazopyridines (**4a-e**) on treatment with sodium nitrite. We had shown previously that bromination of compound **1a** under conditions normally used to prepare 3-bromoimidazopyridines (see [3]), the yield of **3a** was 25%. When **1a** was boiled in liquid bromine for 4 h the yield of the bromination product **3a** was successfully increased to 71%. Note that even when conditions were used which facilitate the introduction of a bromine atom into the adamantane nucleus, containing a strong electron-accepting substituent (see [5]), we did not observe introduction of a bromine atom into the adamantane nucleus. After boiling compound **1a** in liquid bromine in the presence of an excess of aluminum chloride for 3 h, we isolated compound **3a**. It is possible that the heterocyclic system in the imidazopyridines studied binds the Lewis acid as a stable complex which prevents its catalytic influence on the process of substitution in the adamantane nucleus.

We found that the absence of a bromine atom or other good leaving group in the adamantane nucleus did not change their participation in the Ritter reaction.



5a,b

a R^3 = H, **b** R^3 = Br

For example, compounds **1a** and **3a** were converted into the corresponding acetamino derivatives **5a,b** on reaction with acetonitrile in sulfuric acid. However neither the Koch reaction nor phosphorylation with phosphorus trichloride [6] was successful which, in our view, is explained by the milder conditions for carrying out these reactions, which are incapable of forming the corresponding adamantyl cation necessary for these conversions.

TABLE 1. Characteristics of Compounds **1-4**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (aqueous ethanol)	Yield, %
		N	Cl	Br		
1b	$C_{18}H_{22}N_2$	10.43 / 10.52			153-155	80
1d	$C_{17}H_{19}ClN_2$		12.30 / 12.38		271-273	72
1e	$C_{17}H_{19}BrN_2$			23.92 / 24.14	247-249	87
1f	$C_{18}H_{18}ClF_3N_2$	7.74 / 7.89			161-163	75
2a	$C_{17}H_{23}BrN_2O$			22.52 / 22.77	238-240*	81
2c	$C_{18}H_{25}BrN_2O$			21.71 / 21.89	226-228*	77
2d	$C_{17}H_{22}BrClN_2O$			20.52 / 20.73	272-274*	58
2e	$C_{17}H_{22}Br_2N_2O$			18.40 / 18.59	300-301*	52
2f	$C_{18}H_{21}BrClF_3N_2O$			17.51 / 17.62	260-261*	42
3a	$C_{17}H_{19}BrN_2$			24.16 / 24.14	168-170	85
3b	$C_{18}H_{21}BrN_2$			22.90 / 23.16	168-170	69
3d	$C_{17}H_{18}BrClN_2$	7.60 / 7.66			135-137	46
3e	$C_{17}H_{18}Br_2N_2$			38.60 / 38.99	165-167	49
4a	$C_{17}H_{19}N_3O$	14.79 / 14.94			243-245	45
4b	$C_{18}H_{21}N_3O$	14.38 / 14.23			233-235	48
4c	$C_{18}H_{21}N_3O$	14.01 / 14.23			185-187	63
4d	$C_{17}H_{18}ClN_3O$		10.98 / 11.24		215-217	50
4e	$C_{17}H_{18}BrN_3O$			21.92 / 22.20	243-245	45

* Compounds **2a-f** were precipitated from ethanol with ether.

TABLE 2. ^{1}H NMR Spectra of Compounds **1, 3,** and **4**

Com-pound	R	R^1	R^2	R^3	Chemical shifts, δ, ppm, DMSO-d_6 (*J*, Hz)
1a	H	H	H	H	1.75 (6H, s, H-β); 1.95 (6H, s, H-α); 2.04 (3H, s, H-γ); 6.80 (1H, t, ^3J = 8.0, H-6); 7.15 (1H, t, ^3J = 10.0, H-7); 7.45 (1H, d, ^3J = 10.0, H-8); 7.62 (1H, s, H-3); 8.43 (1H, d, ^3J = 8.0, H-5)
1c	H	H	CH_3	H	1.75 (6H, s, H-β); 1.95 (6H, s, H-α); 2.03 (3H, br. s, H-γ); 2.45 (3H, s, CH_3); 6.69 (1H, t, ^3J = 6.5, H-6); 6.95 (1H, d, ^3J = 6.5, H-7); 7.58 (1H, s, H-3); 8.28 (1H, d, ^3J = 6.7, H-5)
1d	Cl	H	H	H	1.75 (6H, s, H-β); 1.94 (6H, s, H-α); 2.05 (3H, br. s, H-γ); 7.40 (1H, d, ^3J = 9.4, H-8); 7.67 (1H, d, ^3J = 9.4, H-7); 7.73 (1H, s, H-3); 8.83 (1H, s, H-5)
1e	Br	H	H	H	1.75 (6H, s, H-β); 1.93 (6H, s, H-α); 2.04 (3H, br. s, H-γ); 7.37 (1H, d, ^3J = 9.5, H-8); 7.54 (1H, d, ^3J = 9.5, H-7); 7.67 (1H, s, H-3); 8.85 (1H, s, H-5)
1f	CF_3	H	Cl	H	1.76 (6H, s, H-β); 1.97 (6H, s, H-α); 2.06 (3H, br. s, H-γ); 7.83 (1H, s, H-7); 7.96 (1H, s, H-3); 9.22 (1H, s, H-5)
3a	H	H	H	Br	1.78 (6H, s, H-β); 2.09 (6H, s, H-α); 2.18 (3H, br. s, H-γ); 7.17 (1H, t, ^3J = 7.0, H-6); 7.47 (1H, t, ^3J = 7.0, H-7); 7.63 (1H, d, ^3J = 7.0, H-8); 8.41 (1H, d ,^3J = 7.0, H-5)
3c	H	H	CH_3	Br	1.76 (6H, s, H-β); 2.06 (3H, br. s, H-γ); 2.16 (6H, br. s, H-α); 2.52 (3H, s, CH_3); 6.95 (1H, t, ^3J = 7.0, H-6); 7.15 (1H, d, ^3J = 7.0, H-7); 8.16 (1H, d, ^3J = 7.0, H-5)
3d	Cl	H	H	Br	1.78 (6H, s, H-β); 2.11 (6H, s, H-α); 2.17 (3H, br. s, H-γ); 7.59 (1H, d, ^3J = 6.0, H-8); 7.65 (1H, t, ^3J = 6.0, H-7); 8.50 (1H, s, H-5)
3e	Br	H	H	Br	1.79 (6H, s, H-β); 2.12 (6H, s, H-α); 2.17 (3H, br. s, H-γ); 7.58 (1H, d, ^3J = 6.0, H-8); 7.61 (1H, d, ^3J = 6.0, H-7); 8.50 (1H, s, H-5)
4a	H	H	H	NO	1.84 (6H, s, H-β); 2.14 (3H, br. s, H-γ); 2.42 (6H, s, H-α); 7.46 (1H, t, ^3J = 7.0, H-6); 7.97 (1H, d, ^3J = 7.0, H-7); 8.02 (1H, d, ^3J = 7.0, H-8); 9.85 (1H, d, ^3J = 8.0, H-5)
4c	H	H	CH_3	NO	1.83 (6H, s, H-β); 2.14 (3H, br. s, H-γ); 2.39 (6H, s, H-α); 2.48 (3H, s, CH_3); 7.33 (1H, d, ^3J = 7.0, H-6); 7.78 (1H, s, H-8); 9.72 (1H, d, ^3J = 7.0, H-5)
4b	H	CH_3	H	NO	1.82 (6H, s, H-β); 2.12 (3H, br. s, H-γ); 2.39 (6H, s, H-α); 2.50 (3H, s, CH_3); 7.33 (1H, d, ^3J = 7.0, H-6); 7.89 (1H, s, H-8); 9.72 (1H, d, ^3J = 7.0, H-5)
4d	Cl	H	H	NO	1.83 (6H, s, H-β); 2.14 (6H, s, H-α); 2.42 (3H, br. s, H-γ); 8.01 (1H, d, ^3J = 9.0, H-8); 8.15 (1H, d, ^3J = 9.0, H-7); 9.90 (1H, s, H-5)
4e	Br	H	H	NO	1.85 (6H, s, H-β); 2.14 (3H, br. s, H-γ); 2.42 (6H, s, H-α); 7.91 (1H, d, ^3J = 9.0, H-8); 8.12 (1H, d, ^3J = 9.0, H-7); 9.94 (1H, s, H-5)

EXPERIMENTAL

^{1}H NMR spectra were recorded with TMS as internal standard on a Bruker WP-200 (200 MHz) instrument.

2-(Adamantan-1-yl)imidazo[1,2-*a*]pyridine (1a) [1], 2-(Adamantan-1-yl)-8-methylimidazo[1,2-*a*]-pyridine (1c), 2-(Adamantan-1-yl)-6-chloroimidazo[1,2-*a*]pyridine (1d), 2-(Adamantan-1-yl)-6-bromo-imidazo[1,2-*a*]pyridine (1e), 2-(Adamantan-1-yl)-8-chloro-6-trifluoromethylimidazo[1,2-*a*]pyridine (1f). A solution of 10 mmol of the corresponding pyridinium bromide in acetic acid was boiled for 1 h (compounds **1a,c**), 1.5 h (compounds **1d,e**), or 3h (compound **1f**), a precipitate was separated, then treated with 40% sodium hydroxide solution, and washed with water.

1-(3-(Adamantan-1-yl)-2-oxoethyl]-2-aminopyridinium Bromide (2a), 1-(3-(Adamantan-1-yl)-2-oxoethyl]-2-amino-3-methylpyridinium Bromide (2c), 1-(3-(Adamantan-1-yl)-2-oxoethyl]-2-amino-5-chloropyridinium Bromide (2d), 1-(3-(Adamantan-1-yl)-2-oxoethyl]-2-amino-5-bromopyridinium Bromide (2e), 1-(3-(Adamantan-1-yl)-2-oxoethyl]-2-amino-3-chloro-5-trifluoromethylpyridinium Bromide (2f). An equimolar amount of bromomethyl (adamantan-1-yl) ketone in ethyl acetate (3 ml) was added in portions and with stirring to a boiling solution of 3.2 mmol of the corresponding 2-aminopyridine in ethyl acetate, the reaction mixture was boiled for 1 h (compounds **2a,c**), 3 h (compounds **2d,e**), or 5 h (compound **2f**) and the precipitate was separated.

2-(Adamantan-1-yl)-3-bromoimidazo[1,2-*a*]pyridine (3a) [1], 2-(Adamantan-1-yl)-3-bromo-7-methylimidazo[1,2-*a*]pyridine (3b), 2-(Adamantan-1-yl)-3-bromo-8-methylimidazo[1,2-*a*]pyridine (3c), 2-(Adamantan-1-yl)-3-bromo-6-chloroimidazo[1,2-*a*]pyridine (3d), 2-(Adamantan-1-yl)-3,6-Dibromo-imidazo[1,2-*a*]pyridine (3e), 2-(Adamantan-1-yl)-3-bromo-8-chloro-6-trifluoromethylimidazo[1,2-*a*]-pyridine (3f) (Table 1). A. A solution of bromine (1.2 mmol) in chloroform (1.5 ml) was added with stirring to a solution of the corresponding imidazopyridine (1.2 mmol) in chloroform (2 ml), the reaction mixture was stirred for a further hour and the precipitate was separated, treated with 2 M sodium hydroxide solution, and washed with water. Compound **3b** (yield 37%) was identical in mp and spectral properties to that described elsewhere [4].

B. Bromine (2.5 ml) was added with stirring to compound **1a** (2 mmol), the reaction mixture was boiled for 4 h and then poured into a mixture of crushed ice and sodium metabisulfite. The precipitate was separated on the following day and washed with water.

2-(Adamantan-1-yl)-3-nitrosoimidazo[1,2-*a*]pyridine (4a) [1]**, 2-(Adamantan-1-yl)-7-methyl-3-nitrosoimidazo[1,2-*a*]pyridine (4b), 2-(Adamantan-1-yl)-8-methyl-3-nitrosoimidazo[1,2-*a*]pyridine (4c), 2-(Adamantan-1-yl)-6-chloro-3-nitrosoimidazo[1,2-*a*]pyridine (4d), 2-(Adamantan-1-yl)-6-bromo-3-nitrosoimidazo[1,2-*a*]pyridine (4e), 2-(Adamantan-1-yl)-8-chloro-3-nitroso-6-trifluoromethylimidazo-[1,2-*a*]pyridine (4f)** (Table 1). A solution of sodium nitrite (1.2 mmol) in water (1 ml) was added with stirring to a solution of the corresponding compound **1** (1 mmol) in glacial acetic acid while keeping the temperature between 0 and 5°C. Stirring was continued for a further hour and the reaction mixture was then poured into water (20 ml). The precipitate was separated on the following day and washed with water.

2-(1-Acetaminoadamantan-3-yl)imidazo[1,2-*a*]pyridine (5a) and 2-(1-Acetaminoadamantan-3-yl)-3-bromoimidazo[1,2-*a*]pyridine (5b) [1]. Compound **1a** or **3a** (2 mmol) was added with stirring to a mixture of conc. H_2SO_4 (10 ml) and oleum (5 ml), cooled to 0-5°C. Acetonitrile (3 ml) was then added at 10-15°C. The reaction mixture was kept with stirring for 9 h at 45-50°C, poured onto ice, neutralized with sodium bicarbonate, and the precipitate was separated. For compound **5a** yield 40%; mp105-107°C (aqueous dioxane). ^{1}H NMR spectrum ($(CD_3)_2SO_2$), δ, ppm (*J*, Hz): 1.67 (2H, s , H-β); 1.75 (3H, s, CH_3); 1.85 (4H, s, H-α); 1.96 (4H, s, H-δ); 2.02 (2H, s, H-ε); 2.18 (2H, br. s, H-γ); 6.75 (1H, t, ^3J = 7.0, H-6); 7.15 (1H, dd, ^3J = 7.0, ^3J = 7.5, H-7); 7.55 (1H, s, H-3); 7.78 (1H, s, NH); 8.40 (1H, s, ^3J = 7.0, H-5). Found, %: N 13.38. $C_{19}H_{23}N_3O$. Calculated, %: N 13.58.

For compound **5b** yield 65%; mp 159-160°C (dioxane–ethanol–water). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.70 (2H, s, H-β); 1.88 (3H, s, CH_3); 2.07-2.25 (10H, m, H-α,γ,δ); 2.38 (2H, s, H-ε); 5.31 (1H, s, NH); 6.85 (1H, t, ^3J = 7.0, H-6); 7.17 (1H, d, ^3J = 7.0, H-7); 7.56 (1H, d, ^3J = 7.0, H-8). Found, %: N 10.69. $C_{19}H_{22}BrN_3O$. Calculated, %: N 10.82.

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