and a reference reagent (physostigmine sulfate NBCo., $I_{50} \pm$ S.E.: $5.24 \pm 0.19 \times 10^{-8} M$).

The rate for the reaction is expressed as

$$V = \left(\frac{(\mu l.\ CO_2 \text{ at } 30 \text{ min.}) - (\mu l.\ CO_2 \text{ at } 10 \text{ min.})}{20}\right) \times 60$$

where V signifies $\mu l.\ CO_2$/hr. evolved within the reaction interval of +10 through +30 min., during which time the rate was linear in all instances. The percentages of inhibition were calculated as follows: $I = ((V_c - V_i)/V_c) \times 100$, where V_c represents the control rate and V_i the inhibited rate.

All compounds were first screened for inhibitory properties at $100 \times 10^{-5} M$ concentrations. For purposes of our evaluation compounds exhibiting less than 15% inhibition under these conditions were considered to have insignificant activity; at least two independent duplicate determinations were run to confirm responses of less than 15% inhibitory action. Conversely, an observed inhibition of 15% or higher at $100 \times 10^{-5} M$ concentration was deemed sufficient to warrant further evaluation.

The effect of such compounds was evaluated at four appropriate concentrations, with at least two independent duplicate determinations for each concentration, and the I_{50} (molarity of compound effecting 50% inhibition) was graphically determined. Since it is our intent to subject the data reported in this communication to further mathematical treatment, we have computed the standard error[12] for each I_{50} value; they are included in Tables I and II.[13]

Acknowledgment.—We wish to express our sincere thanks to Mr. John M. Cole and Dr. Leonard B. Achor of Sandoz Pharmaceuticals for furnishing us with (+)-lysergic acid diethylamide tartrate.

(12) G. W. Snedecor and W. G. Cochran, "Statistical Methods," 5th Ed., Iowa State College Press, Ames, Iowa, 1956, pp. 42–45.

(13) Although standard error values have not been included in the related preceding publications,[2,3] in no instance did the deviations in our determinations exceed the ranges reported in this paper.

N-Alicyclic Amphetamines

MORRIS FREIFELDER

Research Division, Abbott Laboratories, North Chicago, Illinois

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The availability of some aminocyclanes suggested to us that it might be worthwhile to prepare N-alicyclic amphetamines and investigate the physiological effect of these compounds. They were readily prepared by reductively alkylating the amines with 1-phenyl-2-propanone (phenylacetone) in the presence of platinum oxide catalyst under a pressure of a few atmospheres of hydrogen. Hydrogenation proceeded at a moderately rapid rate. The yield of distilled bases ranged from 60 to 83%. The hydrochloride salts were also prepared. As the size of the ring increased, water solubility of the salts decreased.

Pharmacology.—The compounds, as hydrochloride salts, were tested as appetite depressants in normal trained rats at two dose levels: at 0.011 and 0.044 mmole/kg. Compounds I, II, and III were administered in aqueous solution. The salts of IV and V, much less soluble, were used in suspension in 0.3% tragacanth solution. The anorectic effect was determined by comparison of the food intake of the treated and untreated animals.[1]

The only active member of the series was the cyclopropyl derivative. The next in the series, the cyclobutyl derivative, had only slight activity; the remainder were inactive.

Experimental

All melting points were taken in a Thomas–Hoover melting point apparatus calibrated against known standards. The amines used in this work are either available commercially[2] or can be prepared by known methods.[3]

The following is an example of the method used to prepare the amines listed in Table I.

2-(N-Cycloheptyl)-1-methylphenethylamine.—A solution of 20.1 g. (0.15 mole) of 1-phenyl-2-propanone and 16.95 g. (0.15 mole) of cycloheptylamine in 150 ml. of absolute alcohol was allowed to stand for about 1 hr. Platinum oxide catalyst (0.6 g.) was added and hydrogenation then carried out under 2 atm. pressure. When the uptake of hydrogen was complete (less than 2 hr.), the solution was filtered and concentrated. The residue was then distilled and the results recorded (see Table I).

To form the hydrochloride salt, an anhydrous ether solution of the amine was treated with an equivalent of alcoholic hydrogen chloride and allowed to stand. In a short period the salt precipitated. It was filtered, washed with anhydrous ether, and analyzed after thorough drying.

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TABLE I

$C_6H_5CH_2CH(CH_3)NHR$

	R	Yield, %	B.p., °C. (mm.)	$n^{25}D$	Hydrochloride, m.p., °C.	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
I	Cyclopropyl	70.8	123–125 (18)	1.5130		$C_{12}H_{17}N$	82.22	82.12	9.79	10.11	8.01	7.98
					108–109	$C_{12}H_{18}ClN$	68.06	68.12	8.56	8.58	6.61	6.65
II	Cyclobutyl	83	122 (10)	1.5143		$C_{13}H_{19}N$	82.48	82.67	10.11	10.28	7.41	7.56
					126.5	$C_{13}H_{20}ClN$[a]	69.15	68.86	8.93	8.87	6.20	6.02
III	Cyclopentyl	79	126 (5.5–6.0)	1.5148		$C_{14}H_{21}N$	82.69	83.00	10.41	10.57	6.89	7.12
					178	$C_{14}H_{22}ClN$	70.12	69.85	9.37	9.19	5.84	6.03
IV	Cyclohexyl	60	140 (3)	1.5145		$C_{15}H_{23}N$	82.88	83.00	10.66	10.35	6.46	6.88
					184–184.5	$C_{15}H_{24}ClN$	70.98	71.26	9.53	9.48	5.52	5.68
V	Cycloheptyl	72.1	145–147 (4)	1.5193		$C_{16}H_{25}N$	83.04	82.94	10.89	10.84	6.06	6.26
					194	$C_{16}H_{26}ClN$	71.74	71.70	9.78	9.65	5.23	5.04

[a] *Anal.* Calcd.: Cl, 15.74. Found: Cl, 15.84.

(1) A more detailed description of the test method will be published elsewhere by the Pharmacology Department of this Laboratory.

(2) Cyclopropylamine and cyclopentylamine can be purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin; cyclohexylamine is manufactured by Abbott Laboratories.

(3) Cycloheptylamine: M. Freifelder, W. D. Smart, and G. R. Stone, *J. Org. Chem.*, **27**, 2209 (1962). Cyclobutylamine was prepared by a series of reactions described by G. B. Heisig, *J. Am. Chem. Soc.*, **63**, 1698 (1941), starting from cyclobutanecarboxylic acid.