Reaction of 1-Formyladamantane with Heterocyclic Compounds. Mass Spectra, Antibacterial and Antifungal Activity

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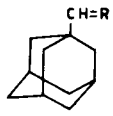
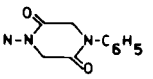
1-Formyladamantane reacts with some amino derivatives to give I, II, III and IV. 3-Substituted 2-adamantyl-4-thiazolidinones (V), (VI) and (VII) were obtained by reacting the above compounds with mercaptoacetic acid. Their structure was established by ir, pmr and mass spectroscopy. All compounds synthesized inhibit the growth of gram-negative and gram-positive bacteria and fungi.

J. Heterocyclic Chem., 16, 347 (1979).

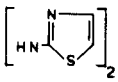
Several adamantane derivatives are known as pharmacologically active agents (1), and have particularly shown antiviral activity (2-3). In this paper we describe some new adamantane derivatives whose synthesis was carried out from 1-formyladamantane and equimolar amounts of biologically active amino derivatives, such as isonicotinylhydrazine, 1-amino-4-phenyl-2,5-piperazinedione, thiosemicarbazide, and 2-aminothiazole. Schiff bases (I) (II) and (III), or a diamino compound (IV) are obtained, depending upon the starting amino derivative, in agreement with previous reports concerning benzaldehyde and 2-aminothiazole (4).



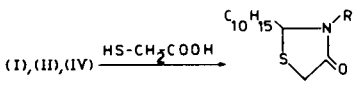
(I) R= N-NH-CO-

(II) R= 

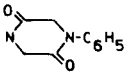
(III) R= N-NH-CS-NH_2

(IV) R= 

Condensation of I, II and IV with mercaptoacetic acid gave the 3-substituted 2-adamantyl-4-thiazolidinones (V-VII), with the exception of III, which did not react, as already observed with other thiosemicarbazones (5). Previous papers, wherein the synthesis and biological activity of several 4-thiazolidinones were reported (6a-b), prompted us to investigate the influence of the adamantane system on the thiazolidinone nucleus.



(V) R= NH-CO- 

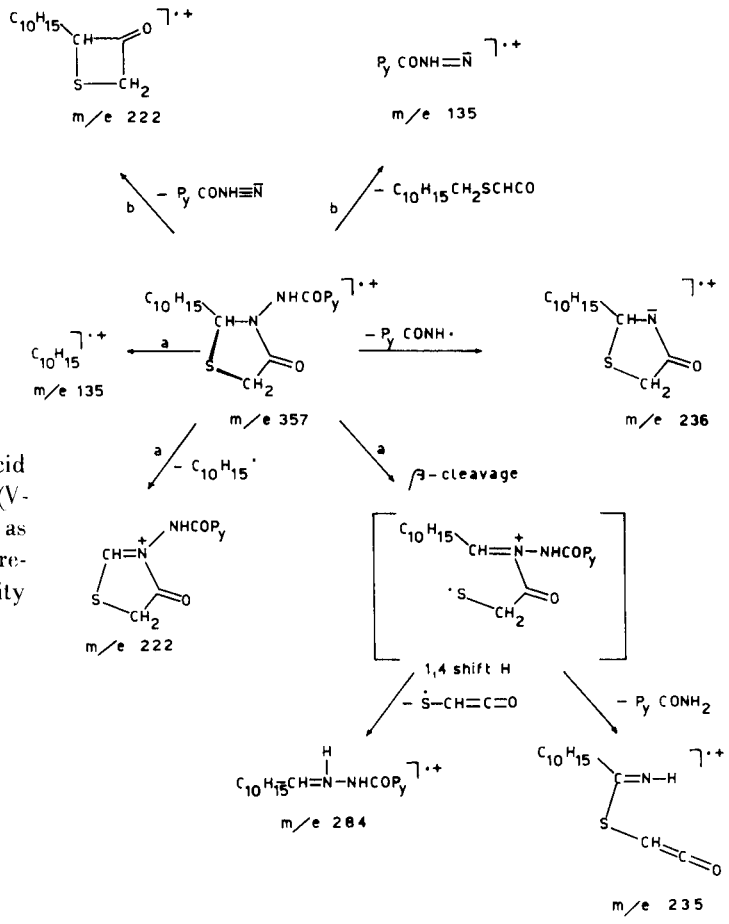
(VI) R= 

(VII) R= 

The structure of all synthesized compounds was established by analytical data as well as by ir, pmr and mass spectroscopy (Tables I to III).

To our knowledge the mass spectra of 4-thiazolidinones have not yet been studied; accordingly, compounds V, VI, VII and 2-phenyl-3-isonicotinylamino-4-thiazolidinone, which has been previously synthesized (7) have been

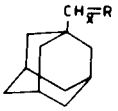
Scheme 1



0022-152X/79/020347-05$02.25

Table I

Ir and Pmr Spectral Data of Compounds I-IV



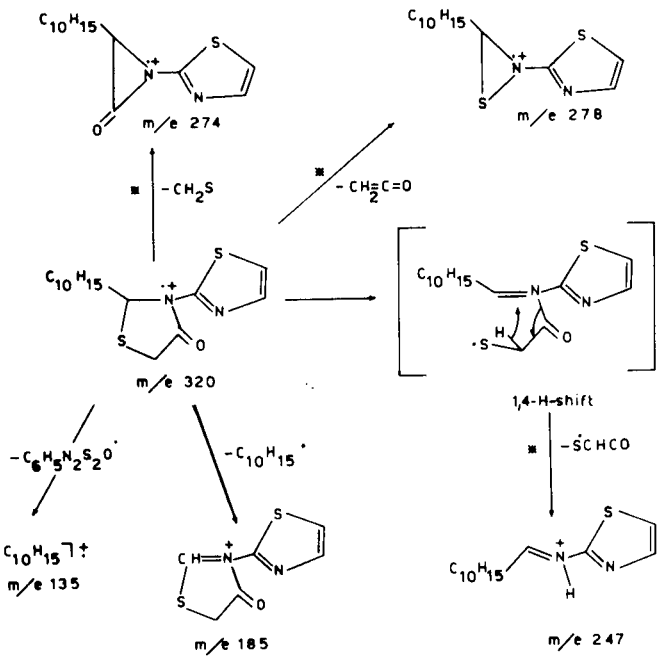
Compound No.	Ir (cm^{-1}) (Esachlorobutadiene) Adamantane				Pmr (δ) (Deuteriochloroform) Adamantane			
	NH_2	NH	CH; CH_2	CO	H_X	CH	CH_2	Other Hydrogen Atoms
I		3190	2902 2850	1699	7.28 (s)	2.03 (s)	1.75 (s)	NH; 9.80 (s) H_2, H_6 pyridine; 8.71 (d) H_3, H_5 pyridine; 7.06 (d) J = 5.7 Hz
II			2900 2850	1667 (b)	7.61 (s)	2.03 (s)	1.73 (s)	C_6H_5; 7.16 (d) CH_2 piperidine; 4.36 (s)
III	3420 3300	3140	2903 2852		7.10 (s)	2.05 (s)	1.76 (s)	NH; 9.56 (s) NH_2; 6.43 (s)
IV		3205	2910 2850		4.81 (s)	2.02 (s)	1.70 (s)	H_5 thiazole; 7.12 (d) H_4 thiazole; 6.50 (d) J = 3 Hz NH; 5.92 (s)

investigated. Mass spectral data for 2-adamantyl-3-isonicotinylamino-4-thiazolidinone (V) and 2-phenyl-3-isonicotinylamino-4-thiazolidinone were recorded for comparison and summarized in Table III.

From mass spectral data for these four thiazolidinones, and taking into account the similar behaviour of 2-adamantyl- and 2-phenyl-3-isonicotinylamino derivatives, it follows that the adamantyl substituent plays only a minor role in the fragmentation processes. The mass spectrum of compound V shows no peak corresponding to the molecular ion. The base peak at m/e 236 corresponds to M^+-PyCONH$^\cdot$ (m/e 357-121) and arises from N-N bond cleavage. The other main fragmentation processes (Scheme 1) proceed according to pathway (a) or (b), and are consistent with the nucleophilic character of both the cyclic and amide nitrogen atoms. The two peaks at m/e 135 and 222 can result from isobaric ions. The CH-S bond cleavage in the molecular ion, followed by a rearrangement through a 1,4-hydrogen shift, leads to m/e 284 and 235 ions (loss of $^\cdot$S-CH-CO and isonicotinamide), as already established for acetanilides (8).

On the contrary, in the mass spectra of VII and VI, which behave similarly under electron impact, the two molecular ions are found at m/e 320 and 425, respectively. The radical ion $C_{10}H_{15}^+$ (m/e 135; base peak) and the two peaks at m/e 185 and 290 (M^+-$C_{10}H_{15}$) arise both from the above molecular ions, by $C_{10}H_{15}$-CH bond cleavage. Most of the fragmentation processes involve rearrangements (1,4 and 1,5 shifts), according to Schemes 2 and 3, and according to the results obtained by the DADI technique (Figure 1) for compound VII.

Scheme 2



The most interesting rearrangement proceeds by adamantyl radical transfer from the thiazolidinone to the thiazole or diketopiperazine nucleus, leading to ions (M^+-101) formed by the loss of the 4-thiazolinone molecule.

Biological Results.

The above compounds were all screened for antibacterial and antifungal activity (9). They were tested

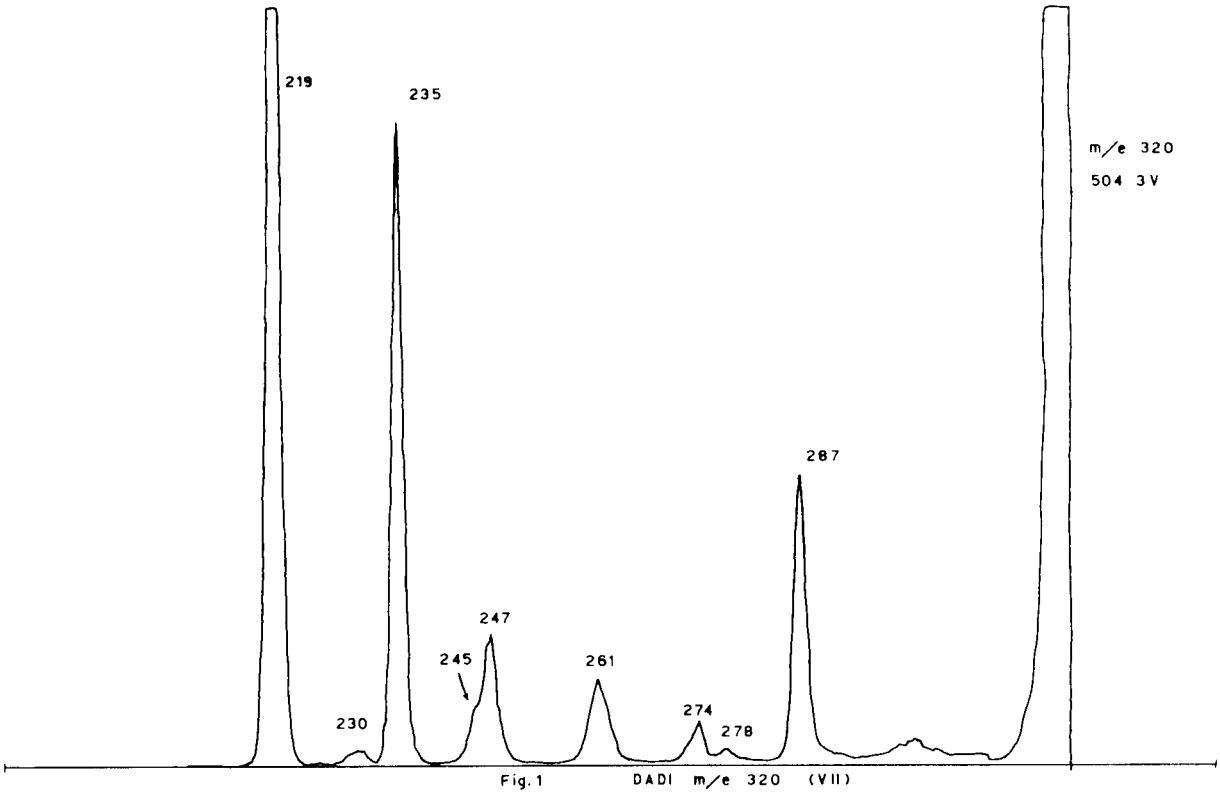
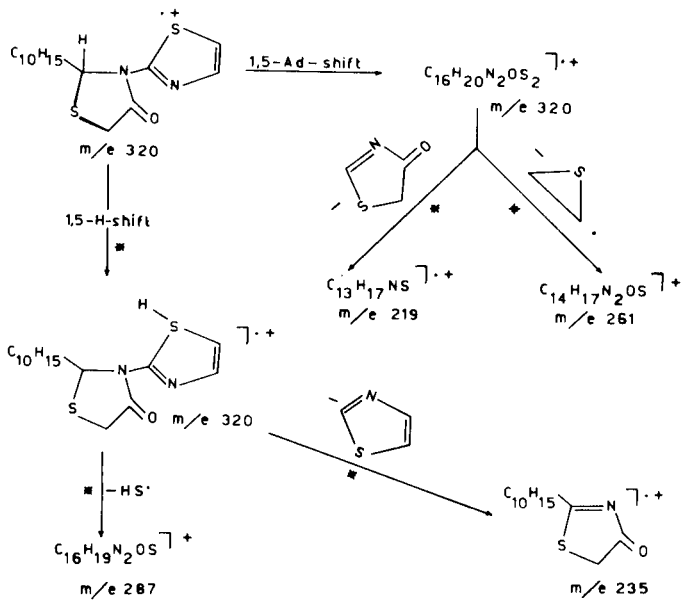


Fig. 1 DADI m/e 320 (VII)

against twelve bacterial strains (5 gram-positive: *Str. pneumoniae, Str. pyogenes, S. aureus, S. aureus Pen-Res* and *Str. faecalis;* 7 gram-negative: *E. coli, K. pneumoniae, Pr. mirabilis, Pr. vulgaris, Ser. marcescens, Ent. cloacae* and *Ps. aeruginosa)* and six fungi (*Candida albicans, Candida tropicalis, Candida krusei, Cryptococcus neoformans, Trichophyton mentagrophytes* and *Microsporum canis).* The MIC data show that compound II is the most active against all of the organism tested. The MIC values range from 32-63 μg/ml. against gram-negative bacteria and fungi, and from 16-125 μg/ml. against gram-positive bacteria. Compound IV is equally as effective as II against the bacterial strains, but is at least half as active as II against fungi. The remaining compounds produce weak antibacterial and antifungal activity (MIC ≥ 125 μg/ml.).

Scheme 3



EXPERIMENTAL

Melting points were determined on a Kofler hotplate and are uncorrected. Tlc was performed on Merck 60 F 254 silica plates, using chloroform and methanol (95:5 v/v) as eluents. Ir spectra (in esachlorobutadiene) were recorded on a Perkin-Elmer Model 257 Spectrometer. The pmr spectra were recorded at room temperature on a Varian T-60A Spectrometer (60 Mc/s), from deuteriochloroform, using TMS as internal standard; chemical shifts are in δ (ppm). A Varian MAT CH5-DF Mass Spectrometer was used.

General Procedure for the Preparation of Compounds I-IV.

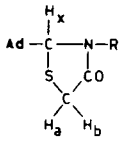
1-Formyladamantane was obtained from adamantane-1-carbonyl chloride, by catalytic hydrogenation in xylene (10).

Method A.

To a cold solution of 1-formyladamantane in xylene (10%) an equimolar amount of the amino derivative in xylene was added.

Table II

Ir and Pmr Spectral Data of Compounds V-VII



Compound No.	Ir (cm^{-1}) (Esachlorobutadiene)				Pmr (δ) (Deuteriochloroform)					
	Adamantane		Thiazole	Other	Adamantane					
	NH	CH; CH_2	CO	CO	H_x	H_a	H_b	CH	CH_2	Other Hydrogen Atoms
V	3225	2905 2850	1705	1662	4.61 (s)	3.49	3.61 (dd) J = 16.5 Hz	2.06 (s)	1.70 (s)	NH; 10.50 (s) N_2, H_6; pyridine; 8.56 (d) H_3, H_5 pyridine; 7.50 (d) J = 5.2 Hz
VI		2906 2850	1725	1685	4.50 (s)	3.47	3.57 (dd) J = 16 Hz	2.08 (s)	1.75 (s)	Ph-N-CH_2 piperidine; 4.68 4.88 (dd) N-N-CH_2 piperidine; 4.36 4.56 (dd) J = 16 Hz
VII		2912 2850	1700		5.69 (s)	3.53	3.84 (dd) J = 16.5 Hz	1.93 (s)	1.63 (s)	H_5 thiazole; 7.43 (d) H_4 thiazole; 7.00 (d) J = 3 Hz

Table III

2-Adamantyl-3-isonicotinyl-amino-4-thiazolidinone (V)			2-Phenyl-3-isonicotinyl-amino-4-thiazolidinone	
m/e	%		m/e	%
357	--	M^+	299	--
284	2	M - 73	226	10
236	100	M - 121 = a	178	100
235	28	a - 1	--	--
222	30	M - 135 = b	--	--
135	97	a - 101	77	15
106	56	(b - 101) - 15	106	65
101	8	b - 121	--	--
78	38	$[C_5H_4N]^+$	78	49
55	17	$[CHNCO]^+$	55	60
--	--	$[C_4H_3]^+$	51	90
46	96	$[CH_2S]^+$	46	95
45	100	$[CHS]^+$	45	98
43	52	$[NHCO]^+$	43	70

After several hours at room temperature the reaction mixture was filtered, and the resulting solid crystallized to give compounds I, II and IV.

Compound I.

This compound had m.p. 230-233° after washing with cyclohexane.

Anal. Calcd. for $C_{17}H_{21}N_3O$ (283.3): C, 72.05; H, 7.47; N, 14.83. Found: C,71.80; H, 7.56; N, 14.41.

Compound II.

This compound, after recrystallization from ethanol, had m.p. 215-218°.

Anal. Calcd. for $C_{21}H_{25}N_3O_2$ (351.43): C, 71.77; H, 7.17; N, 11.96. Found: C, 71.97; H, 7.29; N, 12.20.

Compound IV.

Upon recrystallization from benzene, the product had m.p. 151-154°.

Anal. Calcd. for $C_{17}H_{22}N_4S_2$ (346.38): C, 58.94; H, 6.40; N, 16.18. Found: C, 59.02; H, 6.15; N, 15.90.

Method B.

An ethanolic solution of thiosemicarbazide was added to an equimolar quantity of 1-formyladamantane, followed by the removal of the solvent *in vacuo*. After addition of water to the reaction mixture, the resulting precipitate was filtered, and compound III, m.p. 190-192°, was isolated and purified by repeated washings with cyclohexane.

Anal. Calcd. for $C_{12}H_{19}N_3S$ (237.30): C, 60.73; H, 8.07; N, 17.71. Found: C, 60.50; H, 8.01; N, 17.68.

Ir and pmr spectral data of compounds I-IV are listed in Table I.

General Procedure for the Preparation of Compounds V-VII.

Compounds I, II or III, dissolved in dry benzene and mercaptoacetic acid (1:2), were refluxed at 85° for 50 hours. The solvent was then evaporated and an oily residue obtained. The residue was neutralized with a 2% sodium carbonate solution to give a colorless solid. After recrystallization from ethanol V, VI and VII were obtained.

Compound V.

This compound had m.p. 152-155°.

Anal. Calcd. for $C_{19}H_{23}N_3O_2S$ (357.40): C, 63.85; H, 6.48; N, 11.76. Found: C, 63.91; H, 6.65; N, 11.81.

Compound VI.

This compound had m.p. 265-267°.

Anal. Calcd. for $C_{23}H_{27}N_3O_3S$ (425.47): C, 64.92; H, 6.40; N, 9.88. Found: C, 64.90; H, 6.41; N, 9.85.

Compound VII.

This compound had m.p. 107-109°.

Anal. Calcd. for $C_{16}H_{20}N_2OS_2$ (320.34): C, 59.99; H, 6.29; N, 8.75. Found: C, 60.01; H, 6.27; N, 8.90.

Table II shows ir and pmr spectral data of compounds V, VI and VII.

Acknowledgment.

Thanks are extended to the staff of the Department of Chemistry (Calabria University) for mass spectra.

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