New Compounds

Adamantylamines by Direct Amination of 1-Bromoadamantane

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Received March 25, 1968

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.

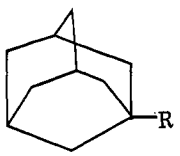
Experimental Section

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



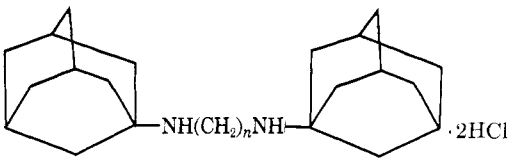
R	Mp, °C	Yield, %	Formula	Analyses
Amino	320	23	$C_{10}H_{17}N \cdot HCl$	C, H, N
γ-Hydroxypropylamino	93–95	14–20	$C_{13}H_{23}NO$	C, H, N
N-Methylanilino	109–111	33	$C_{17}H_{23}N$	C, H, N
m-Toluidino	57.5–59	48.8	$C_{17}H_{23}N$	C, H; N[a]
p-Toluidino	66–67	41	$C_{17}H_{23}N$	C, H; N[b]
m-Xylidino	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.

Acknowledgments.—The authors are grateful for the advice and guidance of Dr. Jack Mills in the execution of this work. The authors also wish to thank Dr. H. E. Boaz and Mr. D. O. Woolf for physicochemical data and Mr. W. L. Brown and his associates for numerous microanalyses. The sustaining interest and advice of Dr. K. Gerzon is worthy of special mention.

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

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Received February 14, 1968

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).