The ppt quaternary salt was filtered; the filtrate was treated with an addnl 10 ml of MeI and refluxed for an addnl 24 hr, and the ppt was filtered. This treatment with MeI was carried out 3 times to give a total of 10.2 g (51%) of product: mp 194–195.5° (EtOH); ν_{max}^{KBr} 1625 cm^{-1} (C=N$^+$=); $\lambda_{max}^{i\text{-PrOH}}$ 217 (22,400), 247 (19,400), 310 (9200), 364 (9450); nmr (TFA) δ 7.25 (1 H, arom), 7.55 (1 H, arom), 4.15 (3 H, CH_3O), 4.18 (3 H, CH_3O), 3.78 (3 H, CH_3N^+), 3.02 (3 H, CH_3C=N), 1.43 (6 H, $[CH_3]_2C$), 1.55 (6 H, $[CH_3]_2C$). *Anal.* ($C_{16}H_{23}NO_2 \cdot CH_3I$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,1,2,3,3,4,4-heptamethylisoquinoline·HCl (27a·HCl).—To a Grignard reagent prepd from 24 g (1 g-atom) of Mg turnings, 700 ml of dry Et_2O, and 142 g (1 mole) of MeI in 1.4 l. of dry Et_2O 20.1 g (0.05 mole) of **26a** was added in 30 min. The mixt was then stirred and refluxed for 20 hr, cooled, poured into 900 ml of ice H_2O contg 90 g of NH_4Cl, and then made alk by the addn of NH_4OH. The product was extd with Et_2O and dried, and the Et_2O soln was treated with dry HCl to form the hydrochloride: yield 9.4 g (61%); mp 232–234° (EtOH–EtOAc). *Anal.* ($C_{18}H_{29}NO_2 \cdot HCl$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dihydroxy-1,1,2,3,3,4,4-heptamethylisoquinoline·HBr (27b·HBr).—A soln of 3.6 g (0.012 mole) of **27a** in 30 ml of 48% HBr was refluxed for 6 hr, and concd *in vacuo* at 35° to dryness. The solid residue was crystd from EtOH–EtOAc: mp 248–250°; yield 3.4 g (80%). *Anal.* ($C_{16}H_{25}NO_2 \cdot HBr$) C, H, N.

Acknowledgment.—We gratefully acknowledge the cooperation of the following members of our Physical Chemistry Department headed by Dr. P. Bommer: Dr. T. Williams (nmr), Dr. V. Toome (uv), and Mr. M. S. Traiman (ir); Dr. F. Scheidl and his associates (microanalyses). The pharmacological data were obtained under the direction of Dr. L. O. Randall, Director of the Pharmacological Laboratories.

Central Nervous System Depressants. 9.[1] Benzodiazepine Sulfonamides

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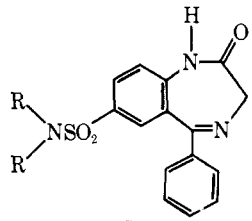
Four 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones with a sulfonamide group in the 7 position (**3**, **6**, **16**, and **17**) and a number of intermediates and by-products are reported. Several of these have been found to be CNS depressants in animals.

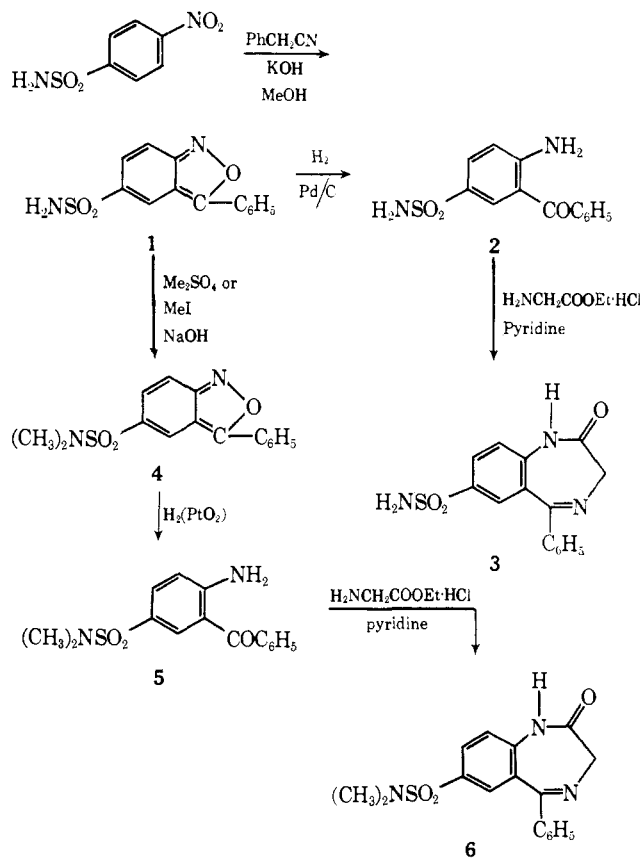
A large number of 1*H*-1,4-benzodiazepines have been prepared and their structure–activity relationships as CNS drugs have been extensively studied.[2] One conclusion from these studies was that an electron-withdrawing group in the 7 position was desirable.[3] Since sulfonamides are compatible with biological systems and are present in many drugs it was thought that compounds of type I might have desirable properties as CNS depressants.



I

Two compounds of this type (R = H, **3**; and R = CH_3, **6**) were prepared as outlined in Scheme I. The preparation of the substituted benzophenones (**2** and **5**) represents modification of the elegant method used by Davis and Pizzini,[4] and Walker[5] for other aminobenzophenones, and the condensations with glycine Et ester are similar to the general method of Sternbach, *et al.*[6] The anthranil **4** was also prepared directly by the condensation of *N*,*N*-dimethyl-*p*-nitrobenzenesulfonamide (**7**) with $PhCH_2CN$. Hydrogenation of anthranil **4** with Pd/C led to the corresponding *o*-aminobenzhydrol

SCHEME I



8 but with Adam's catalyst the desired aminobenzophenone **5** was obtained. Attempts to prepare **5** by selectively acetylating the amine of benzophenone **2** followed by methylation of the sulfonamide group led instead to mixtures from which four new acetylated and/or

(1) Paper 8 of this series: R. B. Moffett, *J. Med. Chem.*, **11**, 1251 (1968).

(2) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr in "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, Chapter 6.

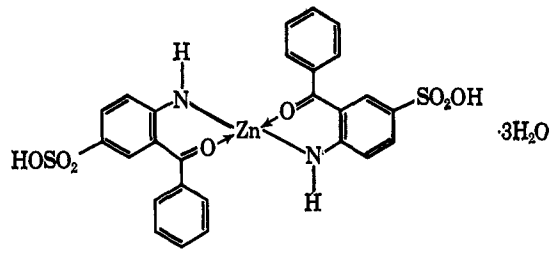
(3) Reference 2, p 247.

(4) R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, **25**, 1884 (1960).

(5) G. N. Walker, *ibid.*, **27**, 1929 (1962).

(6) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

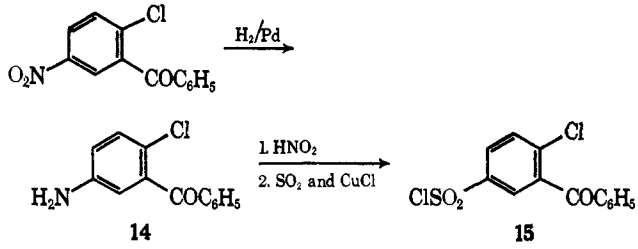
methylated derivatives (**9**, **10**, **11**, and **12**) were isolated (see Experimental Section). An attempt to prepare the benzophenone, **2**, by a Friedel–Crafts reaction with BzCl and $ZnCl_2$ on 4-acetylaminobenzenesulfonyl chloride, followed by treatment with NH_4OH, gave instead a Zn chelate probably having the structure **13**.



13

Another promising approach to the benzophenone **5** involved the reactions of Scheme II.

SCHEME II

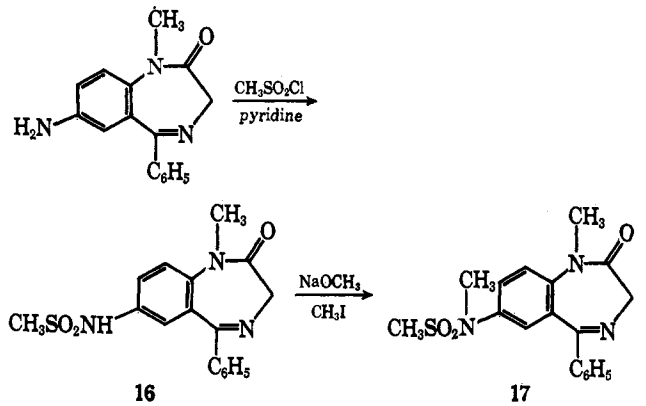


14 **15**

Compound **14** was isolated as its methanesulfonate salt and converted to **15** in 92% yield in an adaption of the method of Meerwein, *et al.*[7]

Our interest in benzodiazepine sulfonamides led us also to make the reverse type, **16** and **17**, where the sulfonamide group is attached at the 7 position through the N (Scheme III).

SCHEME III



16 **17**

Pharmacology.—The 4 benzodiazepines, the intermediates, and by-products were tested in various biological screens. The compounds were relatively nontoxic (LD_{50}'s greater than 1000 mg/kg) and were without effect in all areas tested except the CNS screens. Table I shows the results of the compounds in a battery of CNS screens. In some of the screens, activity was found at a small fraction of the LD_{50} dose. The benzodiazepines (**16**, **3**, **6**, **17**) were active on the chimney, dish, and pedestal in tests and all antagonized the tonic extensor convulsions and lethality of nicotine. The benzodiazepines were much less active than diazepam however. The most active compound in this series was intermediate **7**. This compound inhibited the traction reflex; chimney, dish, and pedestal responses; and nicotine or electroshock-induced convulsions as well as potentiating the response to EtOH.

(7) H. Meerwein, E. Buchner, and K. van Emster, *J. Prakt. Chem.*, **2**, 152, 251 (1939); H. Meerwein, G. Dittmar, R. Goolner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).

Experimental Section[8]

3-Phenyl-2,1-benzisoxazole-5-sulfonamide (1).—A soln of 1.1 kg (16.3 moles) of 85% KOH in 2.1 l. of MeOH was cooled to 0° by an ice–salt bath, and 113.4 g (0.97 mole) of $PhCH_2CN$ was added with stirring. A soln of 178.5 g (0.883 mole) of *p*-nitrobenzenesulfonamide (kept in soln by warming) in 2.1 l. of MeOH was slowly added at 0 ± 5° during 1 hr. After stirring at 0 ± 5° for 4 hr more the dark purple soln was allowed to warm to 18° overnight. It was then recooled and 5.6 l. of H_2O was slowly added at 10–20°. After stirring for 2 hr at room temp, the mixt was filtd, and the filtrate was adjusted to about pH 8.4 by adding about 900 ml of AcOH at 20–25°. The resulting solid was collected, washed (H_2O), and dried giving **118.6 g** of brown solid which gave only one spot on tlc (SiO_2, 20% MeOH in PhH). This was boiled with MeOH (not all in soln), cooled, and filtd yielding 83.5 g (34.5%) of tan solid, mp 234–237.5°. A sample recrystd from EtOAc gave tan needles, mp 235–238°. Ir, nmr, and mass spec support the proposed structure which is in accordance with the structure of analogous compds prepared by Davis and Pizzini.[4] *Anal.* ($C_{13}H_{10}N_2O_3S$) C, H, N, S.

3-Benzoylsulfanilamide (2).—A soln of 27.5 g (0.1 mole) of 1 in 150 ml of DMF and 100 ml of EtOH was hydrogenated with 1 g of 10% Pd/C at 3.5 kg/cm² and room temp. The soln was filtd and evapd giving 35 g of olive-colored cryst residue. This was refluxed with 400 ml of abs EtOH (not all in soln) and cooled giving 23.2 g (84%) of yellow crystals, mp 197–199°. Tlc (SiO_2, 20% MeOH in PhH) gave one spot. A sample was recryst from abs EtOH giving yellow crystals, mp 197.5–199°. *Anal.* ($C_{13}H_{12}N_2O_3S$) C, H, N, S.

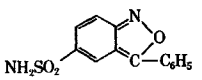
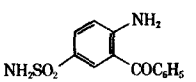
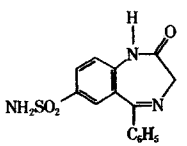
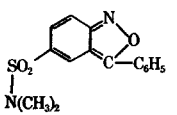
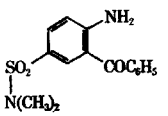
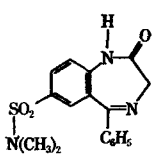
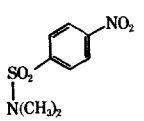
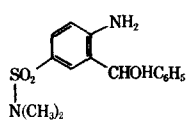
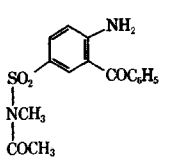
1,3-Dihydro-5-phenyl-7-sulfamoyl-2*H*-1,4-benzodiazepin-2-one (3).—A soln of 19.3 g (0.07 mole) of 3-benzoylsulfanilamide, 29.3 g (0.21 mole) of glycine Et ester·HCl, and 3 ml of piperidine in 300 ml of dry pyridine was stirred under reflux for 18 hr. The dark soln was evapd to dryness under reduced pressure and 18.9 g (0.14 mole) more of glycine Et ester·HCl, 100 ml of pyridine, and 3 ml of piperidine were added. The soln was refluxed for 3 days and again evapd. The residue was well shaken with H_2O and Et_2O and filtd. The resulting solid was boiled with EtCOMe, evapd to remove H_2O, and then boiled with 140 ml more of EtCOMe. After cooling the solid was collected, dried, and recrystd from MeOH (decolorizing charcoal), yielding 7.57 g (34.3%) of white crystals, mp 287–290° dec, showing one spot on tlc (SiO_2, 20% MeOH in PhH). A sample from another run had mp 289–291° dec. *Anal.* ($C_{15}H_{13}N_3O_3S$) C, H, N, S.

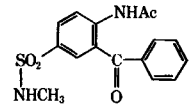
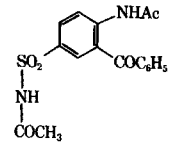
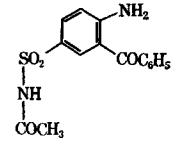
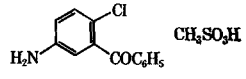
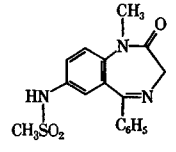
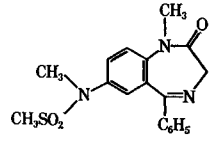
***N*,*N*-Dimethyl-3-phenyl-2,1-benzisoxazole-5-sulfonamide** (4).—A mixt of 27.4 g (0.1 mole) of 1, 500 ml of MeOH, and 1 ml of thymolphthalein test soln was placed in a 2-l. flask fitted with a stirrer, reflux condenser, and two dropping funnels. In one dropping funnel was placed 97 ml (126 g, 0.02 mole) of Me_2SO_4 and in the other 200 ml of 5.32 *N* (20%) NaOH. The flask was heated to reflux on a steam bath and 25 ml of the NaOH was added dissolving all the solid. The Me_2SO_4 was added dropwise during 1 hr and the remaining NaOH was added in 25-ml portions as required to keep the soln strongly basic. After all the reagents had been added the mixt was stirred under reflux for 0.5 hr and about half the solvent was removed *in vacuo*. The mixt was dild to 2 l. with ice water, the product was collected, washed (H_2O), and dried giving 29.6 g (99%) of yellow solid, mp 167.5–

(8) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Ir (Nujol mull), usually nmr spectra (in DMSO-d_6 or $CDCl_3$), and often mass spectra were obtained on pure compounds and were in accordance with the proposed structure. Where analyses are indicated only by symbols of the elements of functions, analytical results obtained for these elements or functions were within ±0.4% of theoretical.

Table I

Pharmacology[a]

No.	Structure	LD_{50}[b]	LRR_{50}[b]	Trs_{0}[b]	Ch_{50}[b]	D_{50}[b]	P_{50}[b]	Nicotine[b] TE	Nicotine[b] L	TSC[c] ED_{50}	Electroshock[c] ED_{50}	Ethanol[d] potentiation ED_{50}
1		>1000	>200	>200	100	>5	18	71	57	>200	>200	>200
2		>1000	>200	>200	>200	89	126	178	178	>200	>200	>200
3		>1000	>200	>200	112	142	>200	126	126	>200	>200	>200
4		>1000	>200	>200	57	>12.5	112	>200	>200	>200	>200	>200
5		>1000	>200	>200	159	8	40	>200	>200	>200	>200	>200
6		>1000	>200	>200	63	18	8.9	112	100	>200	>200	>200
7		ND	>200	100	50	4	7	18	18	>200	126	126
8		>1000	>200	>200	126	28	159	40	45	>200	>200	>200
9		>1000	>200	>200	127	>25	71	89	89	>200	>200	>200

10		ND	>200	>200	45	18	57	126	126	>200	>200	>200
11		>1000	>200	>200	89	112	>200	>200	>200	>200	>200	>200
12		ND	>200	>200	>6.3	16	>200	>200	>200	>200	>200	>200
13	Zn chelate	562	>200	>200	142	5.6	20	89	79	>200	>200	>200
14		ND	>50	>50	>50	36	36	36	36	>50	>50	>50
16		>1000	>200	>200	57	142	>200	25	25	>200	>200	>200
17		1000	>200	>200	50	11	79	50	50	>100	>100	>100
	Diazepam	>200	>200	5.6	1.4	0.2	0.7	0.23	0.25	0.63	28	0.8

[a] Carworth Farms male, albino mice (CF-1) weighing 18–22 g were used for all studies reported here. The test compds were dissolved or suspended in 0.25% aq methylcellulose soln and administered ip. [b] Procedures for measuring acute toxicity (LD_{50}) and the effects of the compound on overt behavior, loss of righting reflex (LRR_{50}), traction (Tr_{50}), chimney (Ch_{50}), dish (D_{50}), pedestal (P_{50}), and antagonism of nicotine-induced tonic extensor convulsions (TE) and death (L) have been described previously [G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DeVanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964)]. [c] Procedures for the antagonism of thiosemicarbazide (TSC) and electroshock convulsions are described [H. H. Keasling, E. L. Schumann, and W. Veldkamp, *ibid.*, **8**, 548 (1965)]. [d] Procedures for measuring potentiation of ethanol narcosis are described [J. B. Hester, A. D. Rudzik, H. H. Keasling, and W. Veldkamp, *ibid.*, **13**, 23 (1970)].

170°. A sample recrystd from *i*-PrOH had mp 168–170°. *Anal.* ($C_{15}H_{14}N_2O_3S$) C, H, N, S.

3-Benzoyl-N^1,N^1-dimethylsulfanilamide (5). Method A.—A mixt of 15.12 g (0.05 mole) of **4** and 200 ml of dioxane was hydrogenated with 0.5 g of PtO_2 at 3.5 kg/cm² and room temp. After filtn the soln was evapd *in vacuo* to about 75 ml and dild with EtOH at the bp. On cooling the product crystd giving 14 g (92%) of light tan crystals, mp 200–205°. A sample recrystd from EtOH had mp 203–205°. *Anal.* ($C_{15}H_{16}N_2O_3S$) C, H, N, S.

4-Amino-α-hydroxy-*N*,*N*-dimethyl-α-phenyl-*m*-toluenesulfonamide (8).—A mixt of 1.37 g (0.0045 mole) of **4** and 150 ml of MeOH was hydrogenated with 0.5 g of 10% Pd/C at 3 kg/cm² and 30–50°. Two equivalents of H_2 was rapidly absorbed. The soln was filtd and evapd giving 1.36 g of gum which crystd on standing. This showed one spot on tlc (SiO_2, 10% MeOH in PhH). This was recrystd from PhH–hexane yielding 1.2 g (87.5%) of colorless crystals, mp 129–131°. *Anal.* ($C_{15}H_{18}N_2O_3S$) C, H, N, S.

***N*,*N*-Dimethyl-*p*-nitrobenzenesulfonamide[9] (7).**—A soln of 135 g (3 moles) of Me_2NH in 400 ml of PhH was cooled to near 0° by an ice bath and a soln of 221.6 g (1 mole) of *p*-nitrobenzenesulfonyl chloride in 800 ml of PhH was slowly added with stirring during 1 hr at 10–25°. After stirring for 1 hr at room temp and then for 1 hr at reflux under a Dry Ice cooled condenser, the excess Me_2NH was distd off up to bp 80°. After cooling, the mixt was stirred with ice water and filtd, and the solid was washed (dil NaOH and water) and dried giving 214 g (95%) of nearly white solid, mp 170.5–172°, showing one spot on tlc (SiO_2, 20% MeOH in PhH). Recrystn from 600 ml of ethylene glycol monomethyl ether yielded 210.1 g (91.4%) of nearly white crystals, mp 170.5–172.5°.[10] *Anal.* ($C_8H_{10}N_2O_4S$) C, H, N, S.

In order to resolve the discrepancy between our mp and that reported by Campbell, *et al.*,[9] a small sample of *p*-nitrobenzenesulfonamide was alkylated with $NaOCH_3$ and CH_3I giving material, mp 168–172°. A mmp showed no depression with a sample of the above material and the ir spectra were identical.

3-Benzoyl-N^1,N^1-dimethylsulfanilamide (5). Method B.—Crude **4** was prepd from 57.5 g of **7** by a procedure similar to that used above for **1**. This was hydrogenated in DMF with PtO_2 at 3.5 kg/cm² and room temp. After filtn and removal of the solvent the dark residue was chromatographed on SiO_2 and eluted with 10% Me_2CO in PhH. The first 10 fractions were combined, boiled with MeOH, filtd hot, concd, and cooled, giving 5.6 g (7.3% overall) of crystals, mp 183–198°. Tlc and ir were identical with **5** prepd as above.

1,3-Dihydro-7-(dimethylsulfamoyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (6).—A mixt of 6.08 g (0.02 mole) of **5** and 8.38 g (0.08 mole) of glycine Et ester·HCl in 100 ml of dry pyridine and 2 ml of piperidine was stirred under reflux for 6.5 hr. Most of the solvent was evapd *in vacuo* and 100 ml more of pyridine, 2 ml of piperidine, and 5.6 g (0.04 mole) of glycine Et ester·HCl were added. The dark soln was refluxed for 20.5 hr more and evapd *in vacuo*. The residue was treated with H_2O and extd with CH_2Cl_2. The CH_2Cl_2 soln was washed (dil AcOH, H_2O) and was well extd with aq NaOH. Evapn of the CH_2Cl_2 gave a gummy solid which tlc (SiO_2, 10% Me_2CO in PhH) showed to be mostly starting material but which contained some product. This was chromatographed on 60 g of SiO_2 and eluted with 10% Me_2CO in PhH in 50-ml portions. Fractions 3–18 were combined and recrystd from abs EtOH giving 2.07 g (34%) of recovered **5**. The elution of the column was contd with 50% Me_2CO in PhH giving 0.9 g of crude product. The aq NaOH extract above was acidified with AcOH giving 2.17 g of gray solid. Tlc indicated that this was mostly the desired product. It was combined with the above crude product and rechromatographed on 150 g of SiO_2. Elution with ten 50-ml portions of 50% Me_2CO in PhH gave first a fraction of impure starting material and then (fractions 16–19 inclusive) the desired product. This was recrystd from 100 ml of *i*-PrOH yielding 2.1 g (30.6%) of nearly white crystals, mp 226–227°. *Anal.* ($C_{17}H_{17}N_3O_3S$) C, H, N, S.

2′-Benzoyl-4′-(acetylsulfamoyl)acetanilide (11) and *N*-(3-Benzoylsulfanilyl)acetamide (12).—A soln of 3.97 g (0.0143 mole) of **2** in 10 ml of dry pyridine and 5 ml of Ac_2O was heated on a steam bath for 1 hr. Evapn and addn of H_2O afforded 4.46 g of a solid mixt. Recrystn from EtOH–MeOH and then from Ac_2O gave 1 g of crystals, mp 239.5–241.5°, which showed only one spot on tlc (SiO_2, 20% MeOH in PhH). This was found by ir, nmr, and anal. to be the diacetyl derivative **11**. *Anal.* ($C_{17}H_{16}N_2O_5S$) C, H, N, S.

The filtrates from the above were evapd, dissolved in 150 ml of MeOH, basified (pH 9) with about 3 ml of 5.3 *N* NaOH, and allowed to stand at room temp for 3 days. Evapn and treatment with H_2O and acidification gave 3 g of solid. This was recrystd twice from AcOH and then from MeOH yielding 0.67 g of white crystals, mp 216–217° dec, showing one spot on tlc (SiO_2, 20% MeOH in PhH). This was found by ir, nmr, mass spec, and anal. to be the monoacetylsulfonamide **12**. *Anal.* ($C_{15}H_{14}N_2O_4S$) C, H, N, S.

***N*-(3-Benzoylsulfanilyl)-*N*-methylacetamide (9).**—A mixt of 1.38 g (0.005 mole) of **2**, 5 ml of $(i\text{-Pr})_2EtN$, 5 ml of THF, and 0.96 ml (1.02 g, 0.01 mole) of Ac_2O was stirred at room temp for 1.75 hr giving 2 liquid phases. To this was added with cooling 0.93 ml (1.26 g, 0.01 mole) of Me_2SO_4. After stirring for 1 hr at room temp and 0.5 hr at reflux the solvent was evapd and the residue was treated with H_2O and extd with Et_2O. The Et_2O soln was washed (dil HCl, NaOH, H_2O), evapd, and recrystd from *i*-PrOH yielding 0.96 g of nearly white crystals, mp 130–132.5°. This was found by ir, nmr, mass spec, and anal. to have the structure **9**. *Anal.* ($C_{16}H_{16}N_2O_4S$) C, H, N, S.

2′-Benzoyl-4′-(methylsulfamoyl)acetanilide (10).—A soln of 2.76 g (0.01 mole) of **2**, 2.89 ml (3.78 g, 0.03 mole) of Ac_2O, 10 ml of $(i\text{-Pr})_2EtN$, and 10 ml of pyridine was stirred on a steam bath for 1 hr and cooled, and 2.79 ml (3.78 g, 0.03 mole) of Me_2SO_4 was added. The mixt, containing 2 liquid phases, was stirred for 15 min at room temp and 1 hr on a steam bath and allowed to stand overnight. After evapn the residue was treated with water and extd with Et_2O. The ether soln and some solid were washed (dil HCl) and extd with dil NaOH. The basic soln was acidified giving 2.58 g of tan solid showing three spots on tlc (SiO_2, 20% MeOH in PhH). This was remethylated with 3 ml of Me_2SO_4 in 10 ml of $(i\text{-Pr})_2EtN$ and 5 ml of THF and was worked up as before. The basic aq soln was neutralized giving 1.05 g of nearly white solid showing mostly one spot on tlc. This was recrystd twice from *i*-PrOH yielding 0.61 g of white crystals, mp 147–149°, showing one spot on tlc. It was found by ir, nmr, mass spec, and anal. to have the structure **10**. *Anal.* ($C_{16}H_{16}N_2O_4S$) C, H, N, S.

Bis(2-benzoyl-4-sulfoanilino)zinc Coordination Complex Trihydrate (13).—A mixt of 100 g (0.7 mole) of (95%) $ZnCl_2$, 133 ml (162 g, 1.15 moles) of PhCOCl, and 200 ml of $PhNO_2$ was heated to 135° and 127 g (0.544 mole) of *N*-acetylphenylsulfonyl chloride was added portionwise with stirring during 0.5 hr at 140–160°. The mixt was heated at 140–160° with stirring for 3 hr and 500 ml of THF was added. Then NH_3 was passed in for 3 hr, the mixt was allowed to stand overnight, and 500 ml of NH_4OH was added. After stirring for 1 hr the mixt was heated under reflux on a steam bath for 4 hr. It was steam distd for 3 hr to remove most of the $PhNO_2$ during which 200 ml more of NH_4OH was added portionwise. After cooling overnight, the resulting solid was collected, washed (very dil NH_4OH and water), and dried giving 296.7 g of brown solid. This was found to contain 9.88% Zn. It was shaken with concd HCl, water, and Et_2O and recrystd from 90% MeOH with decolorizing charcoal treatment, yielding 130 g (74%) of nearly white solid. Although darkening somewhat, it did not melt up to 325°. Ir spectra indicate the presence of SO_2OH arom, NH, H_2O and C=O/C=C/NH. Nmr clearly shows the sulfonic acid at δ 10.3 and NH and H_2O band at 3.45. All the rest of the H's are arom. Mass spec shows *m/e* at 540–550 and above 600 indicating a mol wt much above a monomeric structure and strongly suggesting 2 amino ketones per Zn. Karl Fischer anal. (calcd for $3H_2O$, 8.04; found, 7.23) indicates it is a hydrate. *Anal.* ($C_{26}H_{26}N_2O_{11}S_2Zn$) C, H (calcd, 3.90; found, 4.44), N, S, Zn.

2-Chloro-5-aminobenzophenone Methanesulfonate Salt (14).—A mixt of 2.61 g (0.01 mole) of 2-chloro-5-nitrobenzophenone and 0.1 g of PtO_2 in 150 ml of abs EtOH was hydrogenated at 3.5 kg/cm² and room temp for 5 min. After filtn and evapn, the product was dissolved in dil HCl, washed (Et_2O), and basified with dil NaOH. The free base was extd with Et_2O, dried ($MgSO_4$), filtd, and acidified with $MeSO_3H$ to give 2.43 g of white crystals, mp 198–201°. Two recrystns, once from *i*-PrOH and

(9) This compound has been reported by N. Campbell, B. K. Campbell, and E. M. Salm [*Proc. Indiana Acad. Sci.*, **57**, 97 (1948); *Chem. Abstr.*, **43**, 4630*c* (1949)] to have mp 92–93°.

(10) This compound had previously been prepared by Mr. W. C. Anthony and by Mr. Gay Smith in our laboratories by a similar procedure giving material with the same melting point.

once from EtOH, gave 0.90 g (27.5%), the salt mp 210–212° dec. *Anal.* ($C_{14}H_{14}ClNO_4S$) C, H, Cl, N, S.

3-Benzoyl-4-chlorobenzenesulfonyl Chloride (15).—To a cold soln (0–5°) of 23.8 g of (0.073 mole) of 2-chloro-5-aminobenzophenone in 73 ml of AcOH and 25 ml of concd HCl was added slowly 5.58 g (0.685 mole) of $NaNO_2$ in 9.5 ml of H_2O. This mixt was stirred for 0.5 hr at 0–5°. Then was added 17.3 g (0.27 mole) of SO_2 in 51 ml of AcOH contg 2.9 g (0.017 mole) of $CuCl_2$ in 5.2 ml of H_2O. This mixt was allowed to warm to room temp with stirring during 1 hr and poured into ice water. The solid was collected yielding 21.27 g (92.5%) of pale yellow solid, mp 86.5–89°. A sample was recrystd from methylcyclohexane, mp 90.5–92°. *Anal.* ($C_{13}H_8Cl_2O_3S$) C, H, Cl, S.

1,3-Dihydro-7-(methanesulfonamido)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (16).—To a slurry of 2.65 g (0.01 mole) of 7-amino-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[11] in 20 ml of dry pyridine was added portionwise 1.37 g (0.012 mole) of $MeSO_2Cl$. The mixt was stirred for 1.0 hr at room temp and then warmed on a steam bath for 0.5 hr. Evapn of the reaction mixt *in vacuo* gave a syrup which was taken up in $CHCl_3$, washed (H_2O), dried ($MgSO_4$), and reevapd to give 4.3 g of syrup which crystd from PhH giving 3.01 g of yellow crystals, mp 149–151.5°. Two recrystns, once from EtOAc and once from EtOH, yielded 1.55 g (45%) of nearly white crystals, mp 192–193° dec. *Anal.* ($C_{17}H_{17}N_3O_3S$) C, H, N, S.

1,3-Dihydro-1-methyl-7-(*N*-methylmethanesulfonamido)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (17).—A soln of 1.88 g (0.0055 mole) of 16 in 35 ml of MeOH was converted to the Na salt with 1.4 g (0.0066 mole) of 25% NaOMe and evapd to dryness *in vacuo*. The residue was dissolved in 30 ml of DMF and 1.5 ml of MeI was added dropwise with stirring for 2.0 hr at room temp. The soln was poured into 300 ml of ice water giving 1.45 g of solid, mp 162–166° dec. Recrystn from *i*-PrOH gave 1.25 g (70.5%) of nearly white crystals, mp 174–176° dec. *Anal.* ($C_{18}H_{19}N_3O_3S$) C, H, N, S.

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General Anesthetics. 2. Halogenated Methyl Isopropyl Ethers

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Twenty-two new halogenated methyl isopropyl ethers have been synthesized for evaluation as general inhalant anesthetics. Sixteen stable compounds were evaluated using mice. Twelve of these compounds had anesthetic activity but were irritating and toxic, making them unsuitable for further study or clinical trials.

The first study of the anesthetic properties of fluorinated hydrocarbons was reported by Robbins[1] in 1946. Since that time many fluorinated compounds, both hydrocarbons and ethers, have been found to have anesthetic properties in laboratory animals and several have progressed to clinical trials in humans.[2,3] Fluoroxene ($CF_3CH_2OCH{=}CH_2$), halothane ($CF_3CHClBr$), and methoxyflurane ($CH_3OCF_2CHCl_2$) are presently in clinical use.

The synthesis and pharmacological properties of some methyl ethyl ethers have been reported recently.[4,5] We have continued this investigation by synthesizing 22 new halogenated methyl isopropyl ethers; 16 of these have been evaluated as general anesthetics in mice (Table I). The remaining were too unstable to test.

Synthesis.—The chloro compounds were synthesized by photochlorination of four fluorinated isopropyl methyl ethers. Chlorination of **1**, following the published procedure,[6,7] gave only three products resulting from substitution on the methyl group. The chlorination is described as follows where the percentages in the equation represent the maximum percentage of a given product in any chlorination mixture, the maximum amount of monochloro product being formed with addition of one Cl and so forth. Neither the perhalogenated product, $(CF_3)_2CClOCCl_3$, nor any isomers with Cl on the isopropyl group were found.

$$(CF_3)_2CHOCH_3 \longrightarrow (CF_3)_2CHOCH_2Cl \longrightarrow (CF_3)_2CHOCHCl_2 \longrightarrow (CF_3)_2CHOCCl_3$$
1 **2**, 82% **3**, 58% **4**, 100%

Chlorination of **5** was carried only to the first step, similarly replacing only the H on the methyl group.

$$CF_3(CF_2Cl)CHOCH_3 \longrightarrow CF_3(CF_2Cl)CHOCH_2Cl$$
5 **6**

The isomer, $CF_3(CF_2Cl)CClOCH_3$, was prepared by chlorination of the pentafluoroisopropenyl ether. The physical properties of this dichloro ether were significantly different from those of **6**.[8]

The chlorination of **7** was similar to that of **5** and only the methyl group was chlorinated.

$$(CF_2Cl)_2CHOCH_3 \longrightarrow [(CF_2Cl)_2CHOCH_2Cl] \longrightarrow (CF_2Cl)_2CHOCHCl_2 \longrightarrow (CF_2Cl)_2CHOCCl_3$$
7 **8** **9**

Chlorination of **10** gave essentially only one monochloro product **11** and only one dichloro product **12**. Further chlorination gave complex mixtures of products from which three trichloro products, **13**, **14**, and **15**, and one tetrachloro product, **16**, were isolated.

Substitution of F for Cl in the ethers **3**, **4**, **8**, **12**, **13**, and **14** was done using SbF_3 or anhyd HF. $SbCl_5$ was

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