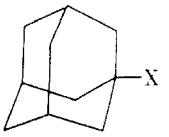
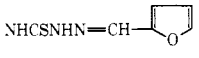
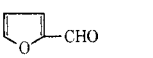
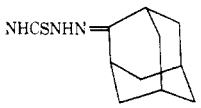
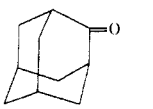
TABLE I
ADAMANTYL CANDIDATE CHEMOSTERILANTS



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		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

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Received February 24, 1970

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

TABLE I

CHARACTERISTICS OF 3,5-DIMETHYL-4-ARYLAZO-N'-CARBAMOYLPYRAZOLES (Ia)

No.	X	Yield, %	Mp, °C	Color[a]	Formula	Analyses
1	2-NO_2	55	204–205	RN	$C_{12}H_{12}N_6O_3$	N
2	3-NO_2	50	210	YO	$C_{12}H_{12}N_6O_3$	N
3	4-NO_2	65	180–182	OC	$C_{12}H_{12}N_6O_3$	N
4	3-Cl	60	156–157	PeYN	$C_{12}H_{12}ClN_5O$	Cl
5	4-Cl	70	159–160	PeYN	$C_{12}H_{12}ClN_5O$	Cl
6	2-Me	65	143–144	YN	$C_{13}H_{15}N_5O$	N
7	4-Me	55	163–164	PeYN	$C_{13}H_{15}N_5O$	N
8	2-OMe	45	153–154	YN	$C_{13}H_{15}N_5O_2$	N
9	3-OMe	50	141–142	PeYN	$C_{13}H_{15}N_5O_2$	N
10	4-OMe	60	164	PeYN	$C_{13}H_{15}N_5O_2$	N
11	2-OEt	50	159	YN	$C_{14}H_{17}N_5O_2$	N
12	3-OEt	45	134–135	YN	$C_{14}H_{17}N_5O_2$	N
13	4-OEt	65	163	Yc	$C_{14}H_{17}N_5O_2$	N
14	4-SO_2NH_2	50	243–245	YN	$C_{12}H_{14}N_6O_3S$	N
15	2,6-Cl_2	65	228–229	Y	$C_{12}H_{11}Cl_2N_5O$	Cl
16	2,5-Me_2	55	201–202	PeYN	$C_{14}H_{17}N_5O$	N
17	2,5-$(OMe)_2$	50	116–118	BN	$C_{14}H_{17}N_5O_3$	N
18	2-Cl-6-Me	60	188–189	O	$C_{13}H_{14}ClN_5O$	Cl

[a] B, brown; C, crystals; D, dark; G, golden; L, light; N, needles; O, orange; P, plates; Pe, pale; R, red; Ru, rust; S, specks; Y, yellow.

TABLE II

CHARACTERISTICS OF 3-METHYL-4-ARYLAZO-5-PHENYL-N^1-CARBAMOYLPYRAZOLES (Ib)

No.	X	Yield, %	Mp, °C	Color[a]	Formula	Analyses
1	2-NO_2	50	206–207	O	$C_{17}H_{14}N_6O_3$	N
2	3-NO_2	55	185–187	Y	$C_{17}H_{14}N_6O_3$	N
3	4-Cl	65	197–198	Y	$C_{17}H_{14}ClN_5O$	Cl
4	3-Me	60	177–178	LY	$C_{18}H_{17}N_5O$	N
5	4-Me	55	166–167	PeY	$C_{18}H_{17}N_5O$	N
6	2-OMe	45	130–131	PeYN	$C_{18}H_{17}N_5O_2$	N
7	3-OMe	50	125–126	Y	$C_{18}H_{17}N_5O_2$	N
8	4-OMe	60	175–176	Y	$C_{18}H_{17}N_5O_2$	N
9	4-OEt	50	178–179	Y	$C_{19}H_{19}N_5O_2$	N
10	4-SO_2NH_2	55	245–246	O	$C_{17}H_{16}N_6O_3S$	N
11	2,5-Cl_2	65	243–245	YO	$C_{17}H_{13}Cl_2N_5O$	Cl
12	2,5-Me_2	60	192–193	YN	$C_{19}H_{19}N_5O$	N

[a] See footnote *a* of Table I.

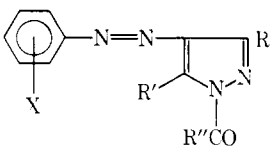
TABLE III

CHARACTERISTICS OF 3,5-DIMETHYL-4-ARYLAZO-N^1-HIPPURYLPYRAZOLES

No.	X	Yield %	Mp, °C	Color[a]	Formula	Analyses
1	Ph	65	133	GYN	$C_{20}H_{19}N_5O_2$	N
2	2-NO_2	60	265–267 dec	OYP	$C_{20}H_{18}N_6O_4$	N
3	3-NO_2	65	278–280 dec	GP	$C_{20}H_{18}N_6O_4$	N
4	4-NO_2	60	278–280 dec	DYS	$C_{20}H_{18}N_6O_4$	N
5	4-Cl	70	209–210	Ru	$C_{20}H_{18}ClN_5O_2$	Cl
6	2-3, Cl_2	75	174–175	GY	$C_{20}H_{17}Cl_2N_5O_2$	Cl
7	2,6-Cl_2-4NO_2	55	215–216	DBN	$C_{20}H_{16}Cl_2N_6O_4$	Cl

[a] See footnote *a* of Table I.

to these[1] gave an incentive to search for new agents.[2] Towards this end, we have synthesized three series of pyrazole derivatives, namely, 3,5-dimethyl-4-arylazo-N^1-carbamoyl- (Ia), 3-methyl-4-arylazo-5-phenyl-N^1-carbamoyl- (Ib), and 3,5-dimethyl-4-arylazo-N^1-hippurylpyrazoles (Ic).



Ia, R = R′ = Me; R″ = NH_2
Ib, R = Me; R′ = Ph; R″ = NH_2
Ic, R = R′ = Me; R″ = $-CH_2NH\cdot Bz$

Precursors 2,3,4-pentanetrione 3-arylhydrazones[3] and 1-phenylbutane-1,2,3-trione 2-arylhydrazones[4] were prepared by the condensation of diazotized anilines with 2,4-pentanedione and 1-phenylbutane-1,3-dione, respectively. Hippuryl hydrazide was synthesized

(1) D. E. Delawater and J. M. Moss, *J. Amer. Med. Ass.*, **181**, 89 (1962); R. A. Camerini-Davalos and A. Marble, *ibid.*, **181**, 176 (1962). Editorial, *ibid.*, **181**, 131 (1962).

(2) H. G. Garg and P. P. Singh, *J. Pharm. Sci.*, in press and ref cited therein.

(3) H. G. Garg and P. P. Singh, *J. Med. Chem.*, **11**, 1103 (1968).

(4) H. G. Garg and P. P. Singh, *J. Chem. Soc. C*, 1141 (1969).

by the conversion of hippuric acid methyl ester into the hydrazide.[5]

The new pyrazoles (Ia,b,c) were prepared by using the conditions for the preparation of N^1-carbamoyl-3,5-diphenylpyrazoles earlier[2] and are listed in Tables I, II, and III.

Biological Results.—During a screening study in CF-1-S mice (Carworth Farms, 25–30 g) at 1.5 mmol/kg, compounds were administered as CMe-cellulose suspension. Controls received an equal volume of the vehicle. Blood samples (0.05 ml), obtained from retrobulbar plexuses at 0.3 and 5 hr after dosing, were assayed for blood glucose using the method of Hoffman[6] adopted for the technicon autoanalyzer. Compounds of the series 3,5-dimethyl-N^1-carbamoyl-pyrazoles, namely, 4-phenylazo-, 4-(2-nitrophenylazo)-, 4-(3-chlorophenylazo)-, 4-(2,5-dimethylphenylazo), 4-(2-methoxyphenylozo)- and 4-(2,5-dichlorophenylazo)-, and of the series 3-methyl-5-phenyl-N^1- carbamoylpyrazole, *viz.*, 4-(2-nitrophenylazo)-, 4-(4-sulfanilamidophenylazo)-, 4-(4-methoxyphenylazo)- were essentially inactive.[7]

Experimental Section

Melting points were determined on a Kofler hot-stage type apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

3-Arylhydrazono-2,3,4-pentanetriones were obtained by the method of Garg and Singh.[3]

2-Arylhydrazono-1-phenyl-1,2,3-butanetriones were synthesized by the procedure of Garg and Singh.[4]

N^1-Carbamoyl(hippuryl-3-methyl-5-methyl)phenyl-4-arylazopyrazoles.—These were prepared by adopting the route of Garg and Singh[2] used for the preparation of 3,5-diphenyl congeners. Characteristics of 3,5-dimethyl-4-arylazo-N^1-carbamoylpyrazoles (Ia), 3-methyl-4-arylazo-5-phenyl-N^1-carbamoylpyrazoles (Ib), and 3,5-dimethyl-4-arylazo-N^1-hippurylpyrazoles (Ic) are given in Tables I, II, and III, respectively.

Acknowledgment.—Two of the authors (P.P.S. and Miss Veena Arora) are thankful to the Council of Scientific and Industrial Research, New Delhi for granting them Junior Fellowships.

(5) S. Grudzinski, *Roczniki Chem.*, **33**, 655 (1959); *Chem. Abstr.*, **50**, 8069 (1960).

(6) W. S. Woffman, *J. Biol. Chem.*, **120**, 51 (1937).

(7) The authors express their appreciation to Dr. D. A. Blickens of the Department of Metabolic Chemotherapy, Lederle Laboratories, Pearl River, N. Y. for testing results.

Insect Chemosterilants. IX.[1] *N*-(Hydroxymethyl)-*N*,*N*′,*N*′,*N*″,*N*″-pentamethylphosphoric Triamide

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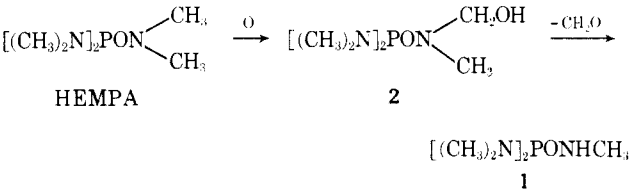
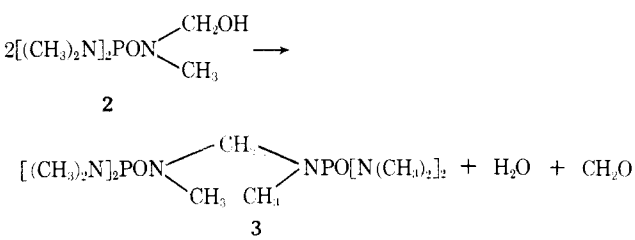
Hexamethylphosphoric triamide (HEMPA) is a chemosterilant of various vertebrate[2] and invertebrate[3] animals but its physiological effects and metabolism have been studied most extensively in the house fly, *Musca domestica* L.[4] Though HEMPA lacks any apparent alkylating properties, its cytological effects in the reproductive organs of flies are similar to those of aziridinyl alkylating agents.[4a,b] The principal metabolic pathway of HEMPA in house flies is its demethylation to pentamethylphosphoric triamide (**1**) which is rapidly excreted.[4c] The demethylation is accomplished by microsomal enzymes[4d] but any further demethylation of the pentamethyl compound is so slow that lower methylphosphoric triamides are never isolated in substantial quantities. Since the pentamethyl compound is almost without any sterilizing activity in house flies, HEMPA itself or its intermediates during the first demethylation appear to be the sterilizing agents. In the previously proposed degradation scheme for HEMPA[5] the formation of formaldehyde was supported by experimental evidence but the intermediate hydroxymethyl compound (**2**) was never isolated or synthesized. We have now prepared **2** by an exceedingly simple procedure, *i.e.*, by treating **1** with aq CH_2O at room temperature. The properties of **2** account for the difficulties connected with its previously attempted isolation and synthesis. Although **2** is stable at 25°, a rapid conversion of **2** into **3** occurs at elevated temperatures. However, aqueous solutions of **2** decompose slowly to **1** even at room temperature. The condensation product **3** is thermally more stable than **2** but on glpc it decomposes to **1**. Consequently, glpc analyses of solutions containing **1**, **2**, **3**, or their mixtures yield only peaks corresponding to **1**.



HEMPA **2**

$[(CH_3)_2N]_2PONHCH_3$ **1**



Because hexamethylphosphorothioic triamide,[6] the sulfur analog of HEMPA, closely resembles the latter in its sterilizing effect we attempted to prepare the corresponding hydroxymethyl compound by a reaction of pentamethylphosphorothioic triamide (**4**) with formaldehyde. However, the only product that could be isolated from this reaction was the bridged compound **5**.

(1) Previous paper in the series: J. A. Settepani, J. B. Stokes, and A. B. Bořkovec, *J. Med. Chem.*, **13**, 128 (1970).

(2) H. Jackson and A. W. Craig, *Nature*, **212**, 86 (1966).

(3) A. B. Bořkovec, "Insect Chemosterilants," Interscience Publishers, New York, N. Y., 1966, p 99.

(4) (a) P. B. Morgan, *Ann. Entomol. Soc. Amer.*, **60**, 812 (1967); (b) B. Řežábová, *Acta Entomol. Bohemoslov.*, **65**, 331 (1968); (c) S. C. Chang, P. H. Terry, C. W. Woods, and A. B. Bořkovec, *J. Econ. Entomol.*, **60**, 1623 (1967); (d) S. Akov, J. E. Oliver, and A. B. Bořkovec, *Life Sci.*, **7** (II), 1297 (1968).

(5) P. H. Terry and A. B. Bořkovec, *J. Med. Chem.*, **11**, 958 (1968).

(6) P. H. Terry and A. B. Bořkovec, *ibid.*, **10**, 118 (1967).