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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Preparative Synthesis of Functionally Substituted Esters of 1-Adamantanecarboxylic Acid

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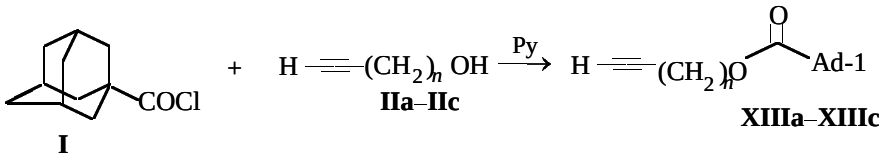
Abstract—A procedure was developed for preparing 1-adamantanecarboxylic acid esters functionally substituted in the alcoholic moiety.

Compounds of the adamantane series exhibit high and diverse biological activity. Effective drugs based on adamantane have been developed, such as Midantane, Memantine, Gludantan, Remantadine, and Adapromine [1]. Some of adamantane derivatives exhibit antiviral, curare-like, myorelaxing, anti-choline esterase, psychostimulating, neurotropic, and local anesthetic activity [2]; compounds with a high surface activity were also found [3]. The main synthetic route to adamantane derivatives involves chemical modificatiomn of substituents in the hydrocarbon framework. Nitrogen-containing adamantane derivatives have been studied most comprehensively [4, 5].

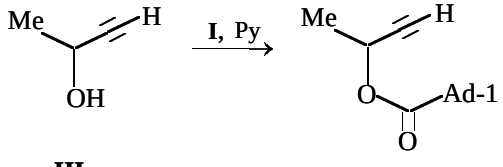
One of promising routes to new adamantane-containing biologically active compounds is preparation of esters. In this case, it is possible to combine in one molecule an adamantane moiety with other functional groups, e.g., aromatic, acetylenic, or bicyclic [6].

Here we report on a new convenient route to functionally substituted esters of 1-adamantanecarboxylic acid, involving the reactions of 1-adamantylcarbonyl chloride **I** with alcohols **II**–**XII** in diethyl ether in the presence of pyridine [7]. Esters **XIII**–**XXIII** are formed under mild conditions (room temperature). No prolonged stirring, heating, or precipitation is required; the reactants can be mixed in any order. The reaction, performed in sealed vessels, is complete in 24–36 h; the yield of esters is 65–83%.

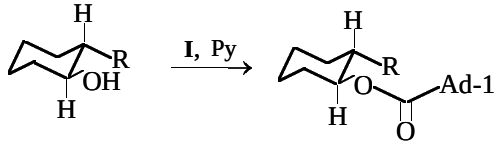


I **IIa**–**IIc** **XIIIa**–**XIIIc**

II, **XIII**, n = 1 (**a**), 2 (**b**), 3 (**c**)

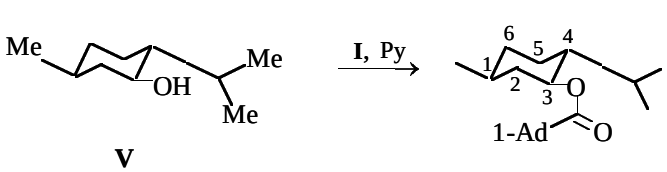


III **XIV**

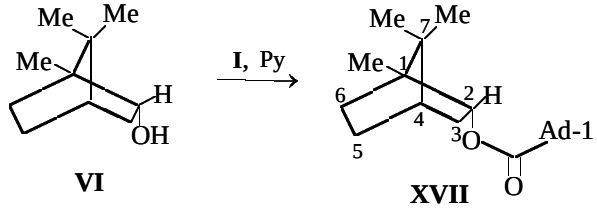


IVa, **IVb** **XVa**, **XVb**

IV, **XV**, R = H (**a**), Me (**b**)



V **XVI**



VI **XVII**

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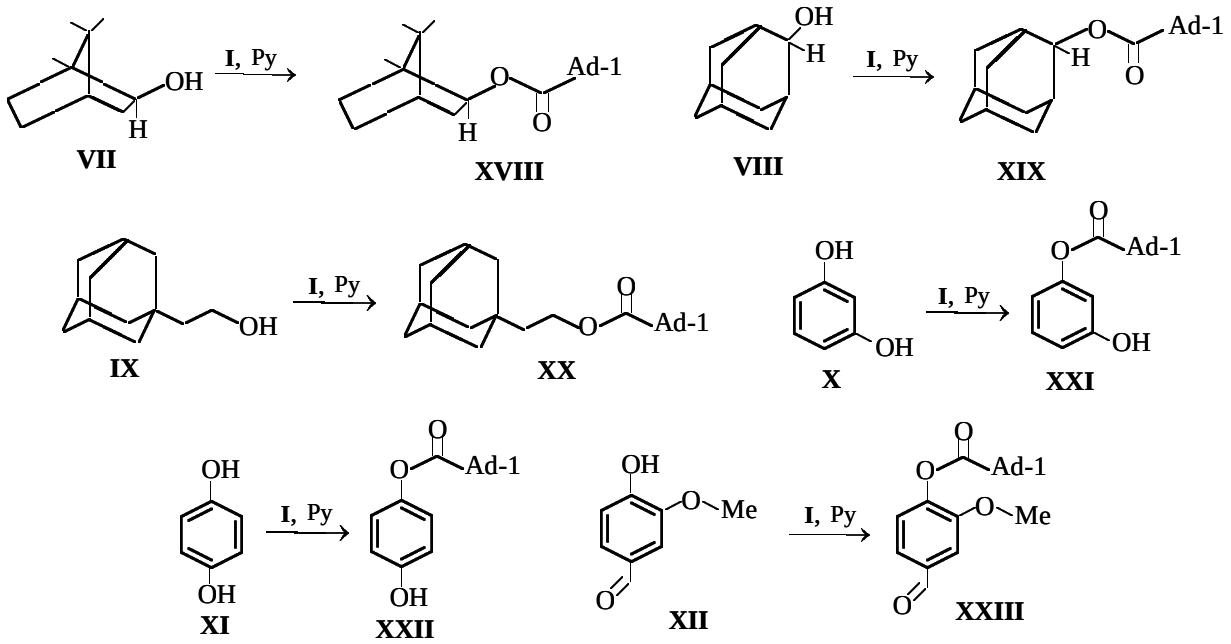

Primary alcohols (**IIa**–**IIc**, **IX**), secondary alcohols (**III**–**VIII**), and phenols (**X**–**XII**) are readily esterified with chloride **I**. Dihydric phenols **X** and **XI** form momoesters only, even at the reactant ratio **I** : (**X** or **XI**) = 3 : 1. Tertiary alcohols (e.g., 2-methyl-2-propanol or 2-methyl-3-butyn-2-ol) do not form the corresponding esters even under severe conditions (prolonged refluxing in dioxane at 100–102°C in the presence of pyridine).

1-Adamantanecarboxylic acid esters are colorless viscous liquids (**XIIIa**, **XVb**, **XVI**) or crystalline substances (**XIIIb**, **XIIIc**, **XIV**, **XVa**, **XVII**–**XXII**); their characteristics are listed in the table.

The IR and NMR spectra of the synthesized esters are consistent with their structure. The IR spectra contain stretching vibration bands of the C=O (1727 ± 5; for **XXIII**, 1742 cm^{-1}) and C–O (1225 ± 15 and 1070 ± 15; for **XXIII**, 1290 and 1155 cm^{-1}) groups. The spectra of acetylenic derivatives **XIIIa**–**XIIIc** and **XIV** also contain absorption bands at 3280 ± 25 (≡C–H) and 2150 ± 15 cm^{-1} (C≡C). Aromatic esters **XXI**–**XXIII** exhibit C–H absorption bands at 3090, 3070, 3030 ± 5; 858, 777, 767, and 680 (**XXI**); 830 and 800 (**XXII**); 865 and 785 cm^{-1} (**XXIII**), and also the bands belonging to the aromatic ring at 1604 and 1487 (**XXI**); 1600 and 1511 (**XXII**); 1601, 1593, and 1509 cm^{-1} (**XXIII**). The spectra of phenols **XXI** and **XXII** contain O–H absorption bands at 3375 (**XXI**) and 3445 cm^{-1} (**XXII**), and also C–OH bands at 1065 ± 5 cm^{-1}. The IR spectrum of aromatic methoxy aldehyde **XXIII** contains the bands of the HC=O (1697 cm^{-1}) and C–O–C (1110 cm^{-1}) groups.

The ^1H NMR spectra of all the esters **XIII**–**XXIII** contain multiplets at 1.6 (6H), 1.9 (6H), and 2.1 ppm (3H), typical of 1-substituted adamantane derivatives. Compounds **XIIIa**–**XIIIc** and **XIV** containing terminal acetylenic groups also give a proton signal at 2.0–2.4 ppm. The CH_2O proton signals in the spectra of **XIIIa**–**XIIIc** and **XX** are observed at 4.1 ppm, and in esters **XV**–**XIX** derived from alicyclic alcohols the α-CH proton in the alcoholic residue gives a signal at 4.7–4.9 ppm. The spectra of these esters also contain signals characteristic of cyclohexane (**XV**), menthane [**XVI**; a doublet of the C^1–CH_3 protons at 0.74 ppm (^3J 1.6 Hz) and a doublet of two methyl groups in the isopropyl substituent at 0.94 ppm (^3J 6.7 Hz)], and camphane [**XVII, XVIII**; singlets of three methyl groups at C^1 (0.8 ppm) and C^7 (1.0 ppm) atoms]. The aryl protons in **XXI**–**XXIII** are manifested at 6.4–7.5 ppm. Also, the spectrum of **XXIII** exhibits a CHO singlet at 9.9 ppm and an OCH_3 singlet at 3.9 ppm.

EXPERIMENTAL

The IR spectra were recorded on a Protege-460 IR Fourier spetrophotometer (Nicolet) from thin films (**XIIIa**, **XVb**, **XVI**) or KBr pellets. The ^1H NMR spectra were recorded on a Tesla BS-567A spectrometer (100 MHz) from 5% solutions in $CDCl_3$, with TMS as internal reference.

The molecular weight was determined by cryoscopy in benzene.

Properties of esters **XIII**–**XXIII**

Ester	Yield, %	mp, °C	Found, %		Formula	Calculated, %		*M*	
			C	H		C	H	found	calculated
XIIIa	79	1.0791* 1.5060	77.28	8.56	$C_{14}H_{18}O_2$	77.03	8.31	214.1	218.3
XIIIb	77	48–49	77.84	8.95	$C_{15}H_{20}O_2$	77.55	8.68	225.8	232.3
XIIIc	83	56–57	78.44	9.19	$C_{16}H_{22}O_2$	78.01	9.00	239.0	246.3
XIV	81	46–47	77.93	8.90	$C_{15}H_{20}O_2$	77.55	8.68	227.4	232.3
XVa	70	29–30	78.13	10.18	$C_{17}H_{26}O_2$	77.82	9.99	249.3	262.4
XVb	80	1.0409* 1.5025	78.45	10.41	$C_{18}H_{28}O_2$	78.21	10.21	262.9	276.4
XVI	78	1.0237* 1.4990	79.50	10.93	$C_{21}H_{34}O_2$	79.19	10.76	306.7	318.5
XVII	82	176–177	80.03	10.25	$C_{21}H_{32}O_2$	79.70	10.19	303.2	316.5
XVIII	84	145–146	80.01	10.32	$C_{21}H_{32}O_2$	79.70	10.19	308.6	316.5
XIX	72	172–173	80.34	9.85	$C_{21}H_{30}O_2$	80.21	9.62	307.0	314.5
XX	82	82–83	80.88	10.12	$C_{23}H_{34}O_2$	80.65	10.00	330.1	342.5
XXI	65	107–108	75.22	7.65	$C_{17}H_{20}O_3$	74.97	7.40	260.4	272.3
XXII	68	179–180	75.21	7.60	$C_{17}H_{20}O_3$	74.97	7.40	262.3	272.3
XXIII	79	118–119	72.71	7.11	$C_{19}H_{22}O_4$	72.59	7.05	303.1	314.4

* Numerator, d_{20}^{20}; denominator, n_D^{20}.

Column chromatography was performed with neutral alumina, Brockmann grade II.

1-Adamantanecarboxylic acid chloride **I** was prepared by refluxing 1-adamantanecarboxylic acid with a 1.5-fold excess of $SOCl_2$ in benzene [5].

1-Adamantanecarboxylic acid esters XIII–**XXIII**. Anhydrous pyridine (3.5 mmol) was added to a solution of 3 mmol of chloride **I** and 3 mmol of alcohols or phenols **II**–**XII** in 70 ml of absolute diethyl ether. The mixture was slightly shaken and allowed to stand at 18–23°C for 24–36 h. The precipitate of pyridine hydrochloride was filtered off and washed with 30 ml of diethyl ether; the combined filtrates were washed with water and saturated aqueous solution of sodium hydrogen carbonate. The ether solution was dried over $CaCl_2$, the solvent was distilled off, and the residue was dried in a vacuum. Ethers **XIIIa**, **XVb**, and **XVI** were purified by column chromatography on Al_2O_3, eluent hexane. Compounds **XIIIb**, **XIIIc**, **XIV**, **XVa**, and **XVII**–**XXIII** were purified by low-temperature crystallization from hexane.

CONCLUSIONS

(1) Functionally substituted primary and secondary alcohols and phenols are readily esterified under mild conditions with 1-adamantanecarboxylic acid chloride in the presence of pyridine.

(2) Dihydric phenols form monoesters only; tertiary alcohols do not undergo esterification.

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REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2001, vols. 1, 2.
2. Morozov, I.S., Petrov, V.I., and Sergeeva, S.A., *Farmakologiya adamantanov* (Pharmacology of Adamantanes), Volgograd: Volgograd. Med. Akad., 2001.
3. Vashkevich, E.V., Yurashevich, N.Ya., Kozlov, N.G., *et al.*, *Zh. Prikl. Khim.*, 2001, vol. 74, no. 11, pp. 1833–1839.
4. Bagrii, E.I., *Adamantany: poluchenie, svoistva, primenenie* (Adamantanes: Preparation, Properties, Applications), Moscow: Nauka, 1989.
5. Ford, R.C., *Adamantane: The Chemistry of Diamond Molecules*, New York: Dekker, 1976.
6. Schulte, K. and Rucker, G., *Prog. Drug Res.*, 1970, vol. 14, pp. 387–563.
7. Dikusar, E.A., Yuvchenko, A.P., Zvereva, T.D., *et al.*, *Zh. Obshch. Khim.*, 1996, vol. 66, no. 11, pp. 1813–1817.