SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF DIAZAADAMANTANE DERIVATIVES

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Included among the amino derivatives of adamantane are recognized antiviral [6], antimicrobial and fungicidal [7] preparations. There has been much less study of the pharmacological activity of the hetero analogs of adamantane. The best known of that group is urotropin, or hexamethylenetetramine (1,3,5,7-tetrazaadamantane), which has been long used in pharmacology as an anti-gout agent, and with various additives for the prevention and treatment of influenzas.

The objects of our study were 2,4,6,8-tetraphenyl-3,7-diazaadamantane-9-one (I) and 2,4,6,8-tetraphenyl-5-methyl-3,7-diazaadamantane-9-one (II).

The reactivity of the carbonyl group of diazaadamantnones I and II were analyzed qualitatively and the biological activity of their derivatives was studied by reacting them with hydrazine-hydrate and hydroxylamine as well as subjecting them to reduction and ethynylation reactions.

Hydrazones I and II (III and IV, respectively) were obtained in a medium of triethyleneglycol at a temperature of 175-180°C with an excess of hydrazine-hydrate.

The oxime I (V) was synthesized by the generally recognized method which employs the strong oximizing agent, pyridine. We were not able to obtain the oxime of diazaadamantanone II with a methyl substituent in the α-position to the carbonyl group under the same conditions.

The sodium reduction of diazaadamantanone I in isopropyl alcohol proceeds in xylene with the formation of a secondary alcohol (VI). The reduction of the ketone II which has a methyl substituent in the α-position to the C=O group could not be performed under the same conditions. This is apparently due to steric hindrance created by the large methyl group that is shielded with respect to the carbonyl group.

The effect of an α-methyl substituent (with respect to the C=O group) has been studied in a number of γ-piperidones [3] of which diazaadamantanone II is a tricyclic analog. The shielding action of the equatorial α-methyl substituent can be evaluated by comparing the results of the reduction of γ-piperidones to one or two similar type substituents. It is apparent from such a comparison that the equatorial α-methyl group increases the barrier to an axial attack by the C=O group.

In consideration of the rigidity of the adamantane system, one might assume that even greater steric hindrances can be expected to block a carbonyl bond attack in this case.

Apparently, the combined effect of the enumerated influences might be explained by the unsuccessful attempt to reduce diazaadamantaneone II with sodium in alcohol.

Diazaaadamantanones I and II were reduced by lithium aluminum hydride in a mixture of ether and benzene. Compound I was reduced by a stoichiometric quantity of the hydride with the formation of a secondary alcohol of VI. At the same time, the presence of an α-methyl substituent in compound II reduced its reactivity to such an extent that reduction could not take place under similar conditions even if the reaction was significantly prolonged.

The carbonyl group of compound II was reduced by a fourfold excess of lithium aluminum hydride with the simultaneous cleavage of the methylene bridge between the two nitrogen atoms which led to the formation of the 3,7-diazabicyclononane derivative (IX) with a methyl group on one of the nitrogen atoms. Tbe IR spectra of compound IX exhibiged "Bohlmann" bands (2750-2840 cm^{-1}) and intensive absorption bands at 2780 cm^{-1} ($N-CH_3$) and at 3340 cm^{-1} (N–H) which rather convincingly attests to the formation of a diazabicyclononane shell [4]. Subse-

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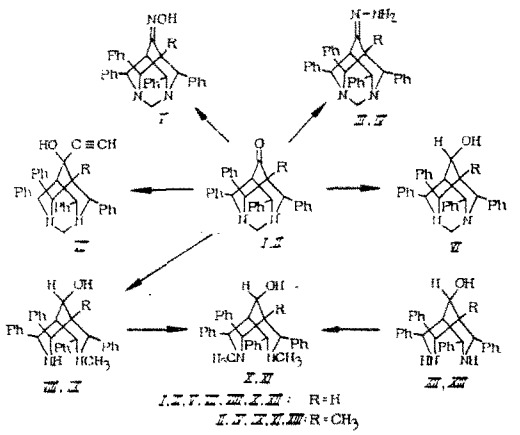
TABLE 1. Physicochemical Properties of the Diazaadamantane Series Derivatives

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			IR spectra, cm^{-1}
			C	H	N		C	H	N	
I	78	226—227	83,83	6,25	5,97	$C_{28}H_{25}N_2O$	84,21	6,14	6,14	1700 (C=O)
II	80	260—262	84,43	6,75	5,96	$C_{29}H_{30}N_2O$	84,25	6,38	5,95	1687 (C=O)
III	63	251—252	81,63	6,31	12,01	$C_{32}H_{30}N_4$	81,70	6,38	11,91	1630 (C=N)
IV	60	269—270	81,67	6,73	11,41	$C_{33}H_{32}N_4$	81,82	6,61	11,57	1635 (C=N)
V	57	237—238	81,37	6,18	8,99	$C_{32}H_{28}N_2O$	81,53	6,16	8,92	1637 (C=N)
VI	70	246—247	83,67	6,50	6,18	$C_{32}H_{30}N_2O$	83,84	6,55	6,11	3572 (C=N) 1060 (C—O)
VII	62	250—251	84,47	6,34	5,50	$C_{34}H_{30}N_2O$	84,65	6,22	5,81	3400 (C=N); 1060 (C—O), 3305 (≡C—H)
VIII	72	255—257	83,37	7,09	6,04	$C_{32}H_{32}N_2O$	83,48	6,96	6,09	3400 (C—N), 1065 (C—O)
IX	82	250—252	83,37	7,23	5,83	$C_{33}H_{34}N_2O$	83,54	7,17	5,91	3575 (C=N), 1060 (C—O)
X	84	248—249	83,61	7,08	5,83	$C_{33}H_{34}N_2O$	83,54	7,17	5,91	3430 (C=N), 1060 (C—O)
XI	70	248—249	83,52	7,49	5,67	$C_{34}H_{36}N_2O$	83,61	7,38	5,74	3390 (C=N), 1068 (C—O)

quent alkylation of IX led to the formation of compound (XI) which was also obtained by direct contact synthesis through the alkylation of compound (XIII).



The reduction of diazaadamantanone I by an excess of lithium aluminum hydride also resulted in the formation of a diazabicyclononane derivative (VIII) whose methylation led to the formation of 3,7-dimethylbispidine (X) which was also directly synthesized from compound XII.

The fragmentation of the diazaadamantanone system apparently can be attributed to the weakening of σ-bonds due to the "cross-bond interaction" and delocalization of the positive charge between the two nitrogen atoms [2].

Our study of the ethynylation of diazaadamantanones established that compound I goes into the condensation reaction with the formation of an acetylene derivative (VII) in a liquid ammonia medium in the presence of powdered alkali where tetrahydrofuran is used as the solvent. Condensation with diazaadamantanone II under the same conditions does not take place.

Thus, the presence of an α-methyl substituent markedly reduces the carbonyl group's ability to undergo reduction and ethynylation. This substituent also shifts the carbonyl group of compound II to a low frequency region of the absorption band (1687 cm^{-1}) in comparison to the carbonyl group of compound I (1700 cm^{-1}).

The physical and chemical characteristics of the synthesized compounds are given in Table 1.

EXPERIMENTAL CHEMICAL

The IR spectra of the synthesized compounds were recorded on a UR-20 (GDR) spectrometer in KBr pellets.

2,4,6,8-Tetraphenyl-3,7-diazaadamantane-9-one (I). A 8.92 g (0.02 mole) portion of 2,4,-6,8-tetraphenyl-3,7-diazabicyclo[3,3,1]-nonane-9-one [6] was dissolved in 150 ml of dioxane and heated for 6 h on a boiling water bath with a large excess of 35% formalin. The reaction mixture was left overnight and the precipitated crystals were filtered off. The filtrate was

distilled to dryness and the residual crystals were combined with the crystals which had been previously filtered and recrystallized from acetone. Yield 7.41 g of product I.

2,4,6,8-Tetraphenyl-5-methyl-3,7-diazaadamantane-9-one (II) was obtained from 2,4,6,8-tetraphenyl-5-methyl-3,7-diazabicyclo[3,3,1]-nonane-9-one [5] by the method described above.

2,4,6,8-Tetraphenyl-3,7-diazaadamantane-9-one Hydrazone (III). A 0.456 g (0.001 mole) portion of I and 10 ml of 99% hydrazine hydrate was heated in 40 ml of triethyleneglycol at 175-180°C with a Dean-Stark trap for 6 h. After the reaction mixture was cooled it was diluted with water and the precipitate was filtered off and recrystallized from ethanol.

2,4,6,8-Tetraphenyl-5-methyl-3,7-diazaadamantane-9-one (IV) was obtained in a similar manner.

2,4,6,8-Tetraphenyl-3,7 diazaadamantane-9-one Oxime (V). A 1.5 ml portion of pyridine and 1.8 g of hydroxylamine HCl were added to a solution of 4.56 g (0.01 mole) of I in 150 ml of ethanol. The reaction mixture was boiled for 4 h after which the solvent was rapidly distilled off. The remaining product was decanted into water, filtered off, and recrystallized from an alcohol-dioxane mixture (1:2).

2.4,6,8-Tetraphenyl-3,7-diazaadamantane-9-ol (VI). a) Sodium Reduction of I in Isopropyl Alcohol. A suspension of 5 g of metallic sodium was prepared in xylene which was transferred to a reaction beaker with 75 ml of dry xylene. This was followed by the gradual addition of 4.56 g (0.01 mole) of I in 40 ml of xylene, followed by the dropwise addition of 50 ml of isopropyl alcohol. The reaction proceeded in an argon stream while the solvent boiled for 7 h. The mixture was then dissociated with 50 ml of water, extracted with benzene, and dried over potash. After the solvent was distilled off, the residue was recrystallized from benzene.

b) Lithium Aluminum Hydride Reduction. A 0.456 g (0.001 mole) portion of I in 25 ml of absolute benzene and 30 ml of absolute ether was added to a solution of 0.038 g (0.001 mole) of $LiAlH_4$ in 30 ml of absolute ether at the boil and heated for 6 h on a water bath. After cooling, the reaction mixture was dissociated with 4 ml of water and restirred for 1 h at room temperature. The organic layer was evaporated and the residue was recrystallized from acetone. Yield 0.38 g of VI.

2,4,6,8-Tetraphenyl-7-methyl-3,7-diazabicyclo[3,3,1]nonane-9-01 (VIII) was obtained by the above-described method in which 0.456 g (0.001 mole) of I was reduced by 0.152 g (0.004 mole) of lithium aluminum hydride. Following appropriate treatment, the yield of VIII was 0.36 g.

2,4,6,8-Tetraphenyl-5,7-dimethyl-3,7-diazabicyclo[3,3,1]nonane-9-01 (IX) was obtained by the similar reduction of 0.470 g (0.001 mole) of II by 0.152 g (0.004 mole) of lithium aluminum hydride. Following appropriate treatment the yield of IX was 0.43 g.

2,4,6,8-Tetraphenyl-3,7-dimethyl-3,7-diazabicyclo[3,3,1]nonane-9-01 (X). A 0.46 g (0.001 mole) portion of VIII, 0.05 ml (0.001 mole) of 85% formic acid, and 0.09 ml (0.001 mole) of 35% formalin were heated on a boiling water bath for 4 h until the evolution of CO_2 stopped. Then the aqueous layer was extracted with benzene and the organic layer was dried over potash. The solvent was distilled off and the residue was recrystallized from acetone with a yield of 0.39 g of X.

2,4,6,8-Tetraphenyl-3,5,7-trimethyl-3,7-diazabicyclo[3,4,1]nonane-9-01 (XI) was obtained in a similar fashion from 0.474 g (0.001 mole) of IX.

2,4,6,8-Tetraphenyl-9-ethynyl-3,7-diazaadamantane-9-ol (VII). A 3.92 g (0.07 mole) portion of powdered KOH in 1.5 liter of liquid ammonia was placed into a three-necked round bottom flask equipped with a stirrer, a drop funnel, and tube for accepting acetylene. The mixture was saturated with acetylene while being vigorously stirred for 2 h. Then, over a period of 3 h at a solution of 15.25 g (0.05 mole) of I in 250 ml of absolute tetrahydrofuran was added dropwise to the mixture. On the next day the reaction mass was hydrolyzed with water. The aqueous layer was repeatedly extracted with chloroform and dried over calcinated sodium sulfate. After the solvent was distilled off, the residue was recrystallized from benzene.

EXPERIMENTAL BIOLOGICAL

The antimicrobial activity of the synthesized compounds was tested by series dilution in a liquid nutrient [1] against gram-positive and gram-negative bacteria, spore-forming bacteria, yeast like fungi, and dermatophyte fungi.

TABLE 2. Antimicrobial Activity of Diazaadamantane Series Derivatives

Microorganism	Minimum suppression concentration, μg/ml					
	I	II	III	IV	VI	VII
Bac. mycoides	—	13,7	—	—	—	—
Bac. sybtilis	0	13,7	—	—	22,2	—
Bac. anthracoides	0	0	66,6	22,2	22,2	66,6
Staph. aureus	0	13,7	22,2	22,2	22,2	22,2
Bact. carativorum	0	41,2	—	—	22,2	—
Corynebacterium	7,4	0	—	—	0,27	—
Escherichia coli	—	41,3	—	—	—	—
Sacch. cerevisiae	—	13,7	—	—	66,6	66,6
Sarcina lutea	—	0,5	—	—	—	—
Ep. rubrum	66,6	—	66,6	66,6	—	66,6
Trich. gypseum	22,2	—	66,6	66,6	—	66,6
Fusarium aolani	22,2	—	22,2	66,6	—	22,2
Candida albicans	—	39,1	66,6	66,6	66,6	66,6

The nutrient media were used: Beef-peptone broth for the bacteria, Sabouraud's agar for the yeast-like fungi and dermatophyte fungi, and Czapek 7 for the phytopathogenic fungus. The suspension of microorganisms was prepared in a physiological solution in accordance with the bacterial turbidity standard.

The activity of the compounds was evaluated by the minimum bacteriostatic or mycostatic concentration (in μg per 1 ml). The experimental results are given in Table 2.

The tested compounds of the diazaadamantane series demonstrated moderate antimicrobial activity with the exception of compounds I and VI which exhibited a high degree of selective action against *Corynebacterium*.

Thus, the data we obtained allow us to conclude that a continued search for biologically active substances in the diazaadamantane series seems warranted.

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