Neuropharmacological Investigation of N-Benzylsulfamides

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A series of 55 benzylsulfamide derivatives have been synthesized and compared for neuropharmacological activity. These compounds produced moderate CNS depressant effects with a spectrum resembling anticonvulsants and/or mild tranquilizers. Propargyl substitution on the amide nitrogen provided substances with greater activity while halogenation of the benzene ring provided a diversity of effects, dependent on amide nitrogen substitution and number and/or position of halogen substituents.

It has been known for some time that alkyl, aryl, or aralkyl derivatives of urea (I) possess anticonvulsant, hypnotic, sedative, and depressant activity.[1] The corresponding derivatives of sulfamide (II), the SO_2

$$\underset{\text{I}}{H_2NCONH_2} \qquad \underset{\text{II}}{H_2N^1SO_2N^3H_2}$$

analog of urea, have not been evaluated for this type of activity.[2] In the present work we wish to report that the N-benzylsulfamides do possess central nervous system activity particularly as anticonvulsants and mild tranquilizers.

The N-benzylsulfamides prepared for this study were obtained by treating sulfamide or dimethylsulfamoyl chloride with a benzylamine (III) in an appropriate

$$\underset{\text{III}}{ArCH_2NHR} + II \xrightarrow[EtOH-H_2O]{R=H} \underset{\text{IV}}{ArCH_2NHSO_2NH_2}$$

$$\xrightarrow[\text{pyridine}]{R=\text{alkyl or aralkyl}} \underset{\text{V}}{ArCH_2NRSO_2NH_2}$$

solvent. Pyridine was a satisfactory solvent for preparing 1-benzyl-1-alkylsulfamides (V) from a secondary amine and II, while a water–ethanol mixture gave a good yield of the 1-benzylsulfamides IV from a primary benzyl amine and II. Dimethylsulfamoyl chloride reacts with excess primary or secondary benzylamine in diethyl ether or toluene below room temperature to give 1-benzyl- and 1-benzyl-1-alkyl-3,3-dimethylsulfamides (VI and VII).

$$\underset{\text{VI}}{ArCH_2NHSO_2N(CH_3)_2} \qquad \underset{\text{VII}}{ArCH_2NRSO_2N(CH_3)_2}$$

Pharmacology.—Preliminary investigations in this laboratory on the CNS effects of N-benzylsulfamide showed this substance to be a moderate CNS depressant with possible anticonvulsant and/or mild tranquilizing properties. On this basis appropriate studies were initiated to determine the relative level of activity of a series of 55 benzylsulfamide derivatives as compared to six standard substances. All substances were submitted to a preliminary screen in mouse behavior tests.[3,4] Studies of lethality (following intraperitoneal administration) were initially made on a few selected compounds with the determination that a general dosage range of 25–300 mg/kg ip would satisfy comparison of substances within the series and comparison with standard agents. The level of anticonvulsant activity was studied in mice, using as indices the antagonism to strychnine[5] and the antagonism to maximal electroshock,[6] with definition of over-all CNS depressant activity represented by the barbiturate reinduction test.[7] Secondary evaluation consisted of investigation of selected compounds on spinal reflex activity in intact chloralose-anesthetized and ether–spinal cats.[8,9]

All compounds were administered intraperitoneally in the mouse tests and intravenously in the cat spinal reflex studies (ten animals per dose were used in each of the mouse tests, and three cats were studied on each compound in secondary tests). Because all the substances were insoluble in H_2O or saline, parenteral administration was accomplished by suspending the compounds in a 1.0% solution of carboxymethylcellulose.

Results of the relative anticonvulsant and hexobarbital-reinducing activities of the series of benzylsulfamide derivatives are summarized in Tables I–IV. Standard compounds utilized for comparison were glutethimide, aminoglutethimide, diphenylhydantoin, methsuximide, and methylpentynol (see Table V).

As can be seen (Table I), the parent molecule, benzylsulfamide (**1**), provides mild antagonism to strychnine and moderate antagonism to maximal electroshock, whereas no reinduction of sleep following hexobarbital anesthesia was obtained at doses up to 200 mg/kg. Addition of alkyl or alkenyl or cycloalkyl groups to the N-1 position provided no remarkable change in activity except in the case of the propargyl entity (**4**), where a significant increase in potency was observed as regards both strychnine antagonism and reinduction of sleep following hexobarbital anesthesia. Interestingly, substitution by the benzyl group at the N-1 position (**13**) provided a compound having convulsant activity and

(1) For reviews on this activity refer to (a) K. S. Wheeler in "Medicinal Chemistry," Vol. VI, E. E. Campaigne and W. H. Hartung, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, pp 1–245; (b) A. Spinks and W. S. Waring, *Progr. Med. Chem.*, **3**, 261 (1963).

(2) After our work had been completed there appeared in the patent literature reports that $C_6H_5(CH_2)_nNHSO_2NH_2$ (n = 2–5) and $C_6H_5CH(CH_3)$-$CHNHSO_2NH_2$ derivatives possess anticonvulsant, antianxiety, sedative, and tranquilizing properties: (a) Ciba Ltd., South African Patent 63/5092 (1963); (b) J. J. Lafferty and B. Loev, U. S. Patent 3,143,549 (1964); *Chem. Abstr.*, **62**, 489 (1965); (c) J. J. Lafferty and B. Loev, U. S. Patent 3,147,305 (1964); *Chem. Abstr.*, **61**, 13243 (1964).

(3) S. Irwin in "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Siegler, Ed., Year Book Publishers, Chicago, Ill., 1964, pp 36–54.

(4) G. Chen, "Symposium on Sedative and Hypnotic Drugs," The Williams and Wilkins Company, Baltimore, Md., 1954.

(5) M. J. Orloff, H. L. Williams, and C. C. Pfeiffer, *Proc. Soc. Exptl. Biol. Med.*, **70**, 254 (1949).

(6) J. E. P. Toman, E. A. Swinyard, and L. S. Goodman, *J. Neurophysiol.*, **9**, 231 (1946).

(7) C. F. Winter, *J. Pharmacol. Exptl. Therap.*, **94**, 7 (1948).

(8) J. del Castillo and T. E. Nelson, *Ann. N. Y. Acad. Sci.*, **86**, 608 (1960).

(9) E. F. Domino, *Ibid.*, **64**, 705 (1956).

Table I
Neuropharmacological Data on 1-Benzyl-1-R-sulfamides
$C_6H_5CH_2NSO_2NH_2$
|
R

No.	R	ED_{50}, mg/kg ip SP[a]	ED_{50}, mg/kg ip MES[b]	HR[c] RD_{50}, mg/kg ip
1	H[d]	238	58	>200
2	CH_3[e]	217	117	248
3	C_2H_5	232	92	>100
4	$HC{\equiv}CCH_2$[f]	75	88	25
5	$H_2C{=}CHCH_2$[g]	92	117	150
6	Cyclopropyl	150	92	138
7	n-C_3H_7	163	>100	>100
8	i-C_3H_7	125	123	133
9	$H_2C{=}CCH_3CH_2$	283	...[i]	>200
10	n-C_4H_9	150	138	88
11	i-C_4H_9	175	92	100
12	Cyclopentyl	300	163	80
13	$C_6H_5CH_2$	...[h]	...[h]	42
14	2-Norbornyl	>300	>300	>300
15	n-$C_{10}H_{21}$	300	300	>300

[a] SP = strychnine protection. Method of M. J. Orloff, H. L. Williams, and C. C. Pfeiffer, *Proc. Soc. Exptl. Biol. Med.*, **70**, 254 (1949), was used with ten animals per dose. The ED_{50} was determined using the Litchfield–Wilcoxon method (J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949)). [b] MES = maximum electroshock. Method of J. E. P. Toman, E. A. Swinyard, and L. S. Goodman, *J. Neurophysiol.*, **9**, 231 (1946), was used with ten animals per dose. [c] HR = hexobarbital reinduction. Modified method of C. F. Winter, *J. Pharmacol. Exptl. Therap.*, **94**, 7 (1948), was used in which animals were administered compound immediately following recovery from hexobarbital anesthesia (70 mg/kg iv) and reinduction of "anesthesia" (loss of righting) was measured from that time. [d] Compound did not affect spinal reflexes in the cat at 100 mg/kg iv. For method, see Table III, footnote *d*. [e] Dose required to produce 50% depression of spinal reflexes was 125 mg/kg. [f] On spinal reflexes, compound produced facilitation at low doses and produced 50% depression at 60 mg/kg. [g] Substance produced only facilitation of spinal reflexes at doses up to 100 mg/kg. [h] Compound provided no protection from convulsants but, instead, produced convulsions at 75 mg/kg ip. [i] Not tested.

yet causing reinduction of sleep following hexobarbital at a dose only slightly greater than that found to be effective with **4**. Substitution by methyl groups on N-3 or on the α carbon in the benzylsulfamide molecule generally decreased the over-all CNS depressant activity and, in the latter instance, tended to produce the opposite effect—locomotor stimulation, reversal of hexobarbital anesthesia, and convulsions at toxic doses (see **21** and **21a**, Table II). Phenyl or benzyl substitution on the α carbon provided compounds having the same spectrum of activity as the parent substance, with the phenyl derivative demonstrating significantly greater over-all CNS depressant effects (see **22** and **23**, Table II).

Halogen substitution on the benzene ring of the parent molecule provided a diversity of results, depending upon the position and number of substitutions (Table III). Compounds having three chlorines located in the 2, 3, and 6 positions (**47** and **48**) produced maximal effects as regards protection from strychnine convulsions and reinduction following hexobarbital anesthesia, whereas changing these substitutions to the 2, 4, and 5 positions markedly decreased these activities. Increasing or decreasing the number of halogen substituents on the benzene ring tended to decrease the aforementioned pharmacological effects (**33**, **36**, **42**–**44**, **50**, and **51**). Of the mono- or dichlorinated derivatives, compounds having substitution in the 2 or 2,4 positions, respectively, provided the most activity as regards protection from strychnine deaths and reinduction of sleep following hexobarbital (**24**, **27**, **33**, and **36**). Notably, the replacement of chlorine by fluorine tended to decrease the anticonvulsant activity and provided no significant increase in hexobarbital reinducing activity (compare **31** and **33**).

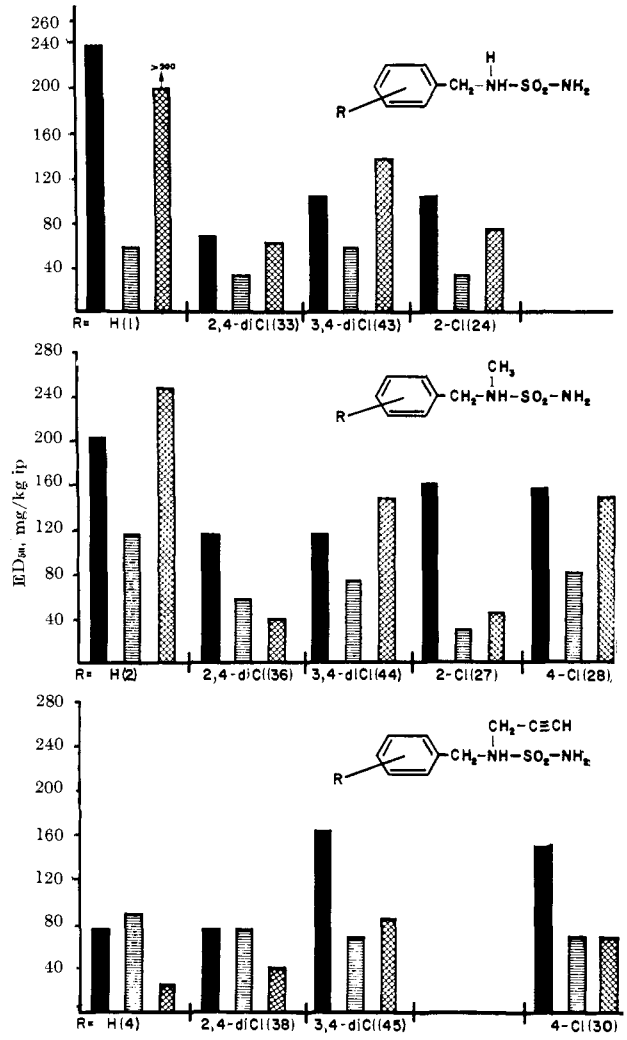


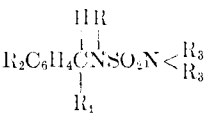
Figure 1.—Effect of halogenation on anticonvulsant and hexobarbital reinducing activities of benzylsulfamide (**1**) and its N-methyl (**2**) and N-propargyl (**4**) derivatives. The numbers in parentheses refer to compounds found in Tables I–IV. See text for explanation. ■, strychnine antagonism; ▤, maximum electroshock antagonism; ▩, hexobarbital reinduction.

An analysis of Table IV shows that cyclization of the nitrogen substituent with the benzene ring results in a marked decrease in over-all activity (compare **54** and **55** with **3** and **23**). This is not the case, however, when cyclization is accomplished with the substituent off the α carbon and the benzene ring (compare **52** and **53** *vs.* **22**). In the latter respect, the anticonvulsant activity is decreased but the total CNS depressant activity (as measured by reinduction of sleep following hexobarbital) is not altered.

Figure 1 presents a graphic summary of effects of compounds having the amide nitrogen unsubstituted *vs.* those having a methyl or propargyl substitution. As can be seen, a structure–activity relationship can be

TABLE II

NEUROPHARMACOLOGICAL DATA ON α-SUBSTITUTED 1-BENZYL-1-R-3,3-R_2-SULFAMIDES

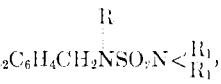


No.	R	R_1	R_2	R_3	ED50, mg/kg ip SP[a]	ED50, mg/kg ip MES[b]	HR[c] RD_{50}, mg/kg ip
16	H	H	H	CH_3	300	75	140
17	CH_3	H	H	CH_3	217	117	75[d]
18	CH_3	H	4-Cl	CH_3	117	75	117[e]
19	$HC{\equiv}CCH_2$	H	H	CH_3	138	138	100[f]
20	$C_6H_5CH_2$	H	H	CH_3	...[g]	...[g]	200
21	CH_3	(+)-CH_3	H	H	...[h]	...[h]	...[h]
21a	CH_3	(−)-CH_3	H	H	...[i]	...[i]	...[i]
22	H	C_6H_5	H	H	69	29	81
23	H	$C_6H_5CH_2$	H	H	177	38	100

[a–c] See corresponding footnotes in Table I. [d] Compound produced 50% depression of spinal reflexes in the cat at 50 mg/kg iv. For method, see Table III, footnote *d*. [e] Compound produced 50% depression of spinal reflexes at 70 mg/kg. [f] Compound produced only facilitation of spinal reflexes at doses up to 80 mg/kg iv. [g] Substance provided no protection from convulsants but, instead, produced convulsions at 300 mg/kg ip. Substance did not demonstrate hexobarbital anesthesia when both compounds were administered simultaneously. [h] Compound produces tonic extensor convulsions at 25 mg/kg ip and also reverses hexobarbital anesthesia at this dose. [i] Compound produces tonic extensor convulsions at 75 mg/kg ip and, at a similar dose, reverses hexobarbital anesthesia (analeptic activity).

TABLE III

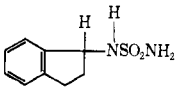
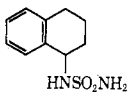
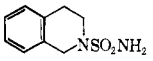
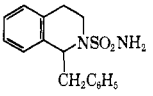
NEUROPHARMACOLOGICAL DATA ON RING-SUBSTITUTED N-BENZYLSULFAMIDES



No.	R	R_1, R_1'	R_2	ED50, mg/kg ip SP[a]	ED50, mg/kg ip MES[b]	HR[c] RD_{50}, mg/kg ip	Spinal refl[d] ED_{50}, mg/kg iv
24	H	H, H	2-Cl	117	34	75	45
25	CH_3	H, H	2-OCH_3	>300	250	75	100
26	CH_3	H, H	4-OCH_3	>300	>200	>300	...
27	CH_3	H, H	2-Cl	163	29	46	75
28	CH_3	H, H	4-Cl	158	81	150	>125
29	CH_3	H, H	3,4-OCH_2O	206	150	>300	...
30	$HC{\equiv}CCH_2$	H, H	4-Cl	150	69	69	...
31	H	H, H	2-Cl-4-F	132	58	88	...
32	H	H, H	2-Cl-6-F	150	46	138	...
33	H	H, H	2,4-Cl_2	69	34	63	13
34	H	H, CH_3	2,4-Cl_2	>300	>200	>200	...
35	H	H, 2,4-$Cl_2C_6H_3CH_2$	2,4-Cl_2	>300	>200	275	...
36	CH_3	H, H	2,4-Cl_2	117	58	40	15[e]
37	CH_3	H, CH_3	2,4-Cl_2	117	150	>100	...
38	$HC{\equiv}CCH_2$	H, H	2,4-Cl_2	75	75	41	30
39	$C_6H_5CH_2$	H, H	2,4-Cl_2	150	244	244	...
40	$C_6H_5CH_2CH_2$	H, H	2,4-Cl_2	>300	>300	>300	>100
41	H	H, H	2,5-Cl_2-4-CH_3	183	150	125	...
42	CH_3	H, H	2,6-Cl_2	183	138	150	...
43	H	H, H	3,4-Cl_2	117	58	138	
44	CH_3	H, H	3,4-Cl_2	117	75	150	20
45	$HC{\equiv}CCH_2$	H, H	3,4-Cl_2	163	69	84	50
46	$C_6H_5CH_2$	H, H	3,4-Cl_2	>300	272	>300	...
47	H	H, H	2,3,6-Cl_3	50	38	19	13
48	CH_3	H, H	2,3,6-Cl_3	63	92	31	...
49	H	H, H	2,4,5-Cl_3	163	163	>200	...
50	H	H, H	2,3,5,6-Cl_4-4-CH_3	175	183	>200	...
51	H	H, H	Cl_5	88	63	>200	...

[a–c] See corresponding footnotes in Table I. [d] Dose (intravenous) required to produce 50% depression of the flexor reflex (obtained by stimulation of the peroneal branch of the sciatic nerve and recording contraction of the achilles tendon) in chloralose-anesthetized cats, as described by E. F. Domino, *Ann. N. Y. Acad. Sci.*, **64**, 705 (1956). Patellar reflex was not affected by any of the compounds studied. Each compound was studied in three animals. [e] Neuropharmacologic activity originally was presented by J. H. Gogerty, W. J. Houlihan, F. Dzamba, E. J. Takesue, and J. H. Trapold, *Federation Proc.*, **24**, 134 (1965). Extensive description of neuropharmacologic activity will be published.

Table IV
Neuropharmacological Data on Miscellaneous "Benzylsulfamides"

No.	Structure	ED50, mg/kg ip SP[a]	ED50, mg/kg ip MES[b]	HR[c] RD50, mg/kg ip
52		138	75	81
53		150	75	75
54		300	150	232
55		>300	>300	>300

[a–c] See corresponding footnotes in Table I.

Table V
Neuropharmacological Values on Some Standard Compounds

Compd	ED50, mg/kg ip SP[a]	ED50, mg/kg ip MES[b]	HR[c] RD50, mg/kg ip	Spinal refl[d] ED50, mg/kg iv
Aminoglutethimide	75	30	33	8
Diphenylhydantoin	20	10	88	11
Glutethimide	38	38	42	20
Meprobamate	127	108	92	70
Methsuximide	100	58	29	15
Methylpentynol	150	150	92	..[e]

[a–c] See corresponding footnotes in Table I. [d] For method, see Table III, footnote *d*. [e] Not tested.

determined only when the benzene ring is unsubstituted. In this respect, one notes that protection from strychnine convulsions and interaction with hexobarbital increases with increase in length of the side chain (compare **1**, **2**, and **4**). Chlorine substitution on the benzene ring generally tends to increase activity of the compound, except in the instance of propargyl substitution on the N-1 nitrogen which appears to "neutralize" any effect of substitution on the benzene ring (compare **4** *vs.* **30**, **38**, and **45**). With no substitution on the amide nitrogen, mono- or dichlorine substitution in the benzene ring increases activity regarding total anticonvulsant effects and reinduction of sleep following hexobarbital (compare **1** *vs.* **24**, **33**, and **43**). This also applies, but to a lesser extent, when methyl substitution is made on the N-1 position (compare **2** *vs.* **27**, **28**, **36**, and **44**).

Of the tests utilized in preliminary screening of the compounds under investigation, the tonic extensor component of maximal electroshock appeared to be the most sensitive as regards the effectiveness of benzylsulfamide derivatives. In this respect, an analysis of structure–activity relationships showed that compounds lacking substitution on either nitrogen were most active, irrespective of halogen substitution on the benzene ring.

Secondary investigations concerned the effects of selected substances on spinal reflexes in anesthetized and spinal cats. Substances lacking substitution on either nitrogen atom but with chlorine substituents on the benzene ring were found to be most active in depressing spinal reflex activity in either chloralose-anesthetized or ether-spinal animals (**33** and **47**). Addition of a methyl group to the N-1 position did not significantly alter this spinal depressant activity (**36** and **44**). However, when propargyl substitution was made, a spinal stimulant activity appeared with lower doses of the compounds (**4**, **19**, and **45**) which appeared to "counteract" the spinal depressant actions, the latter developing with additional doses. Comparison of substances in the intact anesthetized *vs.* decerebrate or spinal preparations indicated that the primary depressant effects originated in medullary or supramedullary structures, whereas the stimulant activity noted with the propargyl derivatives exhibited itself primarily at the spinal level.

Experimental Section[10]

Amine Synthesis.—The amines used to prepare sulfamides **1**, **13**, **16**, **20**, and **22** were obtained from Matheson Coleman and Bell; those for **2**, **4**, **8**, **14**, **17–19**, **23**, **24**, **33–35**, **41**, **52**, and **54** from Aldrich Chemical Co.; for **3**, **7**, **10**, and 11 from Ames Laboratories; for **31** and **32** from Pierce Chemical Co., and **56** from Columbia Organic Chemicals Co.

The other amines used in this work were prepared by the following procedures.

Procedure A.—To 72.5 g (0.5 mole) of 2-chloro-4-fluorotoluene (Pierce Chemical Co.) was added 2 drops of bromine. The stirred solution was heated to 120° and after the color was discharged an additional 85 g (27 ml, 0.53 mole) of bromine was added dropwise while maintaining the internal temperature at 125 ± 5°. After an additional 1 hr at 120°, the residual HBr was removed *in vacuo*. The residue was dissolved in 600 ml of $CHCl_3$, cooled in an ice bath, and treated with a solution of 77 g (0.55 mole) of hexamethylenimine in $CHCl_3$. After 24 hr at room temperature the resultant hexamine salt was filtered off (140.2 g, mp 193–195°) and added to 285 ml of 6 *N* HCl. The slurry was subjected to steam distillation until the resultant distillate gave a negative formaldehyde test. The remaining solution was poured into a mixture of ice and 150 ml of 50% NaOH. The organic material was extracted into ether, washed (H_2O, NaCl solution), and dried ($MgSO_4$). After the removal of ether the residue was distilled through a Claison head. There was obtained 55.6 g of 2-chloro-4-fluorobenzylamine: bp 96–99° (12 mm); $n^{20}D$ 1.5308–1.5312; nmr (CCl_4), 1.52 (NH), 3.82 ppm (CH_2, singlet). *Anal.* Calcd for C_7H_7ClFN: C, 52.7; H, 4.4; Cl, 22.2; N, 8.8. Found: C, 53.3; H, 4.6; Cl, 22.0; N, 8.7.

2,3,6-Trichlorobenzylamine had bp 96–98° (0.7–0.8 mm) [lit.[11] bp 146–147° (10 mm)], $n^{20}D$ 1.5958. *Anal.* Calcd: Cl, 50.5; N, 6.7. Found: Cl, 50.0; N, 6.8.

2,6-Dichlorobenzylamine had bp 79–81° (1.8 mm), $n^{20}D$ 1.5325 [lit.[11] bp 117° (10 mm)].

2,4,5-Trichlorobenzylamine had bp 110° (2.5 mm), $n^{20}D$ 1.5948 (lit.[11] mp 59–60°).

2,3,4,5,6-Pentachlorobenzylamine had mp 138–140° from ether–pentane (lit.[11] mp 139–140°).

2,4-Dichloro-4-methylbenzylamine had bp 82° (0.17 mm). *Anal.* Calcd for $C_8H_9Cl_2N$: Cl, 37.3; N, 7.4. Found: Cl, 37.4; H, 7.2.

2-Chloro-6-fluorobenzylamine had bp 94–96° (18 mm), $n^{20}D$ 1.5330. *Anal.* Calcd for C_7H_7ClFN: C, 52.7; H, 4.4; Cl, 22.2; N, 8.8. Found: C, 53.3; H, 4.8; Cl, 22.3; N, 8.7.

2-Chlorobenzylamine had bp 62.3° (0.7 mm), $n^{20}D$ 1.5540 [lit.[11] bp 219° (749 mm)].

(10) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and have not been corrected. Proton nmr spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in parts per million (δ) from an internal Me_4Si standard. Infrared spectra (KBr) were determined using a Perkin-Elmer Infracord.

(11) J. S. Morley, *J. Chem. Soc.*, 1414 (1961).

2,3,5,6-Tetrachloro-4-methylbenzylamine had mp 150–152°. *Anal.* Calcd for $C_8H_7Cl_4N$: C, 37.1; H, 2.7; Cl, 54.8; N, 5.4. Found: C, 37.1; H, 2.7; Cl, 54.7; N, 5.4.

Procedure B.—Treatment of 29.4 g (0.15 mole) of 2,3,6-trichlorotoluene with 25.2 g (0.15 mole) of bromine by the process given in procedure A gave the crude benzyl bromide. This was dissolved in 50 ml of $CHCl_3$ and then added dropwise to 0.5 mole of methylamine in 250 ml of $CHCl_3$. The mixture was refluxed for 4 hr and then allowed to stand overnight at room temperature. The methylamine hydrobromide (16.8 g, mp 253–255°) that had precipitated was filtered off. The filtrate was concentrated *in vacuo* and the residue was distilled through a Claisen head. There was obtained 24.5 g of 2,3,6-trichloro-*N*-methylbenzylamine, bp 97° (0.07 mm), that crystallized to a solid of mp 51–53°. *Anal.* Calcd for $C_8H_8Cl_3N$: C, 42.8; H, 3.6; Cl, 47.4; N, 6.2. Found: C, 42.9; H, 3.6; Cl, 47.4; N, 6.0.

2,6-Dichloro-*N*-methylbenzylamine had bp 79–81° (1.75 mm); $n^{20}D$ 1.5598; nmr (CCl_4), 1.28 (NH), 2.32 (3 H singlet, CH_3N), and 3.97 ppm (2 H singlet, CH_2Ar).

N-Isobutenylbenzylamine had bp 112–114° (20 mm); $n^{20}D$ 1.5189; nmr ($CDCl_3$), 1.42 (NH), 1.73 (3 H singlet, $CH_3C=C<$), 3.14 (2 H singlet, $=CCH_2N<$), 3.72 (2 H singlet, CH_2-Ar), 4.82 (2 H unresolved, $H_2C=$), and 7.28 ppm (5 H singlet, C_6H_5).

Procedure C.—A stirred solution of 70.5 g (0.50 mole) of 4-chlorobenzaldehyde in 75 ml of 2-propanol was cooled to 10° and then treated dropwise with a solution of 17 g (0.55 mole) of methylamine in 155 ml of 2-propanol. After stirring about 1.5 hr the solution was transferred to a glass high-pressure autoclave liner. Raney nickel (4 g) was added and the mixture was then hydrogenated at 50° internal temperature and an initial hydrogen pressure of 35 kg/cm². After about 3 hr hydrogen uptake was completed. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was distilled through a 90-cm Nester and Faust spinning-band column. There was obtained 46.5 g of 4-chloro-*N*-methylbenzylamine, bp 60° (1.0 mm), $n^{20}D$ 1.5375 [lit.[12] bp 118–121° (23 mm)]. The following compounds were also obtained by this procedure: *N*-benzyl-*n*-decylamine, bp 124° (0.1 mm); *N*-cyclopentylbenzylamine, bp 68–70° (0.25–0.35 mm), $n^{20}D$ 1.5280 (*Anal.* Calcd for $C_{12}H_{17}N$: C, 82.2; H, 9.8; N, 8.0. Found: C, 82.1; H, 9.8; N, 8.0.); 2-methoxy-*N*-methylbenzylamine, bp 78–79° (1.5 mm), $n^{20}D$ 1.5307 (*Anal.* Calcd: N, 9.3. Found: N, 9.4.); 4-methoxy-*N*-methylbenzylamine, bp 63–65° (0.25–0.30 mm), $n^{20}D$ 1.5290 (*Anal.* Calcd: N, 9.3. Found: N, 9.5.) [lit.[12] bp 88–96° (2 mm)]; 2-chloro-*N*-methylbenzylamine, bp 75–76° (2.0 mm), $n^{20}D$ 1.5415 (*Anal.* Calcd: Cl, 22.8. Found: Cl, 23.2.) [lit.[13] bp 83–84° (2 mm), $n^{20}D$ 1.5405]; 3,4-methylenedioxy-*N*-methylbenzylamine, bp 75–77° (0.3–0.5 mm), $n^{20}D$ 1.5435; 3,4-dichloro-*N*-methylbenzylamine, bp 77–79° (1 mm), $n^{20}D$ 1.5562; *N*-2,4-dichlorobenzyl-β-phenylethylamine, bp 174° (1.75 mm), $n^{20}D$ 1.5800; and 2,4-dichloro-*N*-methylbenzylamine, bp 83–85° (0.20 mm), $n^{20}D$ 1.5558 [lit.[14] bp 121–123° (13 mm), $n^{25}D$ 1.5527].

Procedure D.—A stirred solution of 141.0 g (0.8 mole) of 2,4-dichlorobenzylamine in 350 ml of dry toluene was treated dropwise with 46.4 g (0.40 mole) of 3-bromopropyne at such a rate so that the internal temperature did not exceed 35°. After stirring overnight the resultant hydrobromide salt was filtered off. The filtrate was concentrated *in vacuo* and the residue distilled through a 90-cm Nester and Faust spinning-band column. There was obtained 46 g of 2,4-dichloro-*N*-propargylbenzylamine: bp 120° (0.75 mm); $n^{20}D$ 1.5648; nmr (CCl_4), 1.57 (NH), 2.20 (1 H triplet, J = 3.0 cps, $HC\equiv C$), 3.38 (2 H doublet, J = 3.0 cps, $H_2CC\equiv C$), 3.88 ppm (2 H singlet, CH_2Ar).

4-Chloro-*N*-propargylbenzylamine had bp 98–101° (0.2 mm); nmr (CCl_4), 1.28 (NH), 2.17 (1 H triplet, J = 3 cps, $HC\equiv C$), 3.29 (2 H doublet, J = 3 cps, $H_2CC\equiv C$), 3.78 (2 H singlet, CH_2-Ar), 7.22 ppm (4 H singlet, C_6H_4Cl).

3,4-Dichloro-*N*-propargylbenzylamine had bp 115–117° (0.60 mm); $n^{20}D$ 1.5621; nmr (CCl_4), 1.38 (NH), 2.15 (1 H triplet, J = 3.0 cps, $HC\equiv C$), 3.32 (2 H doublet, J = 3.0 cps, $H_2CC\equiv C$), 3.75 ppm (2 H singlet, CH_2Ar).

2,4-Dichlorodibenzylamine had bp 178–181° (0.4 mm), $n^{20}D$ 1.5930. 3,4-Dichlorodibenzylamine had bp 117–9° (1.75 mm), $n^{20}D$ 1.5935.

Procedure E.—An ice-cooled solution of 10.4 g (0.20 mole) of cyclopropylamine in 200 ml of dry benzene was treated dropwise with 14.0 g (0.10 mole) of benzoyl chloride. The mixture was stirred overnight at room temperature. The cyclopropylamine hydrochloride was filtered off and the filtrate was concentrated *in vacuo*. The residue was crystallized from methanol–H_2O to give 9.5 g of *N*-cyclopropylbenzamide, mp 95–97°. *Anal.* Calcd for $C_{10}H_{11}NO$: N, 8.7; O, 9.9. Found: N, 8.6; O, 9.9.

A mixture of 9.5 g (0.06 mole) of *N*-cyclopropylbenzamide, 2.7 g (0.07 mole) of $LiAlH_4$, and 500 ml of anhydrous ether were stirred and refluxed for 12 hr. The complex was decomposed with 5.7 ml of 2 *N* NaOH and 8.1 ml of H_2O. The salts were filtered off, and the filtrate was dried ($MgSO_4$), filtered, and then concentrated *in vacuo*. Distillation through a Claisen head gave *N*-cyclopropylbenzylamine, bp 50–51° (0.3 mm), $n^{20}D$ 1.5195. *Anal.* Calcd for $C_{10}H_{13}N$: C, 81.6; H, 8.9; N, 9.5. Found: C, 81.1; H, 9.3; N, 9.3.

Reaction of Sulfamide with Primary Benzylamines. A mixture of 0.05 mole of sulfamide, 0.05 mole of primary benzylamine in 100 ml of ethanol, and 150 ml of H_2O was stirred and refluxed for 10–15 hr. The reaction mixture was allowed to cool to room temperature and the crystals that had formed were filtered off and washed with H_2O. The solid was then crystallized from an appropriate solvent.

Compounds **1**, **23**, **24**, **31–33**, **41**, **43**, **47**, **49**, **50–53**, and **55** were prepared by the above procedure. The melting points and analyses of these compounds are given in Table VI.

Reaction of Sulfamide with Secondary Benzylamines.—A solution of 0.08 mole of sulfamide, 0.05 mole of secondary benzylamine, and 100 ml of pyridine was stirred and refluxed until the evolution of NH_3, as detected by a bubble detector, had ceased. The solution was cooled to room temperature and filtered to remove any insoluble polymeric sulfamides that had formed. The filtrate was concentrated *in vacuo*. The resultant substance was then crystallized, with charcoal treatment, from an appropriate solvent.

The compounds prepared by this procedure were **2–15**, **21**, **21a**, **22**, **23**, **25–30**, **36**, **38–40**, **42**, **44–46**, **48**, **54**, **and 55**. The analyses and melting points of these compounds are listed in Table VI.

The nmr of the following compounds were obtained in pyridine: N^1-propargyl-*N*-benzylsulfamide (**4**), 3.12 (1 H triplet, J = 3.0 cps, $HC\equiv C$), 4.12 (2 H doublet, J = 3.0 cps, $H_2CC\equiv C$), and 4.17 ppm (2 H singlet, CH_2-Ar); (+)-N^1-methyl-N^1-α-phenylethylsulfamide (**21**), 1.64 (3 H doublet, J = 6.5 cps, CH_3C), 2.73 (3 H singlet, NCH_3), and 5.60 ppm (1 H quartet, J = 6.5 cps); N^1-propargyl-N^1-3,4-dichlorobenzylsulfamide (**38**), 3.21 (1 H triplet, J = 3.0 cps, $HC\equiv C$), 4.32 (2 H doublet, J = 3.0 cps, $H_2CC\equiv C$), and 4.82 ppm (2 H singlet, CH_2-Ar).

The optical rotation of the (+)- and (−)-N^1-methyl-N^1-α-phenylethylsulfamides[11] **21** and **21a** were measured in 95% ethanol at 22° in a Zeiss photoelectric polarimeter. For the (+) isomer (**21**): $[\alpha]_{578}$ +22.3°, $[\alpha]_{546}$ +25.3°, and $[\alpha]_{436}$ +44.9° (*l* 1.0, *c* 3.22). For the (−) isomer (**21a**): $[\alpha]_{578}$ −27.4°, $[\alpha]_{546}$ −31.3°, and $[\alpha]_{436}$ −55.1° (*l* 1.0, *c* 4.10).

Reaction of Benzylamines with N,N-Dimethylsulfamoyl Chloride.—A solution of 12.1 g (0.1 mole) of *N*-methylbenzylamine in 50 ml of dry benzene was cooled in an ice bath and then treated dropwise with 7.2 g (0.05 mole) of dimethylsulfamoyl chloride. The mixture was allowed to stir overnight at room temperature. The salts were filtered off and the filtrate was concentrated *in vacuo*. The resultant solid was then recrystallized from methanol–H_2O to give 10.0 g of N^1,N^2,N^2-trimethyl-N^1-benzylsulfamide (**17**): mp 41–43°; nmr (pyridine), 2.68 (3 H singlet, NCH_3), 2.76 (6 H singlet, $SO_2N(CH_3)_2$), 4.38 ppm (2 H singlet, $CH_2C_6H_5$). The analysis is given in Table VI.

Compounds **16**, **18–20**, and **37** were also prepared by this procedure. Their analyses and melting points (boiling points) are listed in Table VI. In addition nmr data were obtained on the following compounds.

N^2,N^2-Dimethyl-N^1-benzylsulfamide (**16**) in pyridine gave 2.78 (6 H singlet, $N(CH_3)_2$), 4.42 ppm (2 H doublet, J = 6.0 cps, CH_2Ar). N^2,N^2-Dimethyl-N^1-propargyl-N^1-benzylsul-

(12) R. E. Lutz, P. S. Bailey Jr., J. Rowlett, Jr., J. W. Wilson, III, R. K. Allison, M. R. Clark, N. H. Leake, R. H. Jordan, R. J. Keller, III, and K. C. Nicodemus, *J. Org. Chem.*, **12**, 760 (1947).

(13) A. R. Surrey, U. S. Patent 2,862,966 (1950); *Chem. Abstr.*, **53**, 8072 (1959).

(14) The (+)- and (−)-*N*-methyl-α-phenylethylamines were prepared from (±)-α-phenylethylamine by following the procedures of A. Campbell, A. H. J. Houston, and J. Kenyon, *J. Chem. Soc.*, 93 (1947); and R. Boigen and Ch. Rüchardt, *Ann.*, **601**, 30 (1957).

Table VI
Yields, Melting Points and Analysis of Sulfamides Reported in Tables I–IV

No.	Yield, %	Mp, °C	Crystn solvent	Formula	Calcd, % C	H	Cl	S	Found, % C	H	Cl	S
1	45	102–104[a]	*c*	$C_7H_{10}N_2O_2S$	...	...	...	...	...	...	...	...
2	28	91–92	*c*	$C_8H_{12}N_2O_2S$	48.0	6.1	...	16.0	48.7	6.1	...	16.0
3	34	77–78.5	*d*	$C_9H_{14}N_2O_2S$	50.4	6.6	...	15.0	50.8	7.1	...	14.7
4	71	116–118	*c*	$C_{10}H_{12}N_2O_2S$	53.6	5.4	...	14.3	54.0	5.5	...	14.0
5	25	59–61	*d*	$C_{10}H_{14}N_2O_2S$	53.1	6.2	...	14.2	53.2	6.5	...	14.4
6	36	136–137	*e*	$C_{10}H_{14}N_2O_2S$	53.1	6.2	...	14.2	53.1	6.2	...	14.5
7	75	93–94	*c*	$C_{10}H_{16}N_2O_2S$	52.6	7.1	...	14.1	52.8	7.3	...	14.2
8	45	92–94	*c*	$C_{10}H_{16}N_2O_2S$	52.6	7.1	...	14.1	52.4	7.5	...	...
9	29	64–65.5	*c*	$C_{11}H_{16}N_2O_2S$	...	...	...	13.4	...	...	...	13.4
10	38	70–72	*c*	$C_{11}H_{18}N_2O_2S$	54.5	7.5	...	13.2	54.8	7.9	...	13.2
11	35	95–96	*d*	$C_{11}H_{18}N_2O_2S$	54.5	7.5	...	...	54.5	7.6	...	...
12	36	122–124	*f*	$C_{12}H_{18}N_2O_2S$	56.7	7.1	...	12.6	56.7	7.2	...	12.4
13	20	111.5–112.5	*g*	$C_{14}H_{16}N_2O_2S$	60.9	5.8	...	11.6	61.2	6.0	...	11.6
14	19	154–155	*e*	$C_{14}H_{20}N_2O_2S$	60.0	7.2	...	11.4	60.0	7.1	...	11.4
15	60	63–65	*c*	$C_{17}H_{30}N_2O_2S$	62.5	9.3	...	9.8	63.5	9.5	...	9.6
16	75	69–72	*e*	$C_9H_{14}N_2O_2S$	50.4	6.6	...	15.0	50.6	6.8	...	14.9
17	88	41–43	*e*	$C_{10}H_{16}N_2O_2S$	52.6	7.1	...	14.0	52.7	7.1	...	14.3
18	33	49–50	*c*	$C_{10}H_{15}ClN_2O_2S$	45.7	5.8	13.5	12.2	45.7	6.0	13.6	12.0
19	29	144–145	*c*	$C_{12}H_{16}N_2O_2S$	57.1	6.4	...	12.7	57.2	6.6	...	12.8
20	63	178–180	*c*	$C_{16}H_{20}N_2O_2S$	63.2	6.6	...	10.5	63.7	6.9	...	10.3
21	40	86–88	*h*	$C_9H_{14}N_2O_2S$	50.4	6.6	...	15.0	50.5	6.7	...	15.4
21a	31	86–88	*h*	$C_9H_{14}N_2O_2S$	50.4	6.6	...	15.0	50.2	6.8	...	15.1
22	27	135–137	*i*	$C_{13}H_{14}N_2O_2S$	59.5	5.4	...	12.2	59.8	5.3	...	12.1
23	20	108–110	*c*	$C_{14}H_{16}N_2O_2S$	60.8	5.8	...	...	61.4	6.4	...	...
24	53	95–96	*e*	$C_7H_9ClN_2O_2S$	...	...	16.1	14.5	...	...	16.3	14.8
25	35	74–76	*d*	$C_9H_{14}N_2O_3S$	46.9	6.1	...	13.9	47.2	6.3	...	13.9
26	40	133–134	*c*	$C_9H_{14}N_2O_3S$	46.9	6.1	...	13.9	47.1	6.3	...	13.9
27	30	112–113	*j*	$C_8H_{11}ClN_2O_2S$	40.9	4.7	15.1	13.6	41.1	5.0	15.1	13.5
28	35[b]	132–133	*c*	$C_8H_{11}ClN_2O_2S$	40.9	4.7	15.1	13.6	41.3	5.0	15.2	13.5
29	53	127–128	*c*	$C_9H_{12}N_2O_4S$	44.3	5.0	...	13.1	44.3	5.1	...	13.1
30	13	106–108	*k*	$C_{10}H_{11}ClN_2O_2S$	46.4	4.3	13.7	12.4	46.8	4.5	13.5	12.6
31	55	87–89	*c*	$C_7H_8ClFN_2O_2S$	...	...	14.9	13.4	...	...	14.4	14.0
32	36	107–108	*c*	$C_7H_8ClFN_2O_2S$	35.2	3.4	14.9	13.4	35.8	3.4	14.8	13.5
33	48	129–130	*e*	$C_7H_8Cl_2N_2O_2S$	33.0	3.2	27.8	12.5	33.3	3.3	28.3	12.5
34	..	118–121	*d*	$C_9H_{12}Cl_2N_2O_2S$	38.1	4.4	25.1	11.2	37.8	4.2	25.0	11.3
35	30	123–124	*l*	$C_{14}H_{12}Cl_4N_2O_2S$	...	...	34.3	7.7	...	...	33.5	7.8
36	68	113–115	*e*	$C_8H_{10}Cl_2N_2O_2S$	35.7	3.7	26.3	11.9	36.0	4.0	26.2	12.0
37	82	168–170	*c*	$C_{10}H_{14}Cl_2N_2O_2S$	40.4	4.7	24.4	10.8	40.5	5.0	24.4	10.6
38	25	87–88.5	*l*	$C_{10}H_{10}Cl_2N_2O_2S$	41.0	3.4	24.4	10.9	40.8	3.3	24.2	11.3
39	25	95.5–97	*c*	$C_{14}H_{14}Cl_2N_2O_2S$	48.7	4.1	20.5	9.3	49.0	4.3	20.4	9.4
40	33	100–101	*m*	$C_{15}H_{16}Cl_2N_2O_2S$	50.1	4.5	19.7	8.9	50.6	4.4	19.3	9.0
41	30	107–108	*c*	$C_8H_{10}Cl_2N_2O_2S$	...	...	26.3	11.9	...	...	25.2	11.4
42	43	148–148.5	*c*	$C_8H_{10}Cl_2N_2O_2S$	35.7	3.7	26.3	11.9	35.9	4.0	25.9	12.0
43	25	106–107	*c*	$C_7H_8Cl_2N_2O_2S$	33.0	3.2	27.8	12.6	34.5	3.5	27.6	12.8
44	24	92–93	*c*	$C_8H_{10}Cl_2N_2O_2S$	35.7	3.7	26.3	11.9	36.0	4.0	26.3	12.0
45	13	119–120	*c*	$C_{10}H_{10}Cl_2N_2O_2S$	41.0	3.4	24.2	10.9	41.1	3.5	24.3	11.0
46	33	95–96	*n*	$C_{14}H_{14}Cl_2N_2O_2S$	48.7	4.1	20.5	9.3	48.7	4.2	20.3	9.8
47	50	117–119	*e*	$C_7H_7Cl_3N_2O_2S$	29.0	2.4	36.7	11.1	29.4	2.8	36.6	11.2
48	55	128.5–131	*c*	$C_8H_9Cl_3N_2O_2S$	31.7	3.0	35.0	10.6	32.5	2.9	34.7	10.6
49	38	151–152	*c*	$C_7H_7Cl_3N_2O_2S$	29.0	2.4	36.7	11.1	28.7	2.5	35.7	11.6
50	40	215	*c*	$C_8H_8Cl_4N_2O_2S$	28.9	2.3	42.6	9.4	29.4	2.6	41.9	8.9
51	52	204–206	*c*	$C_7H_7Cl_3N_2O_2S$	23.5	0.8	49.8	9.0	23.9	1.5	48.6	9.0
52	25	115–116	*c*	$C_9H_{12}N_2O_2S$	50.9	5.7	...	15.1	50.9	5.8	...	15.2
53	20	99.5–100	*i*	$C_{10}H_{14}N_2O_2S$	53.1	6.2	...	14.2	53.4	6.1	...	14.4
54	39	157–159	*c*	$C_9H_{12}N_2O_2S$	50.9	5.7	...	15.1	51.1	5.9	...	15.0
55	80	135–137	*c*	$C_{16}H_{18}N_2O_2S$	63.6	6.0	...	10.6	63.7	6.1	...	10.6

[a] Farbwerke Hoechst A.-G. vorm. Meister Lucius and Brüning, German Patent 947,554 (1956); *Chem. Abstr.*, **32**, 4426 (1957), report mp 106–107°. [b] J. J. Mc-Manus, J. W. McFarland, C. F. Gerber, W. M. McLamore, and G. D. Laubach, *J. Med. Chem.*, **8**, 766 (1965), report mp 129–131°. [c] Ethanol–H_2O. [d] CCl_4. [e] Methanol–H_2O. [f] 95% ethanol. [g] CH_2Cl_2. [h] CH_2Cl_2–pentane. [i] Methanol–diethyl ether. [j] 1-Butanol. [k] Benzene. [l] 2-Propanol. [m] Methanol–pentane. [n] Diethyl ether–pentane.

famide (**19**) in CCl_4 gave 2.33 (1 H triplet, J = 2.5 cps, HC≡C), 2.81 (6 H singlet, $N(CH_3)_2$), 3.78 (2 H doublet, J = 2.5 cps, $CH_2C{\equiv}C$), 4.42 ppm (2 H singlet, (CH_2Ar). N^2,N^2-Dimethyl-N^1,N^1-dibenzylsulfamide (**20**) in CCl_4 had 2.65 (6 H singlet, $N(CH_3)_2$), 4.18 (4 H singlet, two CH_2Ar), and 7.19 ppm (10 H singlet, $2C_6H_5$). N^1,N^2,N^2-Trimethyl-N^1-2,4-dichlorobenzylsulfamide (**37**) in CCl_4 had 2.72 (3 H singlet, NCH_3), 2.80 (6 H singlet, $N(CH_3)_2$), and 4.38 ppm (2 H singlet, CH_2Ar).

Infrared Data on SO_2 and NH Bands.—All of compounds containing the $NHSO_2NH_2$ grouping gave two NH bands located between 2.95 and 3.00 and 3.06 and 3.09 μ. Some of them also gave a third band located between 3.02 and 3.05 μ. The grouping $NRSO_2NH_2$ gave two bands between 2.93 and 2.95 and 3.05 and 3.08 μ. The $NHSO_2N(CH_3)_2$ system gave a single band located between 3.03 and 3.05 μ. Every sulfamide gave two SO_2 bands located between 7.37 and 7.58 and 8.63 and 8.78 μ.

These values are in very good agreement for the symmetric (8.73–8.77 μ) and antisymmetric (7.46–7.58 μ) SO_2 vibration reported by Vandi, et al.,[15] for some sulfamide derivatives.

(15) A. Vandi, T. Moeller, and L. F. Audrieth, *J. Org. Chem.*, **26**, 3478 (1961).

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Synthesis of Some Dibenzo[*b*,*f*][1,5]diazocines and Dibenzo[*b*,*f*][1,4]diazocines

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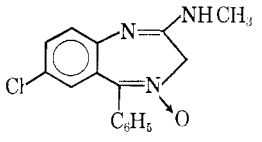
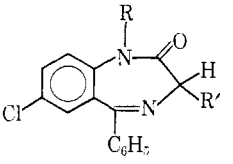
Some dibenzo[*b*,*f*][1,5]diazocines and dibenzo[*b*,*f*][1,4]diazocines, with a number of structural features in common with diazepam, have been synthesized. The pharmacological properties of the compounds were evaluated, and it was shown that they do not have activity profiles comparable to those of diazepam, oxazepam, or chlordiazepoxide. One compound was found to have pronounced antitremorine activity.

Chlordiazepoxide (I), diazepam (II, R = CH_3; R′ = H), and oxazepam (II, R = H; R′ = OH) exhibit sedative, muscle relaxant, and anticonvulsant properties in animals and clinically have application as antianxiety agents.[1]

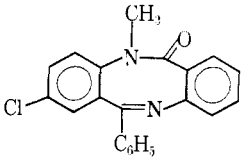


I

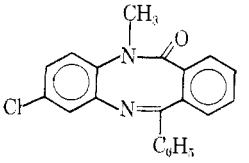


II

We were interested in ascertaining whether the pharmacological properties of appropriately substituted dibenzo[*b*,*f*][1,5]diazocines and dibenzo[*b*,*f*][1,4]diazocines in any way resembled those of 1,4-benzodiazepines such as diazepam. Accordingly, 2-chloro-5,6-dihydro-5-methyl-6-oxo-12-phenyldibenzo[*b*,*f*][1,5]diazocine (III) and 2-chloro-5,6-dihydro-5-methyl-6-oxo-11-phenyldibenzo[*b*,*f*][1,4]diazocine (IV) were selected as



III



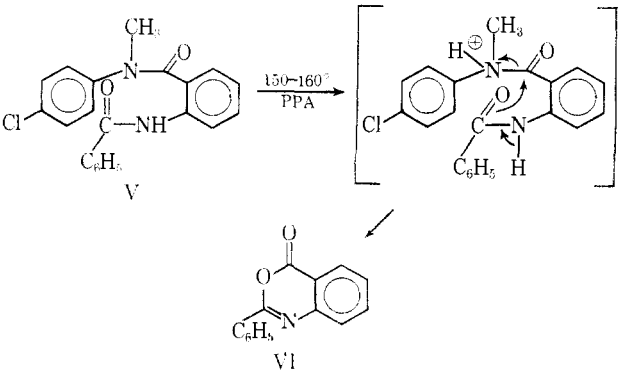
IV

primary synthetic targets.

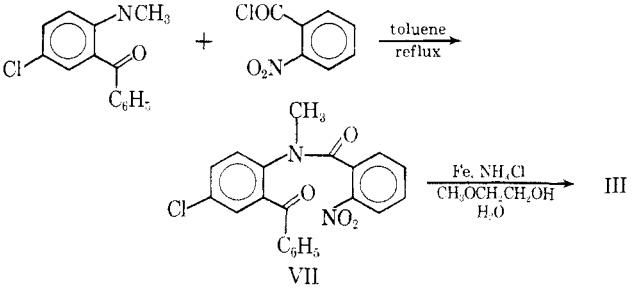
An initial attempt to obtain III by Bischler–Napieralski closure of V in the presence of polyphosphoric acid gave the benzoxazone (VI) (Scheme I). The successful route, outlined in Scheme II, utilized VII which was reduced to III directly.

When the reactions were repeated using 2-amino-5-chlorobenzophenone, reduction of the intermediate VIII afforded the amino compound IX (Scheme III). Attempted crystallization of IX from acetone gave the quinazolinone X which could be readily reconverted to IX by acid hydrolysis. Cyclization of IX furnished XI. Compounds XII and XIII, containing the dimethylaminoethyl and dimethylaminopropyl side chains, respectively, were obtained by alkylation of XI.

Scheme I



Scheme II



Reduction of VII using a palladium catalyst furnished the cyclic compound XIV (Scheme IV). Under different conditions XV could be isolated from the catalytic reduction products. XIV was also formed on reduction of III with PtO_2 in acetic acid. The N-acetyl derivative XVI was obtained by acetylation of XIV with acetic anhydride.

Reduction of III with $LiAlH_4$ gave XVII which was readily acetylated to give XVIII (Scheme V).

For the dibenzo[*b*,*f*][1,4]diazocine system the intermediate XIX was required (Scheme VI). Reaction of *p*-chloro-*N*-methylaniline and the acid chloride (pseudoform) of *o*-benzoylbenzoic acid gave a readily separable mixture of the amide (XX) and the phthalide (XXI). Nitration of XX afforded XIX, the structure of which

(1) (a) L. H. Sternbach, L. O. Randall, and S. R. Gustafson in "Psychopharmacological Agents," M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, Chapter 5; (b) S. J. Childress and M. I. Glueckman, *J. Pharm. Sci.*, **53**, 577 (1964); (c) J. Le Gassicke and F. M. McPherson *Brit. J. Psychiat.* **111**, 521 (1965).