Dried Na salt of 5-[2-(4-phenyl-1-piperazinyl)ethyl]tetrazole[2] (8.41 g, 0.03 mol) in 40 ml of abs EtOH was refluxed with 4.75 g (0.0305 mol) of EtI for 16 hr. After concentrating to about 20 ml, the solution was diluted with 35 ml of H_2O and the pH adjusted to the phenolphthalein endpoint with base. Extraction with five 20-ml portions of Et_2O, followed by drying and evaporation of the extracts, gave 6.55 g (76%) of solid product. Two, well-separated spots of approximately equal size developed in tlc (Eastman Chromatogram Sheet 6060, Silica Gel; 95:5 C_6H_6–abs EtOH). This mixture was chromatographed on 90 g of 2:1 silicic acid–Celite using 95:5 C_6H_6–abs EtOH as the eluting solvent. Between 450 and 500 ml of solvent was required to remove the 2-isomer, which came off the column first.[8] The product (3.76 g) recovered by evaporating the eluting solvent crystallized spontaneously, mp 67–68°. Although a portion (0.6 g, mp 83–84°) of the 1 isomer was later eluted from the column by the same solvent mixture (300 ml), the balance of this isomer was more conveniently recovered by extruding the column packing, boiling the latter with a large volume of the solvent, filtering hot, and evaporating the extract.

Derivatives were prepared from the separated isomers by conventional methods.

(8) This assignment is made for three reasons: a 2 isomer is less polar than the 1 isomer;[7] the melting point of a 2 isomer is usually lower than that for the 1 isomer; and the chemical shift for the protons on a methylene group attached to tetrazole ring nitrogen is always at slightly lower field for the 2 isomer than that for the 1 isomer.[6]

Aminoadamantane Derivatives as Potential Insect Chemosterilants

JAMES E. OLIVER AND JERRY B. STOKES

Entomology Research Division, Agricultural Research Service, United States Department of Agriculture, Beltsville, Maryland 20705

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Since the development of 1-aminoadamantane as an antiviral agent,[1] and subsequent reports that the adamantyl moiety enhances biological activity in a variety of classes of compounds,[2] there has been a marked interest in the synthesis and biochemistry of a wide variety of adamantyl-substituted and closely related compounds.

We wish to describe 16 derivatives[3] of 1-aminoadamantane that were tested as candidate chemosterilants[4] against three species of insects. Our selection of compounds was influenced by the occasional biological activity—*e.g.*, chemosterilant, antitumor, antiviral—associated with ureas and semicarbazides and their thio analogs, thiosemicarbazones, and related hydrazine derivatives. In addition, we incorporated into some of these compounds a dimethylamino group, another functionality frequently associated with chemosterilant activity.[5] Their mode of preparation is shown in Table I.

(1) H. J. Eggers and I. Tamm, *Annu. Rev. Pharmacol.*, **6**, 239 (1966) and ref therein.

(2) K. Gerzon, D. J. Tobias, Sr., R. E. Holmes, R. E. Rathbun, and R. W. Kattau, *J. Med. Chem.*, **10**, 603 (1967) and previous papers.

(3) (a) Compounds **1**, **2**, and **12**, had been reported previously; E. I. duPont de Nemours and Co., Netherlands Application 6,403,294, April 23, 1965 [*Chem. Abstr.*, **63P** 9837*h* (1956)]; (b) Compounds **7**, **13**, and **14** were reported at about the time this work was completed: S. Sallay and S. J. Childress, U.S. Patent 3,406,180, Oct 15, 1968 [*Chem. Abstr.* **70**, 11223 (1969)]. Melting points of **7** and **13** agreed with those reported; the abstract did not contain a melting point for **14**.

(4) A. B. Borkovec, "Insect Chemosterilants," Interscience, New York, N. Y., 1966.

(5) P. H. Terry and A. B. Borkovec, *J. Med. Chem.*, **10**, 118 (1967); A. B. Borkovec and A. B. DeMilo, *ibid.*, **10**, 457 (1967); and unpublished observations.

Chemistry.—Compounds **5**, **7**, and **9** were obtained from the reaction of 1-adamantyl isothiocyanate with Me_2NH, N_2H_4, and 1,1-dimethylhydrazine, respectively. Compounds **4**, **8**, **10**, and **11** were similarly prepared by treating Me_2NH, 1,1-dimethylhydrazine, ethyl carbazate, and semicarbazide, respectively, with 1-adamantyl isocyanate. This isocyanate has been reported,[6] but our synthesis *via* a Schmidt reaction (Experimental Section) provides a particularly convenient preparation on a laboratory scale. With one exception described below, the reactions of nucleophiles with both the isocyanate and the isothiocyanate proceeded smoothly at or below room temperature in any of a variety of solvents, *e.g.*, CH_2Cl_2, THF, C_6H_6, Et_2O. EtOH could be used at low temperatures, although heating the isocyanate with EtOH in refluxing C_6H_6 afforded the carbamate **12**[3a] in high yield. Work-up consisted of simply collecting the solid product if it had separated from solution, or evaporating the reaction mixture to dryness and recrystallizing the residue from an appropriate solvent. A typical example, the preparation of **10**, is described in the Experimental Section. 4-(1-Adamantyl)semicarbazide (**6**) could not be prepared cleanly from 1-adamantyl isocyanate and N_2H_4, and was instead obtained from alkaline hydrolysis of **10**. 4-(1-Adamantyl)thiosemicarbazones (**13**–**16**) were prepared from **7** and the appropriate carbonyl compounds.

Results

In general these adamantyl compounds have not been highly effective as insect chemosterilants against house flies, *Musca domestica* L., screw-worm flies, *Cochliomyia hominivorax* (Coquerel), or boll weevils, *Anthonomus grandis* Boheman. Although **3**, **6**, **7**, and **16** reduced oviposition in some tests when fed to mixed sexes of house flies at a concentration of 1% of the diet,[7] the activity was not sustained at lower concentrations or in male sterilant tests. None of the compounds exhibited significant activity against boll weevils. Compounds **3** and **4** reduced egg hatch when fed to screw-worm flies[8] (1% of diet), and **1** prevented oviposition at this concentration.

Experimental Section[9]

1-Adamantanecarbonyl Azide and 1-Adamantyl Isocyanate.—A solution of 1-adamantanecarbonyl chloride (50 g, 0.24 mol) in Me_2CO (150 ml) was added dropwise to a cold (0–5°) solution of NaN_3 (20 g, 0.31 mol) in H_2O (75 ml) and Me_2CO (50 ml). The mixture was stirred in the cold for 20 min then extracted with Et_2O (3 × 150 ml). The combined Et_2O portions were washed (H_2O, aq $NaHCO_3$, aq NaCl) and then dried. The solvent was stripped at 15–20°, and the azide was obtained as a white solid

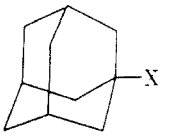
(6) (a) H. Stetter and C. Wulff, *Chem. Ber.*, **95**, 2302 (1962); (b) M. Paulshock and J. C. Watts, U.S. Patent 3,203,970, August 31, 1965 [*Chem. Abstr.*, **64**, PC 615*g* (1966)].

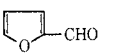
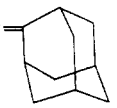
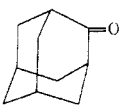
(7) Screening tests on house flies were performed by G. C. LaBrecque and associates, of this Division in Gainesville, Fl.; *cf.* R. L. Fye, G. C. LaBrecque, and H. K. Gouck, *J. Econ. Entomol.*, **59**, 485 (1966).

(8) Screening tests on screw-worm flies were performed by M. M. Crystal and associates, of this Division in Mission, Texas; *cf.* M. M. Crystal, *J. Econ. Entomol.*, **57**, 726 (1964).

(9) Melting points were obtained on a Büchi melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 137 NaCl prism spectrophotometer. $MgSO_4$ was employed as a drying agent. 1-Adamantanecarbonyl chloride and 1-adamantyl isothiocyanate were purchased from the Aldrich Chemical Co. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Table I
Adamantyl Candidate Chemosterilants



No.	X	Preparation (R = 1-Adamantyl)	Yield, %	Mp, °C	Recrystn Solvent	Formula	Analyses
1	$N(CH_3)_2 \cdot HCl$	*a*	59	280	MeOH	$C_{12}H_{21}N$	*a*
2	$N(CH_3)_3I^-$	*a*	78	302 dec	MeOH	$C_{13}H_{24}IN$	*a*
3	CON_3	$RCOCl + NaN_3$	93	68–68.5 dec	Me_2CO–H_2O	$C_{11}H_{15}N_3O$	C, H, N
4	$NHCON(CH_3)_2$	$RNCO + (CH_3)_2NH$	96	181–182	Hexane–C_6H_6	$C_{13}H_{22}N_2O$	C, H, N
5	$NHCSN(CH_3)_2$	$RNCS + (CH_3)_2NH$	83	154–156	EtOH	$C_{13}H_{22}N_2S$	C, H, N, S
6	$NHCONHNH_2$	10 + KOH	76	173–174	Cyclohexane–C_6H_6	$C_{11}H_{19}N_3O$	C, H, N
7	$NHCSNHNH_2$	$RNCS + N_2H_4$	95	211–212	EtOH-DMF	$C_{11}H_{19}N_3S$	C, H, N, S
8	$NHCONHN(CH_3)_2$	$RNCO + (CH_3)_2NNH_2$	99	135.5–136	Hexane	$C_{13}H_{23}N_3O$	C, H, N
9	$NHCSNHN(CH_3)_2$	$RNCS + (CH_3)_2NNH_2$	79	191–191.5	Hexane–C_6H_6	$C_{13}H_{23}N_3S$	C, H, N
10	$NHCONHNHCO_2C_2H_5$	$RNCO + H_2NNHCO_2C_2H_5$	80	152–153	Hexane–EtOAc	$C_{14}H_{23}N_3O_3$	C, H, N
11	$NHCONHNH_2$	$RNCO + H_2NNHCONH_2$	*ca.* 90	230	MeOH	$C_{12}H_{20}N_4O_2$	C, H, N
12	$NHCO_2C_2H_5$	RNCO + EtOH	96	93–94	Hexane	$C_{13}H_{21}NO_2$	*a*
13	$NHCSNHN{=}CHC_6H_5$	7 + C_6H_5CHO	73	200 dec	MeOH	$C_{18}H_{23}N_3S$	*b*
14	$NHCSNHN{=}C(CH_3)_2$	7 + CH_3COCH_3	84	200 dec	MeOH	$C_{14}H_{23}N_3S$	C, H, N
15	NHCSNHN=CH– 	7 + 	85	177–177.5	MeOH	$C_{16}H_{21}N_3OS$	C, H, N, S
16		7 + 	69	217 dec	EtOH	$C_{18}H_{23}N_3O$	C, H, N

[a] Reference 3a. [b] Reference 3b.

(46.5 g, 92%), mp 69° dec. Acidification of the $NaHCO_3$ extract gave 1.35 g (3%) of 1-adamantanecarboxylic acid, mp 177–179° (lit.[10] 181°).

Crystallization of **3** was effected by treating a Me_2CO solution with H_2O at room temperature until precipitation began, then chilling the mixture to −20°. The white solid was collected and dried, mp 69° dec. An analytical sample (mp 68–68.5° dec) was similarly obtained by preparing a concentrated pentane solution at room temperature, then chilling to −20°.[11]

A portion of **3** (75 mg) was heated at reflux in CCl_4 (7 ml) for 40 min, and the ir spectra of the starting and resulting solutions were compared. Absorptions at 1710 and 2130 cm^{-1} (C=O and N_3) had completely disappeared, and a strong band at 2250 cm^{-1} (N=C=O) had appeared. The solvent was stripped and 1-adamantyl isocyanate was recovered as a white solid that began to melt at *ca.* 140–150° (lit.[3] 143–145°) but then apparently polymerized.

1-Adamantyl Isocyanate. General Procedure.—In the preparation of several of the isocyanate derivatives, the acyl azide was not isolated, but rather the product from the acid chloride and NaN_3 was extracted into C_6H_6, the extract was dried and then refluxed 1 hr. Evaporation of C_6H_6 yielded 1-adamantyl isocyanate of good purity.[12] Thus, 20 g of the acid chloride was converted into 17.1 g (96%) of the isocyanate.

Ethyl 3-(1-Adamantylcarbamoyl)carbazate (10).—1-Adamantyl isocyanate (8.85 g, 0.050 mol) and ethyl carbazate (5.20 g, 0.050 mol) were combined in THF (160 ml) and the solution was stirred overnight at room temperature. Evaporation of the solvent and recrystallization of the white solid residue from hexane-EtOAc provided **10** (11.23 g, 80%), mp 152–153°.

4-(1-Adamantyl)semicarbazide (6).—Ethyl 3-(1-adamantylcarbamoyl)carbazate (**10**, 11.23 g) was dissolved in abs EtOH (150 ml) under N_2. KOH (5 g) in H_2O (50 ml) was added at room temperature, whereupon a yellow color developed. The solution was heated at reflux under N_2; after *ca.* 1.5 hr the yellow color disappeared, and a colorless oil began to separate from the solution. Refluxing was continued an additional 0.5 hr, then the mixture was poured into ice–water (300 g). The mixture was stirred until the ice had melted, then the white solid 4-(1-adamantyl)carbazide was collected and dried at reduced pressure (6.32 g, 76%, mp 173–180°). It could be purified by recrystallization (EtOH–H_2O or cyclohexane–C_6H_6), mp 173–174°.

4-(1-Adamantyl)thiosemicarbazones.—A typical example is the preparation of **15**. A solution of freshly distilled furfural (3.0 g, 0.031 mol) in EtOH (6 ml) and AcOH (3 ml) was added to a warm suspension of **7** (3.0 g, 0.013 mol) in DMF (40 ml). After the addition of the aldehyde, **7** gradually dissolved. The solution was warmed gently on a steam bath 15 min, then allowed to stand at room temperature 16 hr. H_2O (300 ml) was added, and the pale yellow solid was collected and recrystallized from MeOH. Two crops (2.78 g, mp 176.5–177° and 0.55 g, mp 175–176°) represented an 85% yield of 2-furfuraldehyde 4-(1-adamantyl)-thiosemicarbazone (**15**).

(10) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).

(11) Although no problems were encountered in handling **3**, a sample that was stored at room temperature for about 1 year had largely rearranged to the isocyanate.

(12) Because of thermal decomposition, the purity judgment was based on excellent yields in several subsequent reactions rather than on the melting point.

Potential Antidiabetics. V. 3,5-Dimethyl-4-arylazo-N^1-carbamoyl-, 3-Methyl-4-arylazo-5-phenyl-N^1-carbamoyl-, and 3,5-Dimethyl-4-arylazo-N^1-hippurylpyrazoles

Wahid U. Malik, H. G. Garg, P. P. Singh, and Veena Arora

Department of Chemistry, University of Roorkee, Roorkee, India

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Although 1-*n*-butyl-3-(4-tolylsulfonyl)urea (tolbutamide), 1-(4-chlorobenzenesulfonyl)-3-*n*-propylurea (chlorpropamide), and a few others have proved to be clinically useful oral antidiabetic agents, recent reports describing the high rate of development of resistance