methanol–water (20:80:12:8). Celite (50 g.) was added and the mixture was packed on top of a column which had been prepared from 400 g. of Celite thoroughly mixed with 200 ml. of the lower phase. The column (5.5 × 60 cm., 900 ml. h.b.v.) was developed with the upper phase and the effluent stream was monitored at 240 mμ. The desired product was eluted in the 5.5–7.5 h.b.v. and was isolated by evaporation of pooled fractions and crystallization from ether–methylene chloride. There was obtained 130 mg. (6.3% over all from II) of XXXI, m.p. 220–223°. A sample recrystallized from the same mixture showed m.p. 221–223°; $[\alpha]^{25}D$ + 54°; λ_{max}. 243 mμ (ε 13,400); ν_{max}. 1666 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.53; H, 8.98.

2,6α-Dimethylprednisolone 20-Ethylene Ketal (21-Acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-2,6α-dimethyl-1,4-pregnadien-3-one, XXXII).—Acetylation of XXXI in the usual manner with acetic anhydride in pyridine gave a crude acetate, which was treated with dichlorodicyanobenzoquinone[7] by the procedure described above for V. Evaporation of the washed and dried benzene solution gave a solid which was dissolved in a small amount of acetone and filtered through activated charcoal. Hexane was added at the boiling point until a solid precipitated as a gel. The dried material weighed 13 mg.; m.p. 163–168°; 92.5% $\Delta^{1,4}$-3-one by polarography[37]; λ_{max}. 250 mμ (ε value inaccurate for lack of sample); ν_{max}. 1748, 1663, 1626 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 67.48; H, 7.71.

Synthesis of Sulfonylhydrazine Derivatives with Monoamine Oxidase Inhibitory Activity[1]

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A number of aralkylsulfonylhydrazine derivatives were prepared as possible inhibitors of monoamine oxidase. *In vitro* results, as well as *in vivo* effects on mouse brain serotonin levels, are reported. Several 1-sulfonyl-1-aralkylhydrazines were strongly active in both tests. Methods of preparation of 1-substituted-sulfonyl-1-aralkylhydrazines are described.

The discovery of the clinically useful antidepressant activity of

1-isopropyl-2-isonicotinoylhydrazine[3] stimulated a widespread search for other hydrazine derivatives possessing equal or greater activity but with reduced side effects. The finding by Zeller *et al.*[4] that the drug was a powerful inhibitor of monoamine oxidase (MAO) provided a convenient biochemical tool to screen other compounds for similar activity. The group of hydrazine derivatives which has found clinical use includes phenethylhydrazine,[5a] α-methylphenethylhydrazine,[5b] 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)-hydrazine,[5c] and 2-[2-(benzylcarbamoyl)-ethyl]-1-isonicotinoylhydrazine.[5d] In addition, other hydrazine derivatives have been claimed to inhibit monoamine oxidase, and to possess antidepressant activity.[6]

These valuable properties of the 1-acyl-2-alkyl(and aralkyl)-hydrazines suggested that the sulfonyl analogs should be studied to determine whether a parallel biological activity existed. An initial attempt to prepare 1-*p*-tosyl-2-benzylhydrazine (I) by the interaction of benzylhydrazine and *p*-toluenesulfonyl chloride led to the formation of 1-*p*-tosyl-1-benzylhydrazine (II). The identity of II was established by its infrared spectrum, its insolubility in aqueous alkali, and by its easy conversion to 1-*p*-tosyl-1-benzyl-2-benzylidenehydrazine (IV) on treatment with benzaldehyde. The preparation of II also was achieved by an independent synthesis using *p*-tosylhydrazine and benzyl bromide. An alternate synthesis of IV involved the interaction of 1-*p*-tosyl-2-benzylidenehydrazine (III) with benzyl bromide.

The synthesis of 1-*p*-tosyl-2-benzylhydrazine (I) was achieved by the catalytic hydrogenation of III. This material was soluble in alkali, and possessed an infrared spectrum consistent with the assigned structure. Compounds I and II were both insoluble in dilute mineral acid.

1-*p*-Tosyl-2-benzylhydrazine (I) was not a MAO inhibitor. However, the isomer, 1-*p*-tosyl-1-benzylhydrazine (II), was shown to be a potent MAO inhibitor *in vitro*, and to produce a marked eleva-

(1) This work has been presented before the Canadian Conference on Pharmaceutical Research, Hamilton, Ontario, August 11, 1961.

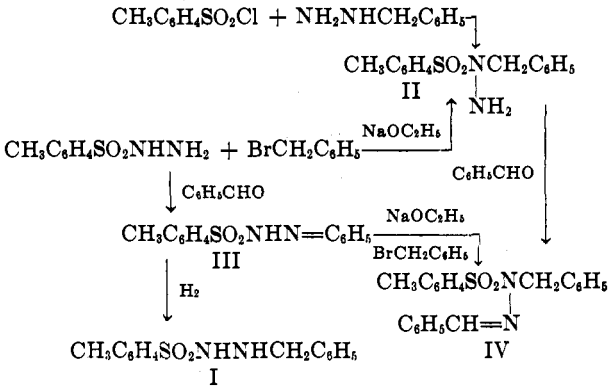
(2) Author to whom correspondence should be addressed at Merck Sharp and Dohme of Canada Limited, Montreal, P. Q., Canada.

(3) Iproniazid, Marsilid®.

(4) E. A. Zeller and J. Barsky, *Proc. Soc. Exp. Biol. Med.*, **81**, 459 (1952).

(5) The generic and registered trademark names for these drugs are: (a) phenelzine, Nardil®; (b) pheniprazine, Catron®; (c) isocarboxazide, Marplan®; (d) nialamide, Niamid®.

(6) (a) T. S. Gardner, E. Wenis and J. Lee, *J. Med. Pharm. Chem.*, **2**, 133 (1960); (b) G. Zbinden, L. O. Randall and R. A. Moe, *Diseases of Nervous System*, **21**, sect. 2, 89 (1960).

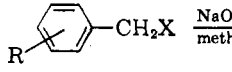
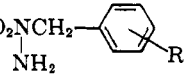


tion of brain serotonin in mice. This observation led to the study of additional 1-aryl(and alkyl)-sulfonyl-1-alkyl(and aralkyl)-hydrazines, as well as a few 1,2-isomers.

The synthetic routes for the 1-acyl-1-alkylhydrazines[7] were not generally applicable to the preparation of sulfonyl analogs because of the greater instability of the latter. Three different methods for the synthesis of this previously unreported class of hydrazine derivatives

Method A. $RNHNH_2 + R'SO_2Cl \xrightarrow[\text{ethanol or chloroform}]{\text{base (1 mole)}} RNSO_2R'$ (NH$_2$)

Method B.

$R'SO_2NHNH_2 +$  $\xrightarrow[\text{methanol}]{NaOCH_3}$ 

Method C. $R'SO_2NHR + NH_3{}^+OSO_2O^- \xrightarrow[\text{ethanol}]{\text{NaOH, H}_2O} R'SO_2N(NH_2)-R$

were devised. The compounds prepared, along with analytical and other data, are presented in Table I.

Direct interaction of a sulfonyl chloride with an unhindered monosubstituted aralkylhydrazine in ethanol or chloroform, in the presence of one mole of base, yielded almost exclusively the 1,1-isomer (Method A). This procedure when applied to hindered hydrazines[8] such as

(7) (a) A. Ebnother, E. Jucker, A. Lindenmann, E. Rissi, R. Steiner, R. Suess and A. Vogel, *Helv. Chim. Acta*, **42**, 533 (1959); (b) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **21**, 356 (1956).

(8) (a) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway and A. Horita, *J. Am. Chem. Soc.*, **81**, 2805 (1959); (b) O. Westphal, *Ber.*, **74**, 759 (1941).

TABLE I

1-SULFONYL-1-ARALKYLHYDRAZINES ($RSO_2NR'NH_2$)

RSO_2	R'	Method	Yield, %	M.p., °C.	Recryst. solvent	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
p-Acetamidobenzenesulfonyl	Benzyl	A	75	131–132[a]	Acetonitrile	$C_{15}H_{17}N_3O_3S$	56.40	5.36	13.16	56.72	5.66	13.36
		B	6	129–131[a]								
Benzenesulfonyl	Benzyl	A	73	114–116[a]	Acetonitrile	$C_{13}H_{14}N_2O_2S$	59.52	5.38	10.68	59.37	5.21	10.75
p-Chlorobenzenesulfonyl	Benzyl	A	43.5	116–117[a]	Benzene	$C_{13}H_{13}ClN_2O_2S$	52.61	4.42	9.44	52.59	4.69	9.35
Methanesulfonyl	Benzyl	A	41	72–75[b]	Benzene	$C_8H_{12}N_2O_2S$	47.98	6.04	13.99	48.18	6.21	14.06
		B	29	75–77								
p-Tosyl	Benzyl	A	62	129–131[a]	Acetonitrile	$C_{14}H_{16}N_2O_2S$	60.85	5.84	10.14	60.86	5.85	10.27
		B	41	127.5–128.5[a]								
		C	59	131–133[a]								
p-Tosyl	3-Chlorobenzyl	B	26	119–122[a]	Acetonitrile	$C_{14}H_{15}ClN_2O_2S$	54.09	4.86	9.01	54.39	4.76	9.16
Ethanesulfonyl	3,4-Dichlorobenzyl	A	44	90–95	2-Propanol	$C_9H_{12}Cl_2N_2O_2S$	38.17	4.27	9.89	38.46	4.31	10.10
Methanesulfonyl	3,4-Dichlorobenzyl	A	51	101–103[a]	Ethanol	$C_8H_{10}Cl_2N_2O_2S$	35.70	3.74	10.41	35.92	3.91	10.62
p-Tosyl	3,4-Dichlorobenzyl	A	51	121–124[a]	Acetonitrile	$C_{14}H_{14}Cl_2N_2O_2S$	48.70	4.09	8.11	48.76	4.23	8.27
Methanesulfonyl	Phenethyl	A	39	65–67	Diethyl ether	$C_9H_{14}N_2O_2S$	50.45	6.59	13.08	50.11	6.73	13.27
p-Tosyl	Phenethyl	A	61	90–96	2-Propanol	$C_{15}H_{18}N_2O_2S$	61.89	6.36	9.56	62.04	6.25	9.65

[a] Melted with decomposition. [b] Decomposed upon storage in a closed vial for several months.

TABLE II

1-SULFONYL-2-ARALKYL(AND ALKYL)HYDRAZINES (RSO_2NHNHR')

RSO_2	R'	Method	Yield, %	M.p., °C.	Solvent	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
p-Tosyl	Benzyl	..	33	127–128[a]	Ethanol–water	$C_{14}H_{16}N_2O_2S$	60.85	5.84	10.14	61.12	5.10	10.19
α-Tosyl	Benzyl	B	19	139–142[a]	2-Propanol	$C_{14}H_{16}N_2O_2S$	60.85	5.84	10.14	60.89	5.26	10.34
p-Tosyl	Isopropyl	A	19	104–107[a]	2-Propanol	$C_{10}H_{16}N_2O_2S$	52.61	7.06	12.27	52.54	7.08	12.34
Methanesulfonyl	*α*-Methylphenethyl	A	55	113–114[a]	Diethyl ether	$C_{10}H_{16}N_2O_2S$	52.61	7.06	12.27	52.74	7.17	12.55
Methanesulfonyl	Phenethyl	A	6	66–69	Diethyl ether	$C_9H_{14}N_2O_2S$	50.45	6.59	13.08	50.59	6.67	13.23

[a] Melted with decomposition.

isopropylhydrazine or α-methylphenethylhydrazine gave the corresponding 2-substituted sulfonylhydrazine. Thus the sulfonyl moiety attached preferentially to the more basic nitrogen unless prevented by steric factors. The interactions of alkyl and aralkylhydrazines with carboxylic acid chlorides and anhydrides, isocyanates, isothiocyanates, alkyl halides and nitrous acid appear to follow the same rule.[9] Instability in the reaction medium apparently prevented the isolation of the desired product from the reactions of benzylhydrazine with 3-pyridylsulfonyl chloride, or with *m*- and *p*-carboxybenzenesulfonyl chlorides. This result probably is related to the instability of sulfonic acid hydrazides possessing a strongly electron attracting substituent.[10]

With Method A in two instances by-products were isolated arising from inadvertent oxidation of unreacted hydrazine by atmospheric oxygen during work-up. From the reaction of ethanesulfonyl chloride and benzylhydrazine, 1-ethanesulfonyl-1-benzyl-2-benzylidenehydrazine was the only pure product isolated. The expected product, 1-ethanesulfonyl-1-(3,4-dichlorobenzyl)-hydrazine, was obtained from the reaction of ethanesulfonyl chloride and 3,4-dichlorobenzylhydrazine in ethanol. The mother liquors, exposed to air for a number of days, became yellow and deposited 3,4-dichlorobenzalazine. Curtius[11] similarly has described the oxidation of benzylhydrazine to 1-benzyl-2-benzylidenehydrazine with a stream of air.

The second method (Method B) for the preparation of 1-sulfonyl-1-aralkylhydrazines involved the interaction of a sulfonylhydrazine with a benzyl halide in the presence of base. This reaction normally yielded a mixture of 1,1- and 1,2-isomers which were separated readily by dissolving the latter in aqueous alkali. The maximum yield of 1,1-isomer was about 40%. Simple alkyl halides were not sufficiently reactive.

From the reaction of α-tosylhydrazine with benzyl bromide, dibenzyl sulfone was isolated in 18% yield as a by-product. Benzyl *p*-tolyl sulfone was identified as a minor product from the reaction

(9) (a) C. Vogelsang, *Rec. trav. chim.*, **62**, 5 (1943); (b) V. Migrdichian, "Organic Syntheses," Reinhold Publishing Corp., New York, 1957, p. 453; (c) R. A. Reed, "Hydrazine and Its Derivatives," Monograph No. 5, The Royal Institute of Chemistry, London, 1957, p. 18; (d) T. W. J. Taylor and W. Baker, "Sidgwick's Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 379; (e) R. L. Hinman and D. Fulton, *J. Am. Chem. Soc.*, **80**, 1895 (1958).

(10) (a) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 4427 (1957); (b) A. T. Dann and W. Davies, *J. Chem. Soc.*, 1050 (1929).

(11) T. Curtius, *J. prakt. Chem.*, **85**, 52 (1912).

of benzyl chloride and *p*-tosylhydrazine. Comrie and Stenlake[12] obtained benzyl 4-pyridyl sulfone from the interaction of 4-pyridylsulfonylhydrazine, benzyl chloride, and base under more drastic conditions. These workers demonstrated that an intermediate sulfinate salt, which reacted directly with benzyl halide to form a sulfone, was produced by the action of alkali on the sulfonylhydrazine. A similar mechanism is presumably responsible for the formation of the two sulfones referred to above.

The third synthetic procedure (Method C) involved the reaction of hydroxylamine-O-sulfonic acid[13] with mono-N-substituted sulfonamides in the presence of aqueous alkali. This method was not studied extensively. The reaction of hydroxylamine-O-sulfonic acid and N-benzyl-*p*-toluenesulfonamide gave a 59% yield of 1-*p*-tosyl-1-benzylhydrazine. In attempting to prepare lower melting, or more water-soluble sulfonylhydrazine derivatives under the same conditions, it appeared that decomposition, probably as described by Nickon and Sinz,[14] took place too readily to allow isolation of a reasonable yield of product. These latter workers reported a method for deamination of primary amines to the corresponding hydrocarbon by the interaction of a suitable sulfonamide derivative with hydroxylamine-O-sulfonic acid. 1,1-Sulfonylhydrazine derivatives were postulated to be intermediates. In support of their mechanism it has been found that 1-*p*-tosyl-1-benzylhydrazine in refluxing 10% sodium hydroxide solution was converted to toluene in at least a 57% yield.

The 1-sulfonyl-2-aralkyl(and alkyl)-hydrazines described in Table II were isolated either as by-products, or as the major product, from attempts to prepare the corresponding 1,1-substituted isomers. Hydrogenation of the corresponding 1-sulfonyl-2-alkylidene(or aralkylidene)-hydrazine is a superior route to these compounds.

For the purpose of biological comparison some 1-acyl-1-aralkylhydrazine derivatives were prepared. 1-Benzoyl-1-benzylhydrazine was obtained in good yield by the interaction of benzoyl chloride and benzylhydrazine in chloroform. Carpino[15] recently reported preparation of this compound by a more involved procedure. 2-Phenethylthiosemicarbazide was synthesized using the method described by

(12) A. M. Comrie and J. B. Stenlake, *J. Pharm. and Pharmacol.*, **13**, 26 (1961).
(13) F. Sommer, O. F. Schulz and M. Nassau, *Z. anorg. u. allgem. Chem.*, **147**, 142 (1925).
(14) A. Nickon and A. Sinz, *J. Am. Chem. Soc.*, **82**, 753 (1960).
(15) L. A. Carpino, A. A. Santilli and R. W. Murray, *ibid.* **82**, 2728 (1960).

Hoggarth and Young[16] for 2-benzylthiosemicarbazide. The structural assignment for 2-phenethylthiosemicarbazide was based on analysis and infrared spectrum, as well as on its conversion to a benzylidene derivative.[17]

Biological Results

The ability of the sulfonylhydrazines to inhibit guinea pig liver MAO, *in vitro*, is illustrated by the data in Table III. 1-*p*-Tosyl-1-benzylhydrazine, 1-methanesulfonyl-1-benzylhydrazine, and 1-*p*-chlorobenzenesulfonyl-1-benzylhydrazine were roughly half as active, on a molar basis, as the unsulfonylated α-methylphenethylhydrazine.[18] However, these three compounds were some 300 times as potent as *in vitro* MAO inhibitors as 1-isonicotinoyl-2-isopropylhydrazine.

A number of the 1-alkylsulfonyl and 1-arylsulfonyl-1-alkylhydrazines were quite good inhibitors of MAO in the brain of intact

TABLE III

MONOAMINE OXIDASE INHIBITION *in vitro*

Warburg flasks contained 3×10^{-3} *M* 5-hydroxytryptamine, 2.5×10^{-3} *M* NaCN, 1.7 ml. of 0.1 *M* phosphate buffer, pH 7.4, 0.5 ml. of fresh guinea pig liver homogenate (1 to 10) in a total volume of 3 ml. Gas phase, air at atmospheric pressure; temperature, 37°. Initial slopes of oxygen consumption curves taken as measure of enzyme activity.

	Inhibition, %, at concn. *M*					
Compound	1×10^{-3}	5×10^{-4}	1×10^{-4}	1×10^{-5}	1×10^{-6}	1×10^{-7}
1-*p*-Tosyl-1-benzylhydrazine	100	100	100	100	31	..
1-Methanesulfonyl-1-benzylhydrazine	100	100	100	100	53	..
1-*p*-Chlorobenzenesulfonyl-1-benzylhydrazine	100	100	100	100	44	..
1-Isonicotinoyl-2-isopropylhydrazine	96	66	5	0	0	..
α-Methylphenethylhydrazine	100	100	100	100	87	41

(16) E. Hoggarth and E. H. P. Young, *J. Chem. Soc.*, 1582 (1950).

(17) Following completion of this work we learned of two recent patents which describe some of the hydrazine derivatives reported in this paper: (a) Hoffman–La Roche, Belgian Patent 585,466 (1959); (b) Hoffmann-La Roche, South African Patent 594,935 (1959). The compounds are 1-*p*-tosyl-1-benzylhydrazine, 1-*p*-chlorobenzenesulfonyl-1-benzylhydrazine, 1-methanesulfonyl-1-benzylhydrazine, 1-*p*-tosyl-2-isopropylhydrazine, and 1-methanesulfonyl-2-(α-methylphenethyl)-hydrazine.

(18) Lakeside Laboratories code name for this compound is JB-516.

mice (Table IV). Administered intraperitoneally, the above three compounds and some closely related derivatives were as potent as α-methylphenethylhydrazine on a molar basis. 1-Benzenesulfonyl-1-benzylhydrazine and 1-*p*-tosyl-1-(3,4-dichlorobenzyl)-hydrazine were 0.6 and 0.4 times as potent as α-methylphenethylhydrazine, respectively. 1-*p*-Tosyl-1-phenethylhydrazine and 1-*p*-acetamidobenzenesulfonyl-1-benzylhydrazine apparently were quite active, but their exact potencies were not determined. Generally, 1-sulfonyl-2-alkylhydrazines were less active than the 1-sulfonyl-1-alkylhydrazines. However, 1-*p*-tosyl-2-(α-methylphenethyl)-hydrazine appeared to be quite active.

Among the non-sulfonyl compounds (Table IVB) only 1-nitroso-1-benzylhydrazine exhibited a noteworthy order of potency, although all those listed had some effect.

TABLE IV

MONOAMINE OXIDASE INHIBITION *in vivo*[a]

Compound	Dose, mg./kg.	Route of administration	Mouse brain serotonin ratio[b]	Relative I.P. potency[c]
A. Sulfonylhydrazines				
1-*p*-Tosyl-1-benzylhydrazine	20	P.O.	1.88	
	5	I.P.	1.85	1
	2.5	I.P.	1.51	
1-Benzenesulfonyl-1-benzyl-hydrazine	19	P.O.	1.37	
	4.5	I.P.	1.58	0.57
	2.4	I.P.	1.21	
1-*p*-Chlorobenzenesulfonyl-1-benzylhydrazine	43	P.O.	1.10	
	5.4	I.P.	1.92	0.89
	2.7	I.P.	1.31	
1-Ethanesulfonyl-1-(3,4-dichloro-benzyl)-hydrazine	20.5	P.O.	1.39	
	5.1	I.P.	1.47	0.81
	2.6	I.P.	1.39	
1-Methanesulfonyl-1-benzyl-hydrazine	14.5	P.O.	2.06	
	3.7	I.P.	2.05	1.19
	1.8	I.P.	1.61	
1-Methanesulfonyl-1-(3,4-dichlorobenzyl)-hydrazine	19.5	P.O.	2.17	
	4.9	I.P.	2.13	1.04
	2.4	I.P.	1.52	
1-*p*-Tosyl-1-(3-chlorobenzyl)-hydrazine	22.5	P.O.	1.39	
	5.6	I.P.	1.76	0.86
	2.8	I.P.	1.44	

TABLE IV (*Continued*)

1-*p*-Tosyl-1-(3,4-dichlorobenzyl)-hydrazine	25	P.O.	1.24	
	6.3	I.P.	1.42	0.41
	3.1	I.P.	1.15	
1-α-Tosyl-2-benzylhydrazine	20	I.P.	0.99	<1
1-*p*-Tosyl-2-benzylhydrazine	40	I.P.	1.29	<1
1-*p*-Tosyl-2-isopropylhydrazine	8.3	I.P.	1.14	<1
1-Methanesulfonyl-2-(α-methyl-phenethyl)-hydrazine	20.5	I.P.	2.15	
1-*p*-Tosyl-1-phenethylhydrazine	10	I.P.	2.91	
1-*p*-Acetamidobenzenesulfonyl-1-benzylhydrazine	100	I P.	3.30	
B. Acylhydrazines and other compounds				
1-Isonicotinoyl-1-benzyl-hydrazine[d]	16.5	P.O.	1.63	
	4.1	I.P.	1.16	<1
	2.1	I.P.	1.12	
1-Benzoyl-1-benzylhydrazine	100	I.P.	2.98	0.23
	10	I.P.	1.57	
2-Benzylsemicarbazide[e]	100	I.P.	2.66	
2-Phenethylthiosemicarbazide	100	I.P.	2.36	0.10
	10	I.P.	1.24	
1-Nitroso-1-benzylhydrazine[f]	100	I.P.	3.11	
α-Methylphenethylhydrazine	5	I.P.	2.33	1
	2.5	I.P.	1.95	
	1.25	I.P.	1.44	
Benzylhydrazine	10	I.P.	2.44	0.44
	5	I.P.	2.15	
	2.5	I.P.	1.51	
1-Isonicotinoyl-2-isopropyl-hydrazine	100	I.P.	1.60	0.02

[a] Groups of 5 mice were given 2 doses of compounds, spaced 16 hr. apart. One hr. after the second dose, the mice were sacrificed, brains pooled within groups and homogenized in water. Serotonin was determined according to S. Udenfriend, H. Weissbach and B. B. Brodie, *Methods of Biochem. Anal.*, **6**, 95 (1958). [b] Ratio of serotonin concentration in the brains of dosed mice to that in control mice. [c] Dose in moles/kg., calculated from log dose-serotonin ratio plots, required to increase brain serotonin 50%, *i.e.*, produce a ratio of 1.5. Activity of 1-*p*-tosyl-1-benzylhydrazine taken as 1. [d] Footnote 7b. [e] W. J. Hale and N. A. Lange, *J. Am. Chem. Soc.*, **42**, 107 (1920). [f] A. Wohl and C. Osterlin, *Ber.*, **33**, 2736 (1900).

Administered orally, the 1-sulfonyl-1-aralkylhydrazines were of the order of one-fourth as potent as when administered intraperitoneally. However, certain of the chloro compounds (see especially 1-*p*-chlorobenzenesulfonyl-1-benzylhydrazine) were quite ineffective

when given orally. Whether lack of oral effectiveness is due to difficulty of absorption in the gut or to some other biological factor is not presently known.

Since 1-*p*-tosyl-1-benzylhydrazine has the same order of MAO inhibitory activity *in vivo* as benzylhydrazine, the question arises whether the tosyl derivative is split, in the intestine or the tissues, to yield benzylhydrazine. After administration of 1-*p*-tosyl-1-benzylhydrazine,[19] labeled in the benzyl methylene group with C^{14}, to rats 96% of the radioactivity in 24-hour urines was accounted for as benzoic and hippuric acids (isotope dilution technic). Schwartz[20] has reported the same acids as the main metabolites from 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)-hydrazine. However it is unknown in either case whether the sulfonyl or acyl group is removed prior to oxidation.

Experimental[21]

Method A. Interaction of Sulfonyl Chloride and Substituted Hydrazine in Ethanol or Chloroform Solution.—The aralkyl(or alkyl)-hydrazine (0.2 mole) was dissolved in absolute ethanol (about 90 ml.) under a nitrogen atmosphere. To this mixture, maintained at about 25°, was added dropwise over one-half hr. a solution of a sulfonyl chloride (0.1 mole) in absolute ethanol (110 ml. or more if necessary). The slurry was agitated an additional 4 hr. The solid which separated usually was a mixture of aralkyl (or alkyl)-hydrazine hydrochloride and the desired sulfonylhydrazine. After filtration and drying, the solids were washed by suspension in water to dissolve hydrochloride salt and dried. If the sulfonylhydrazine was soluble in ethanol, it was necessary to evaporate the ethanol solution to a small volume, and in some instances to add water, in order to obtain a reasonable yield of product.

When chloroform was employed, approximately the same volumes of solvent were used. The sulfonylhydrazines usually were soluble in this solvent so that as a rule only the insoluble hydrazine hydrochloride derivative precipitated from the reaction mixture. The filtrate was washed with water, dilute sodium hydroxide, and water, and then evaporated to dryness. The crystalline product was slurried with ethanol or 2-propanol and filtered.

In practice it was found very convenient to store the monosubstituted alkyl (or aralkyl)-hydrazines as the hydrochloride salts. In order to utilize the hydrochloride directly as the starting material, the procedure for reaction in ethanol was modified through the use of sodium ethoxide. To the hydrazine hydrochloride derivative (0.1 mole) in ethanol (100 ml.), under a nitrogen atmosphere, sodium

(19) The authors are indebted to Dr. C. S. Miller for the preparation of this compound.

(20) M. A. Schwartz, *J. Pharmacol. Exp. Therap.*, **130**, 157 (1960).

(21) Melting points were determined in a capillary tube and are uncorrected. Elemental analyses were carried out by Mr. K. B. Streeter and associates. Infrared spectra of all new compounds were determined by Mr. W. R. McGaughran.

ethoxide (0.1 mole in 60 ml. of ethanol) was added dropwise over 10 min. The sulfonyl chloride (0.05 mole in 50 ml. of ethanol) was added over 10 min. After agitating for 30 min., the dropwise addition of another 0.1 mole of sodium ethoxide (60 ml. ethanol) was begun. After 10 ml. had been added, simultaneous addition of the remaining sulfonyl chloride solution (0.05 mole in 50 ml. ethanol) was started at an equal rate. The rates were such that the addition time was 30 min. The slurry was agitated an additional 3.5 hr. and filtered. The mixture of sodium chloride and product was washed by suspension in water, filtered, and dried.

Method B. Alkylation of Sulfonylhydrazines with Benzyl Halides.—To the suspension of sulfonylhydrazine (0.1 mole) in methanol (or ethanol) (50 ml.) was added dropwise a solution of sodium alkoxide prepared from sodium (0.1 mole) dissolved in methanol (or ethanol) (50 ml.). As a rule the reaction medium became almost clear and then the sodium salt of the sulfonic acid hydrazide precipitated. In some experiments, water (10–20 ml.) was added to solubilize the sodium salt. To this slurry (or solution) the benzyl halide (0.1 mole) was added dropwise over about 30 min. If the halide was not a liquid, it was dissolved in a minimum volume of dry solvent. After agitating the mixture for 2–3 hr., at which point the reaction mixture was neutral, the solid product was removed by filtration, and washed with methanol (or ethanol) and water. If the product was soluble it was necessary to evaporate to a small volume and to add water in order to effect crystallization.

In the reaction of α-tosylhydrazine with benzyl bromide, dibenzyl sulfone crystallized from the 85% ethanol reaction mixture after a few minutes (18% yield). This was recrystallized from hot 2-propanol to give pure material; m.p. 150–152.5° (reported 151°[22]).

Anal. Calcd. for $C_{14}H_{14}O_2S$: C, 68.08; H, 5.77. Found: C, 68.25; H, 5.73.

Method C. Interaction of Sulfonamide and Hydroxylamine-O-sulfonic Acid.—N-Benzyl-*p*-toluenesulfonamide (2 g., 0.0076 mole) was dissolved at 50° in a mixture of ethanol (40 ml.) and water (200 ml.) containing sodium hydroxide (4.1 g., 0.10 mole). Solid hydroxylamine-O-sulfonic acid[13] (5.0 g., 0.044 mole) was added portionwise over 20 min. The slurry was allowed to stand for 15 min. at 50° and then filtered. Attempts to prepare 1-methanesulfonyl-1-benzylhydrazine, 1-*p*-carboxybenzenesulfonyl-1-benzylhydrazine, and 1-(3-pyridylsulfonyl)-1-benzylhydrazine from the corresponding sulfonamides were unsuccessful.

1-*p*-Tosyl-2-benzylhydrazine (I).—To 1-*p*-tosyl-2-benzylidenehydrazine[23] (11.0 g., 0.04 mole) in 250 ml. of methanol was added ethanolic hydrogen chloride (17.5 ml. containing 2.9 g. of hydrogen chloride) and platinum oxide (0.5 g.). The mixture was shaken with hydrogen at 3.3 atm. pressure and room temperature until absorption of hydrogen ceased (0.5 hr.). After removal of the catalyst the solution was evaporated and the residue treated with dilute sodium hydroxide solution. Following filtration of a little undissolved solid, the filtrate was neutralized with acetic acid to yield 3.7 g. (33% yield) of 1-*p*-tosyl-2-benzylhydrazine.

1-*p*-Tosyl-1-benzyl-2-benzylidenehydrazine (IV).—To a solution of 1-*p*-tosyl-

(22) H. Bohme and H. Fischer, *Ber.*, **75**, 1310 (1942).

(23) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

2-benzylidenehydrazine (27.4 g., 0.1 mole) in 175 ml. of ethanol was added sodium ethoxide solution (from 2.3 g., 0.1 mole of sodium in 125 ml. of ethanol). To the resulting suspension was added benzyl bromide (17.1 g., 0.1 mole) in 100 ml. of ethanol over 30 min. After 6 hr. 26.9 g. of product, m.p. 112–113°, was removed by filtration. The filtrate was evaporated to dryness and the combined solids were extracted with 250 ml. of boiling ethanol. After addition of water 31.8 g. (92% yield) of 1-*p*-tosyl-1-benzyl-2-benzylidenehydrazine, m.p. 111–112°, was obtained. Recrystallization from ethanol–water gave pure material, m.p. 112.5–113.5°.

Anal. Calcd. for $C_{21}H_{20}N_2O_2S$: C, 69.20; H, 5.52; N, 7.68. Found: C, 69.34; H, 5.60; N, 7.60.

1-*p*-Tosyl-1-benzylhydrazine (5.0 g., 0.018 mole) and benzaldehyde (1.93 g., 0.018 mole) in 50 ml. of methanol was agitated for 2 hr. at room temperature, and then heated at 70° for 20 min. On cooling 5.3 g. of product m.p. 111–112° was obtained. Recrystallization from ethanol–water gave pure material, m.p. 111–112°.

Anal. Found: C, 68.94; H, 5.68; N, 7.50.

1-Ethanesulfonyl-1-benzyl-2-benzylidenehydrazine.—Interaction of ethanesulfonyl chloride with benzylhydrazine hydrochloride and sodium ethoxide was carried out as described in Method A. Evaporation of the ethanol filtrate and addition of water did not immediately produce crystalline product. Successive small crops were obtained gradually, over a period of about two weeks, melting from as low as about 60° to as high as 121–123°. During work-up the mixture was exposed to air. Recrystallization from methanol yielded one pure compound, m.p. 122–124°.

Anal. Calcd. for $C_{16}H_{18}N_2O_2S$: C, 63.54; H, 6.00; N, 9.26; S, 10.61. Found: C, 63.35; H, 5.62; N, 9.44; S, 10.68.

Comparison of the infrared spectrum with that of 1-*p*-tosyl-1-benzyl-2-benzylidenehydrazine supported the assignment of the above structure.

3,4-Dichlorobenzalazine.—The ethanolic mother liquors from the reaction of ethanesulfonyl chloride and 3,4-dichlorobenzylhydrazine were allowed to stand exposed to air for several weeks. A yellow product separated which after recrystallization from acetonitrile melted at 176–179°.

Anal. Calcd. for $C_{14}H_8Cl_4N_2$: C, 48.60; H, 2.33; N, 8.10. Found: C, 48.47; H, 2.39; N, 8.54.

Interaction of 3,4-dichlorobenzaldehyde and hydrazine in ethanol gave a compound with identical melting point and infrared spectrum.

1-Benzoyl-1-benzylhydrazine.—This compound was prepared according to procedure (A) using chloroform solution. Upon evaporation of the chloroform the product crystallized. After suspending in 50% benzene–petroleum ether (b.p. 30–60°) a 71% yield of desired product was obtained. This was purified readily by recrystallization from ether; m.p. 68–72° (reported m.p. 69–70°[15]).

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.28; H, 6.39; N, 12.52.

2-Phenethylthiosemicarbazide.—A mixture of phenethylhydrazine hydrochloride (8.6 g., 0.05 mole), ammonium thiocyanate (3.8 g., 0.05 mole) and ethanol (100 ml.) was refluxed for 18 hr. The solution was evaporated to a small

volume and 2-propanol added. On cooling crystals formed. After filtration, and washing with 2-propanol and water, the product (1.45 g.) was recrystallized from hot 2-propanol giving 0.7 g. of pure product; m.p. 133–136°.

Anal. Calcd. for $C_9H_{13}N_3S$: C, 55.35; H, 6.71; N, 21.52. Found: C, 55.46; H, 6.84; N, 21.49.

Reaction of this compound with benzaldehyde by the method of Hoggarth and Young,[16] gave an 82% yield of the benzylidene derivative, which after recrystallization from hot 2-propanol melted at 120–128.5°.

Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.57; H, 6.07; N, 14.95.

From the mother liquors of the phenethylhydrazine–thiocyanate reaction, after addition of water and evaporation, a second product (1.1 g.) was obtained. This material after recrystallization from 2-propanol gave 0.8 g. of product m.p. 113–116°.

Anal. Calcd. for $C_9H_{13}N_3S$: C, 55.35; H, 6.71; N, 21.52. Found: C, 55.15; H, 6.63; N, 21.56.

The infrared spectrum of this compound in chloroform solution was essentially identical with that of the higher melting product. This material, therefore, appeared to be a second crystalline form of 2-phenethylthiosemicarbazide.

1-*p*-Tosyl-1-benzylhydrazine and Alkali.—A mixture of 1-*p*-tosyl-1-benzylhydrazine (4.0 g., 0.014 mole) and sodium hydroxide (10 g.) in ethanol (30 ml.)–water (70 ml.) was refluxed for 1 hr. After steam distillation, the condensate was extracted with carbon tetrachloride. The carbon tetrachloride solution was washed well with water and dried over magnesium sulfate. Toluene was identified and analyzed by infrared spectroscopy; yield 0.77 g. (58%).

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