drying *in vacuo*, 10.3 Gm. (73%) of white crystalline solid, melting at 235–236°.

Anal.—Calcd. for $C_{16}H_{18}Br_2Cl_2N_4S_2$: N, 9.98. Found: N, 9.83.

Biological

The methods used for the antituberculous testing have been noted previously and are described in detail in a previous communication (7).

Mice in groups of four, contained in individual cages, were exposed in a closed chamber for 20 min. to an aerosol of the compound being studied. The aerosols were prepared from a solution of 10 mg./ml. of the compound in 1:1 acetone–propylene glycol, and the estimated exposure concentration was 0.5 mg./L. at 20 p.s.i.

Following exposure, the mice were removed and observed for abnormal activities at periods of 5 min. for a total of 20 min. In the absence of continued effects, the mice were sacrificed 24 hr. after completion of the observation period, and the lungs examined for gross pathological changes such as edema or hemorrhage. The most frequently noticed effect was a decreased motor activity ranging from two out of four mice for compounds *5* and *6* to four out of four mice for compounds *1*, *3*, and *4*. One exception to this pattern was seen with compound *8*, where four out of four mice showed increased motor activity. Normal lung size and appearance were noted for all mice except one of the group exposed to compound *1*. In this case the lung appeared slightly hemorrhagic.

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Synthesis and Pharmacological Screening of Aminoalkyl-hydrazines

By TIBERIO BRUZZESE, SILVANO CASADIO, GERMANO COPPI, and ERNESTA MARAZZI-UBERTI

Some aminoalkyl-hydrazines have been prepared by acid hydrolysis of the corresponding sydnones and submitted to pharmacological screening. Some of the compounds displayed a moderate protective action against restraint ulcer in the rat.

THE INTERESTING pharmacological properties shown by several hydrazines (1–4) and the availability of 3-aminoalkyl-sydnones (5) as intermediates, led us to the preparation of some aminoalkyl-hydrazines for pharmacological screening.

Two of these compounds (I and V, Table I) have been recently obtained by Elslager *et al.* (4) through reaction of the appropriate aminoalkyl chloride with excess hydrazine and studied only as central nervous system stimulants and antibacterial compounds. By contrast, the method used in the present work was essentially that of Fugger *et al.* (6), consisting of acid hydrolysis of the corresponding sydnones. Concentrated hydrochloric acid was used for the hydrolysis; an essential factor in obtaining high yields is that the temperature should not exceed 50–70°. Under these conditions the required aminoalkyl-hydrazine could be isolated directly from the reaction mixture as the hydrochloride. The optimal reaction conditions are summarized in Table I.

An example of the method is described under *Experimental*.

Received March 19, 1965, from the Research Laboratories, Istituto De Angeli, Milan, Italy.
Accepted for publication May 3, 1965.
The authors thank Dr. G. Sekules for microanalyses.

EXPERIMENTAL

Melting points were determined on a Townson-Mercer melting point apparatus and are corrected

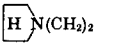
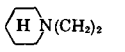
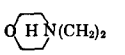
(2-Morpholinoethyl)-hydrazine Dihydrochloride (IV).—A solution of 25 Gm. of 3-(2-morpholinoethyl)-4-methyl-sydnone hydrochloride in 45 ml. of concentrated hydrochloric acid was cautiously heated at 50° for 1 hr., when carbon dioxide was freely given off. The solution was washed with 20 ml. of ether and evaporated to dryness *in vacuo* at approximately 40°. The residue was triturated with a little ethanol, giving 16.6 Gm. of product. The product was crystallized from 95% ethanol, giving colorless crystals, m.p. 163–164° dec.

SCREENING RESULTS

The acute toxicity, behavioral effect, and the analgesic, IMAO, anti-inflammatory, antipyretic, diuretic, hypoglycemic, anti-ulcer, antidepressive, and hypotensive actions were evaluated, along with the coronary dilating activity and the action on isolated vessels as well as the *in vitro* antifibrillar, antibacterial, antiamebic, and antitrichomonas actions. The methods described in a previous paper (5) were used. The compounds were administered by intraperitoneal injection in the form of aqueous solution in all the *in vivo* tests, except for the hypoglycemic and diuretic tests where they were given orally. The highest dose which did not cause death of the animal or an obvious toxic symptomatology was used for each experiment.

The results of the activity tests considered most interesting are given in Table II. Properties common to all the compounds are a low toxicity, moderate antipyretic action, and a mild CNS excita-

TABLE I.—AMINOALKYL-HYDRAZINE DIHYDROCHLORIDES
R—NH—NH_2 · 2HCl

Compd.	R	Reaction Temp., °C. (Time, hr.)	Yield,[a] %	M.p., °C.	Recrystn. Solvent	Formula	Anal. % Calcd.	Found
I[b]	$(C_2H_5)_2N(CH_2)_2$	70 (3)	77	100–102 dec.	Isopropanol	$C_6H_{19}Cl_2N_3$	C, 35.30 H, 9.38 Cl, 34.74 N, 20.58	C, 35.02 H, 9.42 Cl, 34.92 N, 20.20
II		50 (1)	82	123–125 dec.	Ethanol	$C_6H_{17}Cl_2N_3$	C, 35.65 H, 8.47 Cl, 35.08 N, 20.79	C, 35.74 H, 8.49 Cl, 35.00 N, 20.51
III		50 (1)	82	151–152 dec.[c]	Ethanol	$C_7H_{19}Cl_2N_3$	C, 38.89 H, 8.86 Cl, 32.81 N, 19.44	C, 38.44 H, 9.02 Cl, 32.59 N, 19.34
IV		50 (1)	76	163–164 dec.	Ethanol, 95%	$C_6H_{17}Cl_2N_3O$	C, 33.03 H, 7.86 Cl, 32.51 N, 19.27	C, 32.90 H, 7.78 Cl, 32.53 N, 19.09
V[b]	$(CH_3)_2N(CH_2)_3$	70 (5)	91	135–136 dec.	Ethanol	$C_5H_{17}Cl_2N_3$	C, 31.58 H, 9.02 Cl, 37.30 N, 22.10	C, 31.89 H, 9.12 Cl, 37.30 N, 22.28

[a] Crude product. [b] Free base, see *Reference 4*. [c] This compound gives a monohydrate, m.p. 118–119°.

TABLE II.—PHARMACOLOGICAL SCREENING RESULTS

Compd.	LD_{50} (approx.), Mouse mmole/Kg., i.p.	mmole/Kg., i.p.	Action on the CNS, Mouse	Antipyretic—Activity, Rat— mmole/Kg., i.p.	Max. Temp. Decrease, °C.	Hypoglycemic—Action, Rat— mmole/Kg., p.o.	Blood Sugar Decrease, %	Anti-Ulcer—Action,[a] Rat— mmole/Kg., i.p.	Inhibition of Ulcer, %
I	>7.84	1.96	Moderate increase in irritability, curiosity, and response to pain	1.96	0.9	0.24	24	1.96	60
II	>3.96	1.98	Moderate increase in spontaneous activity, curiosity, and irritability	1.98	1.0	0.25	Inact.	1.98	80
III	>3.70	0.92	Moderate increase in spontaneous activity and irritability	0.92	0.9	0.23	10	0.92	20
IV	>3.67	0.92	Moderate increase in spontaneous activity, curiosity, irritability, and response to pain	0.92	0.9	0.23	Inact.	0.92	Inact.
V	7.89–8.94	2.10	Moderate increase in curiosity, irritability, and response to pain	2.10	1.9	0.26	Inact.	2.10	60
Phenylbutazone				0.32	1.6				
Tolbutamide						0.18	48		

[a] Rest;aint ulcer; the ED_{50} value for the standard atropine sulfate is 1 mg./Kg. s.c.

tory action shown by increased spontaneous activity, curiosity, and irritability in mice. It is interesting to observe that the excitatory action is not accompanied by an MAO-inhibiting action, in contrast to what is seen for compounds of similar structure (3, 4). The hypoglycemic action of I is of some interest. The only noteworthy pharmacological action, although occurring only at high doses, was the protective action against restraint ulcer in the rat. Compounds I, II, and V were found to be the most active in this sense.

Phenylbutazone, tolbutamide, and atropine were used as standards for comparison of the antipyretic, hypoglycemic, and anti-ulcer activities.

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