Synthesis and Muscle-Relaxing Activity of *o*-, *m*-, and *p*-Alkylsulfonylbenzamides and Related Isoquinoline Derivatives

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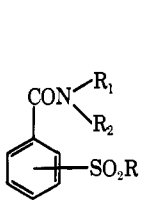
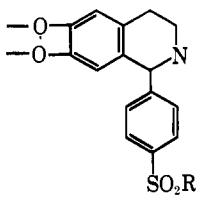
This report is primarily concerned with the synthesis and pharmacological properties of the alkylsulfonylbenzamides and related isoquinoline derivatives. Thirty-three alkylsulfonylbenzene derivatives of series A and B were synthesized and screened for possible pharmacological activities. In both series, 13 compounds showed significant muscle-relaxant properties. The most active were *p*-isopropylsulfonyl-N-isopropylbenzamide (**3**) belonging to series A, and 3,4-dihydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-dimethoxyisoquinoline (**25**) belonging to series B. They also possess anticonvulsant properties. The muscle-relaxing effect of both compounds is of the same order as that of chloromezanone,[1] but much weaker than that of diazepam.[2]

During the course of studies on alkylsulfonylbenzene derivatives, two series of compounds were synthesized and screened for their pharmacological activity: (i) 24 benzamides of the general formula A (Table II), and (ii) nine related 1-[*p*-(alkylsulfonyl)phenyl]isoquinoline derivatives with the skeleton B (Table III).



A



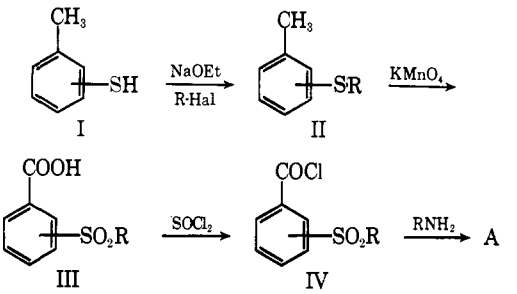
B

Several members of both series exert more or less pronounced muscle-relaxing and anticonvulsant activity. Two of them, *p*-isopropylsulfonyl-N-isopropylbenzamide (**3**, Table II) and 3,4-dihydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-dimethoxyisoquinoline (**25**, Table III) were found to be the most active. Their effect is of the same order as that of chloromezanone and about half of that of chlorodiazepoxide. No simultaneous sedation is observed. Further investigation has shown **3** and **25** to possess distinct anticonvulsant properties; they do not notably influence blood pressure and have no analgetic effect.

The two compounds described earlier, isopropyl phenyl sulfone[3,4] (**22**) and N-isopropylbenzamide[5] (**23**), were compared with **3** and were found to possess no muscle-relaxing effect, indicating that the presence of both the "isopropylsulfonyl" and "N-isopropyl" groups is probably responsible for the activity of **3**.

Chemistry.—Synthesis of the various compounds was effected by using *o*-, *m*-, and *p*-thiocresols (I) as the starting materials (Table I). S-Alkylation[6] gave alkylthiocresols (II) which were oxidized by $KMnO_4$ to the corresponding alkylsulfonylbenzoic acids (III) (Scheme I). The yields in the three steps were excellent. The acid chlorides (IV) obtained in the usual way were then treated with different amines under appropriate conditions to give the amides of the series A (Table II). Analogous hydrazides **19** and **20** were

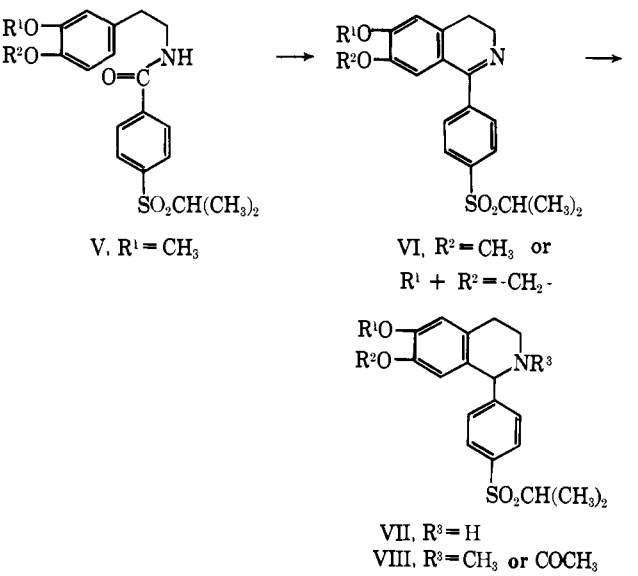
SCHEME I



prepared by reaction of hydrazine hydrate and methylhydrazine or with ethyl *p*-(isopropylsulfonyl)benzoate, respectively. N'-Isopropylhydrazide (**21**) was obtained by catalytic hydrogenation of **19** in the presence of acetone.

Compounds of series B (Table III) were synthesized from N-phenethylamides of type V (Scheme II). 3,4-

SCHEME II



V, $R^1 = CH_3$

VI, $R^2 = CH_3$ or $R^1 + R^2 = -CH_2-$

VII, $R^3 = H$

VIII, $R^3 = CH_3$ or $COCH_3$

Dihydroisoquinolines (VI) were obtained by Bischler–Napieralsky cyclization of V with $POCl_3$ in benzene. These were further reduced with $NaBH_4$ to 1,2,3,4-tetrahydroisoquinolines (VII). N-Methyl derivatives (VIII) were prepared by the formaldehyde–formic acid

(1) Trancopal®.
(2) Valium®.
(3) O. Robert and O. Wilhelm, *Chem. Ber.*, **21**, 998 (1888).
(4) W. A. Baldwin and R. Robinson, *J. Chem. Soc.*, 1445 (1932).
(5) N. Mitlin, S. I. Gertler, and W. A. Gersdorff, *U. S. Dept. Agr., Bur. Entomol. Plant Quarantine, ET828*, 3 (1951).
(6) Identical procedure used for the preparation of phenyl *n*-propyl sulfide: A. I. Vogel, *J. Chem. Soc.*, 1822 (1948).

TABLE I

THIOCRESOLS, ACIDS, AND ACID CHLORIDES

Intermediate	Method	Yield, %	Bp (mm) or mp, °C	Recrystn solvent	Formula	Analyses
p-Isopropylthiocresol (a)	A	84	96–97 (14)		$C_{10}H_{14}S$	C, H, S
p-Methylthiocresol (b)[a]	A	84	88–90 (14)		$C_8H_{10}S$	C, H, S
o-Isopropylthiocresol (c)[b]	A	86	93–95 (14)		$C_{10}H_{14}S$	C, H, S
m-Isopropylthiocresol (d)[c]	A	94	104–107 (14)		$C_{10}H_{14}S$	C, H, S
p-Isopropylsulfonylbenzoic acid (e)	B	80.5	192–193	H_2O	$C_{10}H_{12}O_4S$	C, H, S
p-Methylsulfonylbenzoic acid (f)	B	80	274–276	H_2O	$C_8H_8O_4S$	C, H, S
o-Isopropylsulfonylbenzoic acid (g)	B	65	152–153	H_2O	$C_{10}H_{12}O_4S$	C, H, S
m-Isopropylsulfonylbenzoic acid (h)	B	65	131–134	H_2O	$C_{10}H_{12}O_4S$	C, H, S
p-Isopropylsulfonylbenzoyl chloride (i)	C	83	83–85	C_6H_6–petr ether	$C_{10}H_{11}ClO_3S$	C, H, Cl, S
p-Methylsulfonylbenzoyl chloride (j)[d]	C				$C_8H_7ClO_3S$	
o-Isopropylsulfonylbenzoyl chloride (k)[d]	C				$C_{10}H_{11}ClO_3S$	
m-Isopropylsulfonylbenzoyl chloride (l)[d]	C				$C_{10}H_{11}ClO_3S$	

[a] Prepared from *p*-thiocresol and MeI. [b] From *o*-thiocresol and *i*-PrI. [c] From *m*-thiocresol and *i*-PrI. [d] These were further employed without purification.

method.[7] Treatment of the dimethoxy compounds VI and VII with HBr–AcOH gave the corresponding 6,7-dihydroxy analogs (**29**, **30**, Table III).

Pharmacology with Special Assessment of 3 and 25. (a) **Muscle-Relaxing Effect.**—Muscle relaxation was determined by measuring impairment of postural and righting reflexes in six mice (female, 19–21 g) per dose using a slowly rotating horizontal metal rod. The 50% effective dose (ED_{50}) was the dose which caused sufficient relaxation to reduce by half the time the animal could maintain its position on the "rotating rod." An estimate of the lethal dose (LD_{50}) was obtained using one mouse (female or male, 18–22 g) per dose. The ratio LD_{50}/ED_{50} gives an estimate of the therapeutic range in this acute test.

Tables IV and V show that of the 33 compounds tested, 13 exert a more or less pronounced muscle-relaxing activity in the doses tested. The activity is much weaker than that of diazepam, and the therapeutic range is smaller. In general, the effect was obtained after 30 min and lasted for about 3 hr. Compounds **3** and **25** were particularly active; but because of its higher acute toxicity, the therapeutic range of **25** is smaller. The muscle-relaxing effect was confirmed in the cat (female and male, 2–3 kg). Thirty minutes after oral administration of 100 mg/kg of preparation **3** or **25**, muscle relaxation became apparent and was marked after 1 hr.

(b) **Sedative Effect.**—Preparations with hypnotic–sedative properties also curtail the time a mouse can remain on the rotating rod. In the two compounds, **3** and **25** producing the most marked muscle relaxation, more detailed studies excluded the possibility that a sedative effect was responsible for the muscle relaxation because they did not potentiate subthreshold doses of ethanol (Table VI). Sedation was obtained with **3** only in the high oral dose of 300 mg/kg and with **25** in a slightly lower dose.

(c) **Anticonvulsant Effect.**—In the electroshock test[8] in the mouse, **3** and **25** showed anticonvulsant properties both for threshold convulsions (minimal shock) and maximal convulsions (maximal shock). Table VII shows that the relatively potent effect of **3** against maximal electric shock in the mouse (indicating efficacy against grand mal type seizures) could be confirmed in the cat. This was not so for the weaker **25**.

At a dose of 300 mg/kg *po* preparation **3** gave full protection against convulsions produced by intravenous injection of pentylenetetrazole;[9] no tonic extension of the hind limbs occurred in ten mice (female, 19–21 g); with 100 mg/kg *po*, almost twice the pentylenetetrazole dose had to be infused. According to the classical method, *i.e.*, after intraperitoneal injection of a lethal concentration of pentylenetetrazole in batches of ten mice per dose (female and male, 23–25 g), 50% survival was attained with 450 mg/kg *po* of **3**. Thus a clear antagonism against pentylenetetrazole effects was obtained only at sedative doses as referred to above.

After only 30 mg/kg *po* of **25**, twice the pentylenetetrazole dose was required to produce tonic extension of the hind limbs. Using the classical method of intraperitoneal injection of a lethal concentration of pentylenetetrazole (ten mice per dose), 50% survival was obtained only with 250 mg/kg. This dose is also in the range of incipient sedation.

(d) **Effect on Blood Pressure.**—Apart from a slight initial hypotensive effect of 3 mg/kg iv of **25** in anesthetized cats (female and male, 2–3 kg) and a similar effect at an oral dose of 30 mg/kg in the nonanesthetized hypertensive rat, the blood pressure was not noticeably affected by oral doses of up to 50 mg/kg of **3** and up to 100 mg/kg of **25**, either under the above-mentioned conditions or in the unanesthetized cat with carotid artery loop (van Leersum).

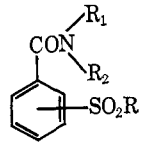
(7) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

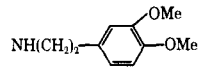
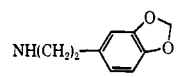
(8) Method based on that of E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

(9) Method based on that of M. J. Orloff, H. L. Williams, and C. C. Pfeiffer, *Proc. Soc. Exp. Biol. Med.*, **70**, 254 (1949).

TABLE II

o-, *m*-, AND *p*-ALKYLSULFONYLBENZAMIDES



No.	R	NR_1R_2	Position of alkylsulfonyl group	Yield, %	Bp (mm) or mp, °C	Crystn solvent	Method	Formula	Analyses
1	$CH(CH_3)_2$	NH_2	*p*	65	168–170	EtOH		$C_{10}H_{13}NO_3S$	C, H, N, S
2	$CH(CH_3)_2$	$NHCH_3$	*p*	70	128–132	EtOH–Et_2O	D[a]	$C_{11}H_{15}NO_3S$	C, H, S
3	$CH(CH_3)_2$	$NHCH(CH_3)_2$	*p*	82	136–138	EtOH	D	$C_{13}H_{19}NO_3S$	C, H, S
4	$CH(CH_3)_2$	$NHCH(CH_3)_2$	*m*	41	122–124	Et_2O–petr ether	D	$C_{13}H_{19}NO_3S$	C, H, S
5	$CH(CH_3)_2$	$NHCH(CH_3)_2$	*o*	~25	115–117	C_6H_6–petr ether	D	$C_{13}H_{19}NO_3S$	C, H, S
6	$CH(CH_3)_2$	$N(C_2H_5)_2$	*p*	62	129–131	EtOH	D	$C_{14}H_{21}NO_3S$	C, H, N, S
7	$CH(CH_3)_2$	$N(C_2H_5)_2$	*o*	35	88–90	Et_2O–petr ether	D	$C_{14}H_{21}NO_3S$	C, H, S
8	$CH(CH_3)_2$	$NHCH_2CH{=}CH_2$	*p*	71	126–127	C_6H_6	D	$C_{13}H_{17}NO_3S$	C, H, S
9	$CH(CH_3)_2$	$NHCH_2CH_2OH$	*p*	61	106–107	EtOH–Et_2O	E	$C_{12}H_{17}NO_4S$	C, H, N, S
10	$CH(CH_3)_2$	$NC(CH_3)_3$	*p*	68	149–151	EtOH	D	$C_{14}H_{21}NO_3S$	C, H, S
11	$CH(CH_3)_2$	$NH(CH_2)_2N(C_2H_5)_2$	*p*	44	207.9 (0.04)			$C_{16}H_{26}N_2O_3S$	C, H, N, S
12	$CH(CH_3)_2$		*p*	55	150–152	EtOH	D	$C_{15}H_{21}NO_3S$	C, H, N, S
13	CH_3	$NHCH(CH_3)_2$	*p*	84	185–187	EtOH	D	$C_{11}H_{15}NO_3S$	C, H, N, S
14	CH_3	$N(C_2H_5)_2$	*p*	61	67–69	Et_2O–petr ether	D	$C_{12}H_{17}NO_3S$	C, H, S
15	$CH(CH_3)_2$		*p*	49	98–99	*i*-PrOH–*i*-Pr_2O	E	$C_{20}H_{25}NO_5S$	C, H, S
16	$CH(CH_3)_2$		*p*	44	145–147	EtOH	E	$C_{19}H_{21}NO_5S$	C, H, N, S
17	$CH(CH_3)_2$	NHC_6H_4Cl-*p*	*p*	65	205–206	EtOH	D	$C_{16}H_{16}ClNO_3S$	C, H, Cl, S
18	$CH(CH_3)_2$	NHC_6H_3-3,4-Cl_2	*p*	54	244–246	Me_2CO	D[b]	$C_{16}H_{15}Cl_2NO_3S$	C, H, Cl, N, S
19	$CH(CH_3)_2$	$NHNH_2$	*p*	98	182–184	H_2O–EtOH		$C_{10}H_{14}N_2O_3S$	C, H, N, S
20	$CH(CH_3)_2$	$NHNHCH_3$	*p*	75	120–122	C_6H_6–petr ether		$C_{11}H_{16}N_2O_3S$	C, H, S
21	$CH(CH_3)_2$	$NHNHCH(CH_3)_2$	*p*	81	119–121	C_6H_6–petr ether		$C_{13}H_{20}N_2O_3S$	C, H, S
22	$CH(CH_3)_2$	($CONR_1R_2$ = H)		70	153–155 (14)			$C_9H_{12}O_2S$	C, H, S
23	(SO_2R = H)	$NHCH(CH_3)_2$		62	98–101	H_2O		$C_{10}H_{13}NO$	C, H, N
24	Cl	$NHCH(CH_3)_2$	*p*	40	142–145	C_6H_6		$C_{10}H_{12}ClNO$	C, H, Cl

[a] The reaction was carried out below 0°. [b] The reaction solvent was C_6H_6.

(e) **Analgetic Effect.**—"Writhing" (pain produced in the mouse by intraperitoneal injection of dilute AcOH) was not significantly reduced by either **3** or **25**, in groups of four animals at various dose levels.

Experimental Section

Melting points and boiling points are uncorrected. 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. Analyses, yields, melting points, boiling points, and other relevant data are recorded in Tables I–III.

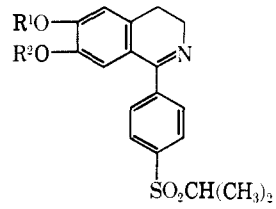
Method A. *p*-Isopropylthiocresol or *p*-Thiocresol Isopropyl Ether (a).—To an EtOH solution of NaOEt prepared from Na (23 g, 1 g-atom) and absolute EtOH (600 ml) was added dropwise with stirring *p*-thiocresol (124 g, 1 mole). The mixture was stirred for 1 hr at room temperature and then *i*-PrI (170 g, 1 mole) was added drop by drop with stirring and maintaining the temperature of the reaction below 30° during addition. After refluxing the mixture for 5 hr, the solvent was distilled off under reduced pressure. The resulting residue was decomposed with H_2O (300 ml) and extracted (Et_2O, three 150-ml portions). The combined etheral extract was washed (H_2O, 10% NaOH, H_2O, 10% H_2SO_4, H_2O). After drying (Na_2SO_4) the ether was evaporated to dryness to give a yellowish oil which was distilled in a high vacuum.

Method B. *p*-Isopropylsulfonylbenzoic Acid (e).—A mixture of *p*-isopropylthiocresol (49.8 g, 0.3 mole), $KMnO_4$ (190 g, 1.2 moles), 10% NaOH (30 ml), and H_2O (1.5 l.) was refluxed on an oil bath for 3 hr. After cooling, the reaction mixture was decolorized with 40% aqueous $NaHSO_3$ (1.5 l.) and filtered. The residue was washed (H_2O) and the washings were combined with the filtrate, which on acidification with concentrated HCl gave a white crystalline precipitate.

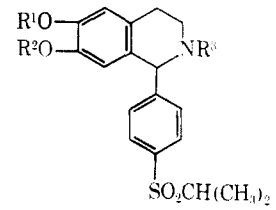
Method C. *p*-Isopropylsulfonylbenzoyl Chloride (i).—*p*-Isopropylsulfonylbenzoic acid (10 g) was mixed with dry THF

TABLE III

1-[*p*-(ISOPROPYLSULFONYL)PHENYL]ISOQUINOLINES



VI



VII or VIII

No.	Type	R_1	R_2	R_3	Yield, %	Mp, °C	Crystn solvent	Formula	Analyses
25	VI	CH_3	CH_3		98	156–166	EtOAc	$C_{20}H_{23}NO_4S$	C, H, S
26	VII	CH_3	CH_3	H	76	115–116	EtOAc	$C_{20}H_{25}NO_4S$	C, H, S
27[a]	VIII	CH_3	CH_3	CH_3	98	232–235	EtOH	$C_{21}H_{27}NO_4S \cdot HCl$	C, H, Cl, S
28	VIII	CH_3	CH_3	$COCH_3$	81	181–182	EtOH	$C_{22}H_{27}NO_5S$	C, H, N
29[a]	VI	H	H		71	320–323 dec	EtOH	$C_{18}H_{19}NO_4S \cdot HBr$	C, H, Br, S
30	VII	H	H	H	59	135 dec	EtOH	$C_{18}H_{21}NO_4S$	C, H, N, S
31	VI	$-CH_2-$			78	193–195	EtOAc	$C_{18}H_{19}NO_4S$	C, H, S
32	VII	$-CH_2-$		H	74	123–126	EtOAc–petr ether	$C_{18}H_{21}NO_4S$	C, H, S
33[a]	VIII	$-CH_2-$		CH_3	80	173–174	MeOH–Et_2O	$C_{20}H_{23}NO_4S \cdot HCl$	C, H, Cl

[a] Hydrochloride or hydrobromide.

TABLE IV

ACUTE TOXICITY AND MUSCLE-RELAXING EFFECT. *o*-, *m*-, AND *p*-ALKYLSULFONYLBENZAMIDES

No.	LD_{50}, mg/kg *po*	ED_{50}, mg/kg *po*	Approx therap ratio	Onset of effect, min	Duration of effect, hr
1	2500–5000	>300	Inactive	~60	
2	600–1200	200	5	30	3
3	1250–2500	55	35	30	3
4	1250–2500	150	10	30	2
5	1250–2500	>300	Sl active	30	
6	1250–2500	200	10	30	4
7	20–40	>10	Inactive		
8	600–1200	100	10	30	3
9	2500–5000	>300	Sl active	60	
10	2500–5000	110	35	30	3
11	1250–2500	>300	Inactive	~30	
12	1250–2500	>300	Sl active	60	
13	2500–5000	200	20	60	3
14	600–1200	>300	Inactive		
15	>5000	>300	Inactive		
16	>5000	>300	Inactive		
17	>5000	120	>40	60–120	4
18	>5000	>300	Inactive		
19	300–600	>100	Inactive		
20	1250–2500	300	6	60	3
21	600–1200	230	5	30	3
22	2500–5000	>300	Inactive	~30	
23	600–1200	>100	Inactive	~30	
24	1250–2500	190	10	30	2

(25 ml) and freshly distilled $SOCl_2$ (15 ml) was added to the mixture. After standing at room temprature for 0.5 hr, the mixture was refluxed for another 0.5 hr; excess $SOCl_2$ was distilled under reduced pressure and by codistillation with benzene. The resulting brownish solid was dissolved in C_6H_6 (200 ml), refluxed with charcoal (2 g) for 30 min, and filtered and the filtrate was evaporated to about 50 ml. By addition of petroleum ether (bp 60–80°) until turbid and cooling overnight a granular, colorless crystalline solid was obtained.

Ethyl *p*-Isopropylsulfonylbenzoate (m). Method i.—The crude acid chloride prepared from *p*-isopropylsulfonylbenzoic acid (30 g) was treated with EtOH (200 ml) and gradually heated to reflux for 1 hr. The alcohol was distilled under reduced pressure and an oily residue obtained from which a fraction distilling at 154–156° (0.04 mm) was separated as the desired ester; yield 23 g.

TABLE V

ACUTE TOXICITY AND MUSCLE-RELAXING EFFECT. 1-[*p*-(ISOPROPYLSULFONYL)PHENYL]ISOQUINOLINES

No.	LD_{50}, mg/kg *po*	ED_{50}, mg/kg *po*	Approx therap ratio	Onset of effect, min	Duration of effect, hr
25	350	30	10	30	3
	(1250 sc)	(20 sc)	(10)	(30)	3
26	300–600	>100	Inactive		
27	300–600	>300	Sl active	30	
28	>5000	>300	Inactive	30	
29	>5000	>300	Inactive		
30	2500–5000	>300	Inactive		
31	600–1200	170	5	30–60	2
32	150–300	>100	Inactive		
33	600–1200	>300	Sl active	60	
Diazepam	700	4	175	30	>4

TABLE VI

POTENTIATION OF THE SEDATIVE EFFECT OF ETHANOL[a]

No.	Dose corresponding to ED_{50} on rotating rod[b]	Min recumbent
3	55 mg/kg *po*	2
25	30 mg/kg *po*	2

[a] 3.75 g/kg ip in ten mice each (male, 18–20 g). [b] See Table IV and V.

TABLE VII

50% PROTECTIVE DOSE IN THE ELECTROSHOCK TEST

	PD_{50}, mg/kg *po*		
	Mouse		
No.	Min *shock*	Max *shock*	Cat[a]
3	230	70	25
25	100	200	250

[a] The 50% protective dose is that which raises the convulsive threshold by 50% in cats.

Method ii.—*p*-Isopropylsulfonylbenzoic acid (30 g), EtOH (200 ml), and concentrated H_2SO_4 (15 ml) were refluxed together for 5 hr. After distilling the solvent under reduced pressure, the residue was treated with a mixture of CH_2Cl_2 (100 ml) and H_2O (50 ml). The CH_2Cl_2 solution was once again washed (H_2O) and dried (Na_2SO_4), and the solvent was removed by distillation. The residual oil was distilled in a high vacuum, giving a product identical with the above; yield 28 g. *Anal.* ($C_{12}H_{16}O_4S$) C, H, S.

***p*-Isopropylsulfonylbenzamide (1).**—*p*-Isopropylsulfonylbenzoyl chloride (crude) prepared from *p*-isopropylsulfonylbenzoic acid (20 g) was mixed with 28% NH_4OH (50 ml) and the mixture warmed on a water bath for 30 min. The reaction mixture was then diluted (H_2O, 200 ml) and the resulting solid was collected by filtration. It was dissolved in EtOH, treated with charcoal, and filtered. The filtrate on cooling gave needles.

Method D. *p*-Isopropylsulfonyl-N-isopropylbenzamide (3).—To a solution of *p*-isopropylsulfonylbenzoyl chloride (37 g, 0.15 mole) in dry Et_2O (250 ml), was added with stirring a solution of isopropylamine (120 g, 0.75 mole) in dry Et_2O (200 ml) drop by drop, maintaining the temperature of the reaction mixture during addition below 15°. After the addition was complete, stirring was continued for another 2–3 hr below 20° and then the solution stood at room temperature overnight. The white solid was collected by filtration, washed (Et_2O), and dried. It was then mixed with H_2O (800 ml), thoroughly stirred, filtered, and recrystallized.

Method E. N-(2-Hydroxyethyl)-*p*-(isopropylsulfonyl)benzamide (9).—This reaction was carried out in THF instead of ether under identical conditions as for **3**. THF was removed and the gummy residue was treated with CH_2Cl_2 (200 ml), the CH_2Cl_2 solution was washed with dilute HCl (25 ml 1 *N*), dried (Na_2SO_4), and evaporated to dryness, and the gummy product crystallized.

N-[2-(Diethylamino)ethyl]-*p*-(isopropylsulfonyl)benzamide (11).—At the end of the reaction of *p*-isopropylsulfonylbenzoyl chloride and diethylaminoethylamine carried out in Et_2O under identical conditions as for **3**, ether was evaporated to dryness. The residue was treated with 1 *N* HCl and Et_2O. The acidic solution was separated, made alkaline with 28% NH_4OH, and extracted (Et_2O). After washing (H_2O) and drying (Na_2SO_4) ether was evaporated to give a thick oil, which was distilled under high vacuum. The **oxalate** prepared in ethereal solution was recrystallized from EtOH–Et_2O, mp 116–118°. *Anal.* ($C_{16}H_{26}N_2O_3S \cdot H_2C_2O_4$) C, H, N, S.

***p*-(Isopropylsulfonyl)benzhydrazide (19).**—A mixture of the stoichiometric proportions of ethyl *p*-isopropylsulfonylbenzoate (44.0 g) and hydrazine hydrate (44.0 g) was heated on a water bath at 80–100° for 2 hr. Then the reaction mixture was cooled, diluted with H_2O (50 ml), and filtered. The solid was washed (H_2O), dried, and recrystallized.

***p*-(Isopropylsulfonyl)-N'-methylbenzhydrazide (20).**—Stoichiometric proportions of ethyl *p*-isopropylsulfonylbenzoate (10.0 g) and methylhydrazine (10.0 g) were initially warmed together at 80° in the presence of EtOH (10 ml) for 1 hr and then refluxed for 3–4 hr. The pale yellow clear solution was evaporated under reduced pressure, and the residue was dissolved in C_6H_6 (30 ml), treated with charcoal, and filtered. To the filtrate was added petroleum ether until turbidity developed and on cooling a pale yellow solid was formed. The **hydrochloride** was prepared in EtOH; white crystalline salt, mp 240–243°. *Anal.* ($C_{11}H_{16}N_2O_3S \cdot HCl$) C, H, Cl, S.

N'-Isopropyl-*p*-(isopropylsulfonyl)benzhydrazide (21).—*p*-(Isopropylsulfonyl)benzhydrazide (30.0 g) in Me_2CO (300 ml) and absolute EtOH (300 ml) was hydrogenated (PtO_2, 300 mg) until no more H_2 was taken up (24 hr). The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure, to give a solid residue which after treatment with charcoal in C_6H_6 and addition of petroleum ether to turbidity gave colorless crystals.

***p*-Chloro-N-isopropylbenzamide (24).**—*p*-Chlorobenzoyl chloride (crude) obtained from *p*-chlorobenzoic acid (31.3 g) was dissolved in C_6H_6 (100 ml) and to the resulting solution isopropylamine (40 g) in C_6H_6 (50 ml) was added dropwise with stirring under 10°. After stirring for another 2 hr at room temperature, the solvent was evaporated to dryness. From the residual solid a neutral fraction was isolated by extraction as the desired product.

1-[(*p*-Isopropylsulfonyl)phenyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (25).—To a suspension of N-(3,4-dimethoxyphenethyl)-*p*-(isopropylsulfonyl)benzamide (25 g) in C_6H_6 (250 ml) was added cautiously at room temperature $POCl_3$ (25 ml) and the mixture was gradually refluxed for 3 hr. From the clear solution, a yellow precipitate separated out. The solvent was removed by distillation under reduced pressure. The residue was carefully dissolved in MeOH and to the methanolic solution Et_2O was added until turbidity developed and a yellow crystalline solid was formed, mp 225–226°. *Anal.* ($C_{20}H_{33}NO_4S \cdot HCl$) C, H, Cl, S. This was dissolved in H_2O and made alkaline with NH_4OH, when a colorless solid precipitated out.

1,2,3,4-Tetrahydro-1-[(*p*-isopropylsulfonyl)phenyl]-6,7-dimethoxyisoquinoline (26).—$NaBH_4$ (5 g) was added in portions with stirring to 3,4-dihydro-1-(*p*-isopropylsulfonyl)phenyl-6,7-dimethoxyisoquinoline hydrochloride (10 g) in MeOH (100 ml) at a temperature below 10°. After the addition was complete, the reaction mixture was left standing overnight at room temperature, the solvent was removed by distillation under reduced pressure, and the residue was treated with CH_2Cl_2 (100 ml) and dilute HCl (150 ml, 1 *N*). The acidic solution was separated, made alkaline with 28% NH_4OH, and extracted (CH_2Cl_2). After washing (H_2O) and drying (Na_2SO_4), CH_2Cl_2 was removed to give a colorless oil which was recrystallized. The hydrochloride was prepared in EtOH, mp 238–239°. *Anal.* ($C_{20}H_{25}NO_4S \cdot HCl$) C, H, Cl, S.

1,2,3,4-Tetrahydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-dimethoxy-2-methylisoquinoline (27) and Hydrochloride.—1,2,3,4-Tetrahydro-1-[(*p*-isopropylsulfonyl)phenyl]-6,7-dimethoxyisoquinoline (15 g), formic acid (15 ml, 99%), and formaldehyde (22.5 ml, 40%) were mixed together and heated at 100° for 3 hr. The mixture was then evaporated under reduced pressure and the resulting residue was treated with dilute HCl (75 ml, 1 *N*). This was washed (Et_2O, 50 ml), made alkaline with 28% NH_4OH, and extracted (CH_2Cl_2). After washing (H_2O) and drying (Na_2SO_4), CH_2Cl_2 was removed by distillation under reduced pressure when a yellowish oil was obtained. The **hydrochloride** was prepared in Et_2O and recrystallized.

2-Acetyl-1,2,3,4-tetrahydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-dimethoxyisoquinoline (28).—1,2,3,4-Tetrahydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-dimethoxyisoquinoline (10 g) was dissolved in pyridine (40 ml) and to the clear solution Ac_2O (40 ml) was added at room temperature. The mixture was allowed to stand overnight, the excess pyridine and Ac_2O were removed by distillation, and the residue (a brown oil) was decomposed with ice-cold H_2O (60 ml). It was then extracted (CH_2Cl_2) which after washing (H_2O, dilute HCl, and H_2O) again was dried ($NaSO_4$) and evaporated to dryness under reduced pressure. The resulting residue was recrystallized.

3,4-Dihydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-isoquinolinediol Hydrobromide (29).—1-[(*p*-Isopropylsulfonyl)phenyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (5 g) was mixed together with glacial AcOH (25 ml) and HBr (20 ml, 60%) and the mixture was refluxed for 7 hr and then evaporated to dryness under reduced pressure. The residual solid was treated with EtOH (25 ml) and filtered. The filtrate was discarded and the solid was recrystallized.

1,2,3,4-Tetrahydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-isoquinolinediol (30).—1,2,3,4-Tetrahydro-1-[*p*-(isopropylsulfonyl)-phenyl]-6,7-dimethoxyisoquinoline (11 g) was mixed with glacial AcOH (60 ml) and HBr (80 ml, 60%) and heated at 125° (bath temperature) overnight. It was then evaporated under reduced pressure and the residue was dissolved in dilute HCl (75 ml, 1 *N*). The acidic solution was made alkaline (NH_4OH) and extracted (CH_2Cl_2). After washing (H_2O), drying (Na_2SO_4), and removing the solvent, the residue was recrystallized. The **hydrochloride** was prepared in EtOH; mp 165–170° dec. *Anal.* ($C_{18}H_{21}NO_4S \cdot HCl$) C, H, Cl, N, S.

3,4-Dihydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-(methylenedioxy)isoquinoline (31).—To a suspension of *p*-(isopropylsulfonyl)-N-[(3,4-methylenedioxy)phenethyl]benzamide (95 g) in C_6H_6 (950 ml), $POCl_3$ (150 ml) was added at 20° and in about 15 min. The mixture was then gradually refluxed for 4 hr, during which time a clear solution turned out into a suspension. After cooling, the solid was collected by filtration and dissolved in H_2O (800 ml) and the acid solution was made alkaline with 28% NH_4OH and extracted (CH_2Cl_2). After washing (H_2O) and drying (Na_2SO_4), CH_2Cl_2 was removed under reduced pressure to give a solid. The **hydrochloride** was prepared in EtOH; mp 245–248° dec.

1,2,3,4-Tetrahydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-meth-

ylenedioxyisoquinoline (32).—To a suspension of 3,4-dihydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-(methylenedioxy)isoquinoline (70.8 g) in EtOH (500 ml) was added at room temperature with stirring $NaBH_4$ (23 g) in portions and the mixture was heated on a water bath (90°) for 5 hr. The solvent was then removed and the residue was treated with dilute HCl (3.5 l., 0.5 *N*) and filtered. The filtrate was made alkaline with 28% NH_4OH and extracted (CH_2Cl_2), and the latter was washed (H_2O), dried (Na_2SO_4), and removed to give a viscous oil. The **hydrochloride** was prepared in EtOH; mp 267–269°.

1,2,3,4-Tetrahydro-1-[*p*-(isopropylsulfonyl)phenyl]-2-methyl-6,7-(methylenedioxy)isoquinoline Hydrochloride (33).—1,2,3,4-Tetrahydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-(methylenedioxy)isoquinoline (10 g), formic acid (10 ml, 99%), and formaldehyde (15 ml, 40%) were allowed to react and the reaction product was isolated exactly in the same way as for **27**.

The Synthesis and Pharmacology of 2-(2-Aminoethyl)imidazole (2-Isohistamine)[1]

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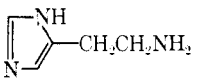
The compound prepared by Jones, which was assigned the structure 2-(2-aminoethyl)imidazole (**3**), is actually 5-aminomethyl-2-methylimidazole (**14**). Authentic **3** has been synthesized from 1-benzyl-2-chloromethylimidazole (**7**) by cyanide displacement in DMSO to yield nitrile **10**, followed by reduction to the amine **12** and debenzylation. Reaction of 1-benzyl-2-lithioimidazole (**15**) with N-(2-bromoethyl)phthalimide (**16**) gave 2-(2-aziridinocarbonylbenzoyl)-1-benzylimidazole (**19**) rather than the expected alkylation product **17**. Compound **3** has weak histamine-like activity on smooth muscle and on blood pressure but none on gastric secretion.

Extensive investigations on the chemistry and pharmacology of heterocyclic analogs of histamine (**1**) have been in progress in these laboratories for more



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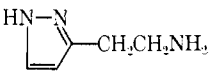

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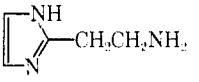
than two decades.[2] As a result of these studies 3-(2-aminoethyl)pyrazole (**2**)[3] has been introduced into clinical medicine. This drug, which is an effective stimulant of gastric secretion, is used in place of histamine in tests of gastric function. Because of its minimal side effects it is more convenient to use than is histamine itself.

Recently Jones[4] has reviewed the structure–activity relationships of some 210 derivatives and analogs of histamine and has concluded that "compounds possessing appreciable histamine-like activity consist of small nitrogen heterocyclic rings to which are attached 2-aminoethyl side chains." Among the very few exceptions to this simple generalization, one has appeared especially anomalous. It would be anticipated *a priori* that one of the most interesting analogs of histamine would be the isomer, 2-isohistamine (**3**), with the



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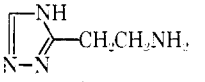

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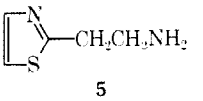
side chain in the 2 rather than in the 4 position. This compound was reported from these laboratories in 1949,[2a] but unexpectedly it was found[2i] to be devoid of histamine activity. In contrast to this observation, heterocyclic ethylamines containing the 3-(1,2,4-triazolyl) (**4**),[2j] 2-thiazolyl (**5**), and 4-pyrazolyl (**6**) moie-



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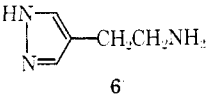

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ties showed very significant activity.[4] This inconsistency was without an explanation until recently Gutsche and Voges[5] provided evidence that the structure assigned to analog **3** was incorrect.

The method devised originally by Jones[2a] for the synthesis of **3** involved reaction of 1-benzyl-2-chloromethylimidazole (**7**) with cyanide to yield 1-benzyl-2-cyanomethylimidazole (**10**). The nitrile **10** was then to be reduced to the β-aminoethyl derivative **12**, which on debenzylation would afford "2-isohistamine" (**3**). Gutsche showed by nmr analysis that the nitrile isolated in the procedure of Jones was in fact not **10** but rather the isomer **11** (see Chart I). This meant that subsequent reduction gave **13**, not **12**, and debenzylation led to 5-aminomethyl-2-methylimidazole (**14**) rather than to 2-isohistamine (**3**). Since **14** is a benzylamine and not an aminoethyl derivative, it is not surprising that it showed no histamine-like activity.

Although the rearrangement that occurred in the cyanide reaction with the chloride **7** to yield **11** was unexpected, it is not without explanation or precedent. Ionization of **7** would give the resonance hybrid [**8a** ↔ **8b**], which with cyanide ion could react at either the "normal" benzylic position or at the 5 position to give the nitrile **10** or its isomer **11**, respectively. Analogy for this dichotomy is found in the similar behavior of furfuryl chloride, which with cyanide gives either 2-cyano-

(1) After this manuscript was completed an independent synthesis of 2-isohistamine was reported in a preliminary communication by G. J. Durant, M. E. Foottit, C. R. Ganellin, J. M. Loynes, E. S. Pepper, and A. M. Roe, *Chem. Commun.*, 108 (1968).

(2) (a) R. G. Jones, *J. Amer. Chem. Soc.*, **71**, 383 (1949); (b) *ibid.*, **71**, 3994 (1949); (c) *ibid.*, **74**, 4207 (1952); (d) R. G. Jones, E. C. Kornfeld, and K. C. McLaughlin, *ibid.*, **72**, 3539 (1950); (e) *ibid.*, **72**, 4526 (1950); (f) R. G. Jones and M. J. Mann, *ibid.*, **75**, 4048 (1953); (g) R. G. Jones and K. C. McLaughlin, *ibid.*, **71**, 2444 (1949); (h) R. G. Jones and K. C. McLaughlin, *J. Org. Chem.*, **19**, 1428 (1954); (i) H. M. Lee and R. G. Jones, *J. Pharmacol. Exp. Ther.*, **95**, 71 (1949); (j) T. M. Lin, R. S. Alphin, F. G. Henderson, and K. K. Chen, *ibid.*, **134**, 88 (1961); (k) T. M. Lin, R. S. Alphin, F. G. Henderson, D. N. Benslay, and K. K. Chen, *Ann. N. Y. Acad. Sci.*, **99**, 30 (1962); (l) T. M. Lin, F. G. Henderson, K. K. Chen, and D. N. Benslay, *Proc. Intern. Pharmacol. Meeting, 1st, Stockholm, 1961*, **7**, 351 (1962); (m) C. Ainsworth, *J. Amer. Chem. Soc.*, **75**, 5728 (1953); (n) *ibid.*, **79**, 5242 (1957); (o) C. Ainsworth and R. G. Jones, *ibid.*, **75**, 4915 (1953); (p) *ibid.*, **76**, 3172 (1954); (q) *ibid.*, **76**, 5651 (1954); (r) *ibid.*, **77**, 621 (1955).

(3) Histalog®, betazole hydrochloride, Lilly. G. B. Clayman, J. B. Kirsner, and H. Ford, *J. Amer. Med. Ass.*, **175**, 908 (1961).

(4) R. G. Jones in "Handbook of Experimental Pharmacology," Vol. XVIII/1, Springer-Verlag, Berlin, 1966, Chapter 1.

(5) C. D. Gutsche and H. Voges, *J. Org. Chem.*, **32**, 2685 (1967).