New Compounds

Adamantylamines by Direct Amination of 1-Bromoadamantane

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In the course of our research, it became necessary to synthesize a number of substituted adamantylamines for our testing program. As some of the derivatives involved diadamantyl-substituted amines, we began to investigate a direct high-temperature nucleophilic substitution of bromoadamantanes with the desired amine moiety. The unusual reactivity of 1-bromoadamantane is illustrated by the use of heterocyclic amines, such as pyridine or isoquinoline, as the reaction media.

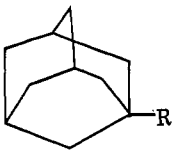
Experimental Section

Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Melting points were taken in an open capillary tube and are uncorrected.

N,N-Diadamantylamine Hydrobromide (General Method).—In a high-pressure, stainless steel bomb were charged 10.6 g (0.07 mole) of 1-aminoadamantane and 10.7 g (0.049 mole) of 1-bromoadamantane. The bomb was closed and heated overnight at 255°. The container was then cooled to room temperature and the solidified product was removed. The crude reaction mixture was dissolved in about 200 ml of hot absolute EtOH, treated with decolorizing carbon, and filtered. The desired product, N,N-diadamantylamine hydrobromide, precipitated on cooling. Recrystallization from EtOH yielded 12.3 g (67.2%), mp 334°. *Anal.* ($C_{20}H_{31}N \cdot HBr$) C, H, N.

Other adamantylamines prepared by this and subsequent procedures are listed in Tables I and II.

TABLE I



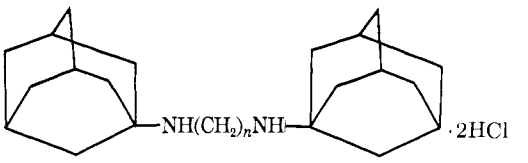
R	Mp, °C	Yield, %	Formula	Analyses
Amino	320	23	$C_{10}H_{17}N \cdot HCl$	C, H, N
γ-Hydroxypropylamino	93–95	14–20	$C_{13}H_{23}NO$	C, H, N
N-Methylanilino	109–111	33	$C_{17}H_{23}N$	C, H, N
m-Toluidino	57.5–59	48.8	$C_{17}H_{23}N$	C, H; N[a]
p-Toluidino	66–67	41	$C_{17}H_{23}N$	C, H; N[b]
m-Xylidino	140–141	40–45	$C_{18}H_{25}N$	C, H, N
Piperidino	312–314	54	$C_{15}H_{25}N \cdot HCl$	C, H, N
4-Methylpyridinium	240–242 dec	24	$C_{16}H_{22}BrN$	C, H, N

[a] N: calcd, 5.80; found, 5.27. [b] N: calcd, 5.80; found, 6.38.

2-(1-Adamantyl)isoquinolinium Bromide.—1-Bromoadamantane (5 g, 0.023 mole) and 30 g (0.23 mole) of isoquinoline were heated in an oil bath at 220° for 16 hr. The flask was cooled and the solution was concentrated *in vacuo*. The solid residue was washed with 250 ml of dry ether. Recrystallization from EtOH-Et_2O gave 5.4 g (68.3%) of product, mp 272–273°. *Anal.* ($C_{19}H_{22}BrN$) C, H, N.

N,N′-Bis(1-adamantyl)butanediamine Dihydrochloride.—In a high-pressure, stainless steel bomb were charged 15 g (0.069 mole) of 1-bromoadamantane and 2.64 g (0.030 mole) of 1,4-butanediamine. The bomb was then heated at 200° for 16 hr and cooled, and its contents were added to 5% HCl. Extraction with ether removed unreacted adamantyl bromide. The aqueous acid layer was made basic and the diamine was extracted (Et_2O). The ether layer was washed (H_2O) until neutral, dried (Na_2SO_4), and concentrated *in vacuo*. The product was then converted to the dihydrochloride, which, after recrystallization from EtOH-Et_2O, gave 6 g (46.6%) of product, mp 225–227° (Table II). *Anal.* ($C_{24}H_{40}N_2 \cdot 2HCl$) C, H, N.

TABLE II



n	Mp, °C	Yield, %	Formula	Analyses
3	290–291	30	$C_{23}H_{38}N_2 \cdot 2HCl$	C, H; N[a]
5	303	33	$C_{25}H_{42}N_2 \cdot 2HCl$	C, H, N
7	283–285	20	$C_{27}H_{46}N_2 \cdot 2HCl$	C, H, N
10	323	55	$C_{30}H_{52}N_2 \cdot 2HCl$	C, H, N

[a] N: calcd, 6.74; found, 7.11.

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Potential Antidiabetics. I. 1-(2,4-Dinitrophenyl)-3,5-dimethyl-4-arylazopyrazoles

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3,5-Dimethylpyrazole was found to be 50 times as potent as tolbutamide in lowering blood sugar in glucose-primed, fasted, intact rats.[1] Our interest in drugs having hypoglycemic activity led us to prepare a series of compounds containing either a pyrazole or an isoxazole ring.[2-5] This report includes the synthesis of 1-(2,4-dinitrophenyl)-3,5-dimethyl-4-arylazopyrazoles.

Experimental Section[6]

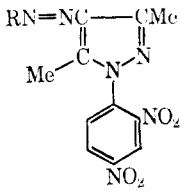
2,3,4-Pentanetrione 3-arylhydrazones were prepared by coupling diazotized anilines with 2,4-pentanedione[7] by the method of Garg and Joshi;[8] the compounds so obtained are summarized in Table I.

Pyrazole Derivatives.—2,4-Dinitrophenylhydrazine (0.01 mole) dissolved in concentrated H_2SO_4 (6 ml) and EtOH (50 ml) was added to the 2,3,4-pentanetrione 3-phenylhydrazone (0.01 mole) in AcOH and refluxed for 1–3 hr. On cooling shiny crystals

(1) G. C. Gerritsen and W. E. Dulin, *Diabetes*, **14**, 507 (1965).
(2) H. G. Garg and S. S. Joshi, *J. Org. Chem.*, **26**, 946 (1961).
(3) H. G. Garg, *ibid.*, **26**, 948 (1961).
(4) H. G. Garg, *J. Indian Chem. Soc.*, **39**, 563 (1962).
(5) H. G. Garg, *ibid.*, **40**, 135 (1963).
(6) Melting points were taken on a Kofler hot stage apparatus.
(7) A product of British Drug House Ltd.
(8) H. G. Garg and S. S. Joshi, *J. Indian Chem. Soc.*, **37**, 626 (1960).

TABLE I

1-(2,4-DINITROPHENYL)-3,5-DIMETHYL-4-(SUBSTITUTED ARYLAZO)PYRAZOLES AND 2,3,4-PENTANETRIDIONE 3-ARYLHYDRAZONES



RNHN=C(COCH$_3$)$_2$

No.	R	Mp, °C	Color	Formula[b]	Mp, °C	Color	Formula[c]
1	Phenyl	259–260	Dark red	$C_{17}H_{14}N_6O_4$	84–85[a]	Bright yellow needles	
2	2-$NO_2C_6H_4$	216–218	Dull red	$C_{17}H_{13}N_7O_6$	175[a]	Yellow plates	
3	3-$NO_2C_6H_4$	236–237	Orange	$C_{17}H_{13}N_7O_6$	131[a]	Golden yellow plates	
4	3-ClC_6H_4	257	Dark red	$C_{17}H_{13}ClN_6O_4$	78–79[a]	Reddish yellow plates	
5	4-ClC_6H_4	254–255	Dark red	$C_{17}H_{13}ClN_6O_4$	129[a]	Yellow needles	
6	4-$CH_3C_6H_4$	252	Red	$C_{18}H_{16}N_6O_4$	90–91[a]	Yellow needles	
7	2-$CH_3OC_6H_4$	Above 300	Dark brown	$C_{18}H_{16}N_6O_5$	135	Yellow needles	$C_{12}H_{14}N_2O_3$
8	3-$CH_3OC_6H_4$	Above 300	Orange	$C_{18}H_{16}N_6O_5$	76	Reddish yellow needles	$C_{12}H_{14}N_2O_3$
9	4-$CH_3OC_6H_4$	242–243	Brown	$C_{18}H_{16}N_6O_5$	95[a]	Yellow needles	
10	2-$C_2H_5OC_6H_4$	260–262	Purple	$C_{19}H_{18}N_6O_5$	128	Bright yellow needles	$C_{13}H_{16}N_2O_3$
11	3-$C_2H_5OC_6H_4$	130	Reddish yellow	$C_{19}H_{18}N_6O_5$	102	Yellow	$C_{13}H_{16}N_2O_3$
12	4-$C_2H_5OC_6H_4$	134–135	Reddish yellow	$C_{19}H_{18}N_6O_5$	118	Bright red needles	$C_{13}H_{16}N_2O_3$
13	2,5-$Cl_2C_6H_3$	213–214	Orange	$C_{17}H_{12}Cl_2N_6O_4$	120	Light yellow needles	$C_{11}H_{10}Cl_2N_2O_2$
14	2,5-$(CH_3)_2C_6H_3$	203	Yellowish orange	$C_{19}H_{18}N_6O_4$	103–104	Yellow needles	$C_{13}H_{16}N_2O_2$
15	2,5-$(CH_3O)_2C_6H_3$	236–238	Brownish red	$C_{19}H_{18}N_6O_6$	128–129	Golden yellow needles	$C_{13}H_{16}N_2O_4$
16	2,4-$(O_2N)_2C_6H_3$	255–257	Orange	$C_{17}H_{12}N_8O_8$	163–164	Yellow needles	$C_{13}H_{14}N_4O_6$
17	2-Cl-4-$O_2NC_6H_3$	254–255	Orange	$C_{17}H_{12}ClN_7O_6$	180[a]	Yellow plates	
18	4-$H_2NSO_2C_6H_4$				205	Yellow plates	$C_{11}H_{13}N_3O_4S$

[a] Reference 8 and other references cited therein. [b] All compounds were analyzed for N, and the analytical values were within ±0.4% of the calculated values. [c] As in footnote *b*, except for **1–6, 9, 17**.

separated which were recrystallized either from EtOH, DMF or DMF–EtOH. They were almost insoluble in H_2O and soluble in organic solvents. The substituted pyrazoles which were prepared are also summarized in Table I.

Acknowledgments.—The authors wish to thank Professor W. U. Malik, Head of the Chemistry Department, for providing the necessary facilities for this work and the C.S.I.R., New Delhi (India), for a junior research fellowship (held by P. P. S.).

Potential Antidiabetics. II. 1-(2,4-Dinitrophenyl)-3-methyl-4-arylazo-2-pyrazolin-5-ones

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In order to examine their hypoglycemic activity a series of 1-(2,4-dinitrophenyl)-3,5-dimethyl-4-arylazopyrazoles has been reported in the previous communication.[1] The present report concerns the synthesis of 1-(2,4-dinitrophenyl)-3-methyl-4-arylazo-2-pyrazolin-5-ones.

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

Experimental Section[2]

Ethyl 2,3-dioxobutyrate 2-arylhydrazones were prepared by coupling diazotized anilines with ethyl acetoacetate[3] by the method of Garg[4] and are summarized in Table I on the following page.

1-(2,4-Dinitrophenyl)-3-methyl-4-arylazo-2-pyrazolin-5-ones.—Ethyl 2,3-dioxobutyrate 2-arylhydrazone (0.002 mol) was dissolved in 20 ml of glacial AcOH. To it was added a hot saturated solution of 2,4-dinitrophenylhydrazine (DNP) (0.004 mol) in glacial AcOH (nearly 1 g of DNP in 15 ml of AcOH). The contents were refluxed for 1 hr. On cooling, shining crystals separated out which were recrystallized either from DMF or AcOH. These derivatives are insoluble in H_2O, soluble in $CHCl_3$ and C_5H_5N, and sparingly soluble in EtOH, C_6H_6, AcOH.

These colored substances on treatment with H_2O followed by KOH solution give color changes. Similar results are obtained with piperidine.

The substituted pyrazoles which were prepared are also summarized in Table I on the following page.

Acknowledgment.—The authors wish to thank Professor W. U. Malik, Head of the Chemistry Department, for providing the necessary facilities for carrying out the work and the C.S.I.R., New Delhi (India), for a Junior Research Fellowship (held by P. P. S.).

(2) Melting points are uncorrected.

(3) Commercially available.

(4) H. G. Garg, Ph.D. Thesis, University of Agra, 1950.