Methyl 3,6-Dimethylsalicylate.—The acid (20 g., 0.133 mole), dimethyl sulfate (16.8 g., 0.133 mole), and potassium bicarbonate (100 g., 1.0 mole) were stirred in refluxing acetone (230 ml.) for 17 hr. After addition of acetic acid (10 ml.), the reaction mixture was filtered, and the filtrate was concentrated to 50 ml., poured into water (800 ml.), and extracted with ether. The desired ester (13%) was isolated by extraction into 2 *N* NaOH. It was purified as needles from petroleum ether (b.p. 40–60°), m.p. 34–35°, ν_{max}^{Nujol} 1666 and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.71. Found: C, 66.62; H, 6.65.

2,3-Dihydroxy-4-methylbenzoic Acid.—3-Methylcatechol (250 g., 2.01 moles) was carbonated in the same way as 2,5-xylenol. The temperature was raised to 140° (74 atm.) over 3 hr., and then the autoclave was allowed to cool over about 18 hr. The acid was crystallized from aqueous alcohol in two crops (220 g., m.p. 206–208°, and 9.5 g., m.p. 201–204°; 68%). The pure acid has m.p. 211–211.5°; ν_{max}^{Nujol} 3528, 3520, and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_8H_8O_4$: C, 57.15; H, 4.80. Found: C, 57.12; H, 5.09.

The **methyl ester** was obtained (83%) by reaction of the acid with methanol and sulfuric acid. It crystallized from aqueous ethanol: m.p. 44–44.5°; ν_{max}^{Nujol} 3560, 3507, 3477, 1680, and 1665 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.17; H, 5.48.

Reduction of the ester with lithium aluminum hydride in the usual way afforded **2,3-dihydroxy-4-methylbenzyl alcohol** (55–94%). It crystallized from ether–petroleum ether (b.p. 60–80°), m.p. 108–112°*, ν_{max} 3600–3100 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.31; H, 6.54. Found: C, 62.53; H, 6.58.

3,6-Dimethylcatechol.—2,3-Dihydroxy-4-methylbenzyl alcohol (50 g., 0.325 mole, m.p. 102–105°) in ethanol (1 l.) containing 10% palladium on charcoal (4 g.) was shaken under hydrogen and absorbed 7.37 l. in 5 hr. (calcd., 7.9 l.). After filtration and evaporation under reduced pressure, the brown tarry residue was extracted into boiling petroleum ether (b.p. 40–60°; four 150-ml. portions). The extracts were concentrated to give two crops of the catechol (16.5 g., m.p. 100–100.5°, and 26.9 g., m.p. 99–100°; 95%). The pure catechol was identical with a sample, m.p. 101°, kindly supplied by Professor W. Baker.[25b]

Acknowledgments.—We are very grateful to Dr. W. A. Bain for his interest throughout this work, and we thank Dr. A. L. Green for the tissue norepinephrine estimations.

Diuretics. 6-Substituted 3-Ketoalkyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-Dioxides and Related Anils, Oximes, and Hydrazones[1]

JERRY E. ROBERTSON,[2] DONALD A. DUSTERHOFT, AND THOMAS F. MITCHELL, JR.

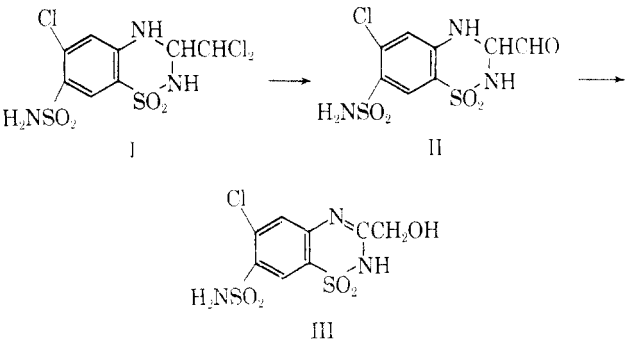
Lakeside Laboratories Division of Colgate-Palmolive Company, Milwaukee, Wisconsin

Received June 15, 1964

Condensation of appropriate ketoaldehydes with 5-substituted 2,4-disulfamylanilines under acid catalysis provided a group of 6-substituted 3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxides containing 3-ketoalkyl substituents. When β-ketoaldehydes were used and the 2-sulfamyl group was at least monosubstituted, either the usual ring-closure products or isomeric enol–anils were isolated depending on reaction conditions. Evidence for the enol–anil structures included interconversions between isomeric pairs and spectral and degradative studies. Unusual hydrazones and oximes were prepared and studied. Pharmacologic evaluation revealed several potent diuretic agents and other, less anticipated, biological properties for the compounds reported.

The pioneering work of Novello and Sprague, deStevens and Werner and their co-workers, as well as many other investigators, has led to an important class of diuretic and antihypertensive agents which contain a 1,2,4-benzothiadiazine ring system.[3] One especially potent member of this group reported by Topliss, *et al.*,[4] and others[3] is 6-chloro-3-dichloromethyl-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (I, trichlormethiazide). The present authors speculated that the *gem*-dichloro moiety present in this drug might be rapidly hydrolyzed *in vivo* to afford the corresponding aldehyde II. However, Sherlock[5] has shown that the acid-catalyzed reactions of glyoxaldehyde and phenylglyoxal with *o*-sulfamylanilines gave tautomeric alcohols analogous to III. This suggested that hydrolysis of I might form the alcohol rather than the isomeric aldehyde (Chart I).

CHART I



The rate of chloride ion formation from I in very dilute alkali was compared to, and found much greater than, the rate of ring opening as determined by appearance of arylamine. It was, therefore, postulated that the aldehyde II or tautomeric alcohol III might be the active metabolite of trichlormethiazide. To study this, a series of 3,4-dihydro-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxides substituted in the 6-position with chloro, trifluoromethyl, or nitro groups and in the 3-position with carbonyl-containing moieties was prepared. The well-known acid-catalyzed ring-closure reactions (Chart II) of *o*-sulfamylanilines (IV) with al-

(1) Presented before the Division of Medicinal Chemistry, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1962.

(2) Central Research Laboratories, Minnesota Mining and Manufacturing Company, St. Paul, Minnesota.

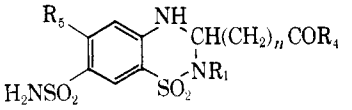
(3) For a recent review see E. Schlittler, G. deStevens, and L. Werner, *Angew. Chem. Intern. Ed. Engl.*, **1**, 235 (1962).

(4) J. G. Topliss, M. H. Sherlock, F. H. Clarke, M. C. Daly, B. W. Pottersen, J. Lipski, and N. Sperber, *J. Org. Chem.*, **26**, 3842 (1961).

(5) M. H. Sherlock, J. G. Topliss, and N. Sperber, Abstracts, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1959, p. 14-O.

TABLE I

SUBSTITUTED 3,4-DIHYDRO-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES

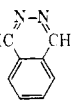
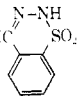


n	R_1	R_4	R_5	M.p., °C.[a]	Formula	Calcd., % N	Calcd., % S	Found, % N	Found, % S	Relative diuretic potency, oral, dog[d]
b	H	CH_3	Cl	300–301	$C_9H_{10}ClN_3O_5S_2$	12.37	18.86	12.03	18.75	<0.05
1	H	CH_3	Cl	202–204	$C_{10}H_{12}ClN_3O_5S_2$	11.88	18.12	11.77	18.27	0.05
1	H	CH_3	CF_3	206–209	$C_{11}H_{12}F_3N_3O_5S_2$	10.86	16.53	10.83	16.53	<0.05
1	H	CH_3	NO_2	211–213	$C_{10}H_{12}N_4O_7S_2$	15.39	17.59	15.16	17.66	<0.05
1	CH_3	CH_3	CF_3	175–177	$C_{12}H_{14}F_3N_3O_5S_2$	10.47	15.94	10.30	15.71	0.8
2	CH_3	CH_3	CF_3	177–179	$C_{13}H_{16}F_3N_3O_5S_2$	10.11	15.43	10.09	15.09	1.2
2	C_2H_5	CH_3	Cl	215–216	$C_{13}H_{18}ClN_3O_5S_2$	Cl, 8.96	16.19	Cl, 9.04	16.28	0.05
1	$CH_2C_6H_5$	CH_3	CF_3	145–149	$C_{18}H_{18}F_3N_3O_5S_2$	8.78	13.38	8.63	13.29	0.1
1[c]	CH_3	CH_3	Cl	163–169	$C_{13}H_{16}ClN_3O_5S_2$	Cl, 9.29	16.81	Cl, 9.23	16.94	0.7
1	CH_3	C_6H_5	CF_3	213–223	$C_{17}H_{16}F_3N_3O_5S_2$	13.83	9.01	13.75	9.00	0.5

[a] Melting points are corrected. [b] No methylene. [c] 7-SO_2NHCH_3. [d] Trichlormethiazide = 1; see Pharmacology.

TABLE II

HYDROXYLAMINE AND HYDRAZINE ADDUCTS OF TYPE VI

R_6	R_5	R_1	Z	M.p., °C.[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % S	Calcd., % N or Cl	Found, % C	Found, % H	Found, % S	Found, % N or Cl
H	CF_3	CH_3	OH	210–212	$C_{12}H_{15}F_3N_4O_5S_2$			15.39	N, 13.46			15.00	N, 13.25
H	Cl	H	$OCH_2C_6H_5$	171–173	$C_{17}H_{19}ClN_4O_5S_2$	44.53	4.17	13.97	Cl, 7.73	44.72	4.05	14.03	Cl, 7.68
CH_3	Cl	CH_3	$OCH_2C_6H_5$	212–215	$C_{19}H_{23}ClN_4O_5S_2$	46.86	4.76	13.17	Cl, 7.28	46.87	4.93	13.28	Cl, 7.49
H	Cl	H			$C_{18}H_{18}ClN_7O_4S_2$	43.60	3.66		N, 19.27	43.65	3.95		N, 19.27
CH_3	Cl	CH_3		160–162	$C_{20}H_{22}ClN_7O_4S_2$			12.21	Cl, 6.75			12.00	Cl, 6.66
H	CF_3	CH_3			$C_{20}H_{20}F_3N_7O_4S_2$			11.79	N, 18.04			11.89	N, 18.14
H	CF_3	CH_3		146–149	$C_{19}H_{20}F_3N_7O_6S_3$	38.33	3.88	16.15		38.44	3.33	16.06	

[a] Melting points are corrected.

dehydes or aldehyde derivatives such as acetals gave compounds of type V which are listed in Table I. When pyruvaldehyde was used, the type V ketone was isolated in poor yield rather than the tautomeric alcohol corresponding to III. Some 3-ketoalkyl compounds closely related to those listed in Table I have subsequently appeared in the literature.[6]

Disulfamylanilines were prepared by aminolysis of appropriate known disulfonyl chlorides or by selective alkylation of 3-oxo-6-substituted 3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxides (VIII, Chart III) followed by hydrolysis according to the method of Close, *et al.*[7] Yale and Sheehan[8] demonstrated that some 4-alkylation of VIII occurs. However, the small amount of aniline-nitrogen-substituted product which results after hydrolysis is adequately removed during recrystallization as these authors suggested.

The 3-ketoalkyl group in type V compounds was utilized synthetically to provide new compound classes. Several carbonyl compounds (V) were condensed with hydroxylamine and O-benzylhydroxylamine to afford the anticipated oximes of type VI which are listed in Table II. Also listed in this table are adducts with certain substituted hydrazines. 1-Hydrazinophthalazine is an established antihypertensive agent[9] which is judiciously administered concomitantly with a "thiazide" diuretic for the treatment of hypertension.[10] Druey[9] indicated that simple hydrazones of 1-hydrazinophthalazine retain antihypertensive properties after apparent hydrolysis *in vivo*. It was felt that hydrazones of 1-hydrazinophthalazine and "3-ketoalkylthiazides" might have especially desirable antihypertensive properties. Compounds of this class (VI) were prepared and are listed in Table II. When 1,1-dimethylhydrazine was used in an attempt to prepare a simple hydrazone of IX as shown in Chart IV, chlorothiazide (X) was isolated in 60% yield *via* a route best interpreted as a reverse-aldol reaction.

4-Hydrazino-2H-1,2,3-benzothiadiazine 1,1-dioxide (XI) was first prepared by Schrader[11] through treatment of *o*-cyanobenzenesulfonyl chloride with excess

(6) (a) R. M. Taylor and J. G. Topliss, *J. Med. Pharm. Chem.*, **5**, 312 (1962); (b) F. J. Lund and W. Kobinger, *Acta Pharmacol. Toxicol.*, **16**, 297 (1960).

(7) W. J. Close, L. R. Swett, L. E. Brady, J. H. Short, and M. Vernsten, *J. Am. Chem. Soc.*, **82**, 1132 (1960).

(8) H. L. Yale and J. T. Sheehan, *J. Org. Chem.*, **26**, 4315 (1961).

(9) J. Druey and A. Marxer, *J. Med. Pharm. Chem.*, **1**, 1 (1959).

(10) E. D. Freis, *J. Am. Med. Assoc.*, **169**, 105 (1959).

(11) E. Schrader, *J. prakt. Chem.*, **96**, 180 (1917).

CHART II

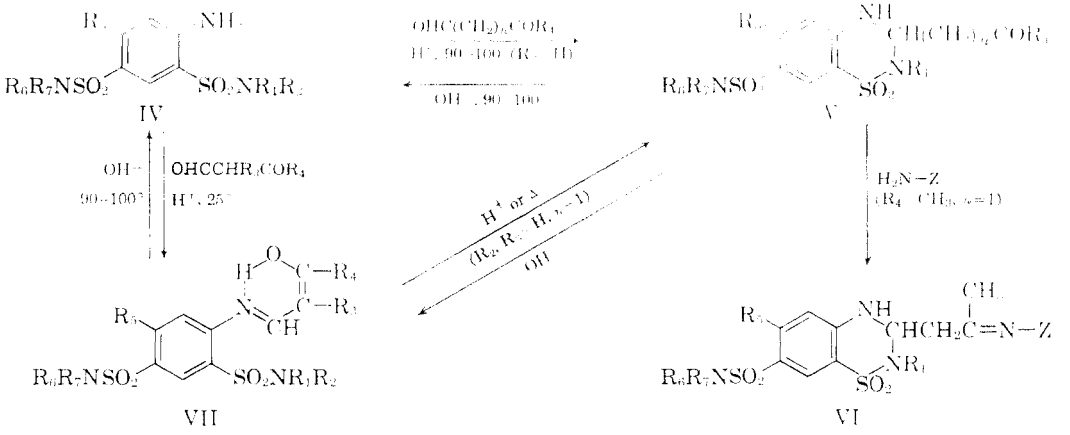


CHART III

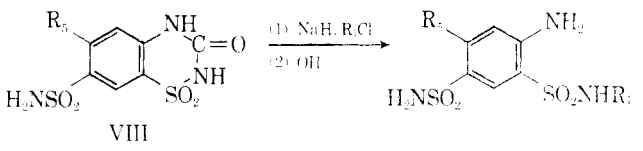
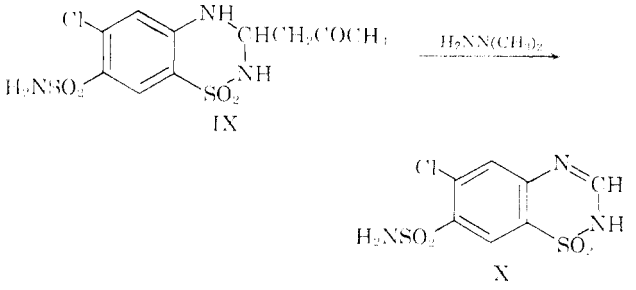
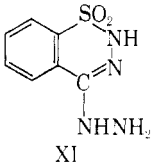


CHART IV



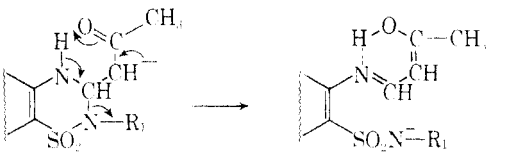
hydrazine. The incorporation of structural features present in both 1-hydrazinophthalazine and the "thiazides" prompted our interest in XI. This material was found to possess interesting cardiovascular properties.[12] Schmidt and co-workers have recently reported on work sparked by the same compound.[13] One adduct of XI with a type V material was prepared and is listed in Table II.



When β-ketoaldehydes were used in the ring-closure reaction (IV → V) and the adjacent sulfamyl group was at least monosubstituted (IV, R_1 = alkyl), an unexpected and new compound class designated enol–anils and shown by structure VII in Chart II could be isolated. These enol–anils, listed in Table III, were readily prepared in generally good yield at room temperature under acid catalysis. Evidence for the assigned structure is based on elemental analysis, method of synthesis, spectral data discussed later, and on interconversion and degradative studies. For example, both enol–anils and the more usual ring-closed compounds are, unsurprisingly, converted to the starting disulfamylanilines on vigorous alkaline hydrolysis.

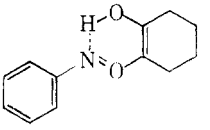
Enol–anils are cyclized to isomeric 1,2,4-benzothiadiazines on mild acid treatment or by heating and, more interestingly, enol–anils can be regenerated by treatment with base. These phenomena have been studied in solution where the unequivocal spectral evidence discussed later could be collected. Isolation of enol anils in the presence of acid was accomplished by exploiting their relative insolubility in ethanol. A reasonable mechanistic course for the base-catalyzed ring-opening reaction involves an initial abstraction of a proton on the carbon between the carbonyl and the ring followed by a concerted electron shift to the anion XII as shown in Chart V. A strongly hydrogen-bonded,

CHART V



cyclic structure for enol–anils is proposed to account for the observed stability. Since enol–anils could not be formed when the 2-sulfamyl group was unsubstituted, it is assumed that a steric factor plays a vital role in enol–anil stability.

Spectral Properties.—Infrared spectra of the enol–anils of Table III had a strong band at 6.03–6.09 μ attributable to –C=N– absorption which was also present in the simple model compound XIII, and which was reported for anils by Topliss[4] and others.[14] Ring-closed compounds were readily distinguished from isomeric enol–anils *via* solid-state infrared spectra. The ring-closed materials (V, R_4 = alkyl or aryl) exhibit a



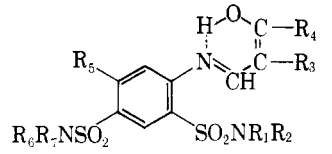
(12) Studies with XI and its chemical relatives will be the subject of a later report.

(13) P. Schmidt, K. Eichenberger, and M. Wilhelm, *Helv. Chim. Acta*, **45**, 996 (1962).

(14) For a discussion of the infrared spectral properties of imines of 1,3-dicarbonyl compounds and a list of pertinent references, see the recent report by D. Heinert and A. E. Martell, *J. Am. Chem. Soc.*, **84**, 3257 (1962).

TABLE III

ENOL–ANILS OF TYPE VII



R_1	R_2	R_3	R_4	R_5	R_6	R_7	M.p., °C.[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Calcd., % S	Found, % C	Found, % H	Found, % N	Found, % S	Relative diuretic activity, i.v., dog[b]
C_2H_5	H	H	CH_3	Cl	H	H	236–237	$C_{12}H_{16}ClN_3O_5S_2$	37.74	4.23			37.98	4.17			+1
C_2H_5	H	H	C_6H_5	Cl	H	H	253–254	$C_{17}H_{18}ClN_3O_5S_2$	45.98	4.09	9.46		46.00	4.10	9.31		*c*
CH_3	H	H	CH_3	Cl	CH_3	H	188–190	$C_{12}H_{16}ClN_3O_5S_2$	37.74	4.23	11.01		37.95	4.12	11.06		+2
CH_3	CH_3	H	CH_3	Cl	CH_3	CH_3	144–146	$C_{14}H_{20}ClN_3O_5S_2$	41.03	4.92	Cl, 8.75	15.64	41.15	4.92	Cl, 8.76	15.65	*d*
$CH_2CH{=}CH_2$	H	H	CH_3	Cl	H	H	205–207	$C_{13}H_{16}ClN_3O_5S_2$	Cl, 9.00		10.67	16.27	9.05 9.05		10.79	16.32	+4
$CH_2CH{=}CH_2$	H	H	C_6H_5	Cl	H	H	233–234	$C_{18}H_{18}ClN_3O_5S_2$	47.50	3.98	Cl, 7.78	14.07	47.45	3.78	Cl, 7.83	14.08	+3
CH_3	H	—$(CH_2)_4$—		CF_3	H	H	215–217	$C_{16}H_{18}F_3N_3O_5S_2$			9.52	14.52			9.42	14.40	+1
$CH_2CH{=}CH_2$	H	—$(CH_2)_4$—		Cl	H	H	198–200	$C_{16}H_{20}ClN_3O_5S_2$	44.28	4.65			44.32	4.64			+3
CH_3	CH_3	*e*	*e*	Cl	CH_3	CH_3	198–200	$C_{17}H_{19}Cl_2N_3O_5S_2$	42.54	3.99	Cl, 14.75	13.35	42.60	3.81	Cl, 14.89	13.37	0

[a] Melting points are corrected. [b] Trichlormethiazide = +4; See Pharmacology. [c] Not tested by this method, but less active than hydrochlorthiazide in oral test. [d] Too insoluble to test by this method. [e] Anil from 5-chlorosalicylaldehyde.

normal, strong keto-carbonyl band at 5.81–5.88 μ while the enol–anils show no absorption in this region.

5-Chloro- and 5-trifluoromethyl-2,4-disulfamylanilines and corresponding benzothiadiazines have three ultraviolet maxima appearing at 225 mμ (ϵ 35,000–40,000), 265–275 (15,000–20,000), and 310–330 (3500–4000). Enol–anils listed in Table III did not show the 270-mμ maximum. The principal maximum for this compound class appears at 335–365 mμ with enol–anils from 2-formylcyclohexanone absorbing at about 365 mμ, while those from 3-ketopropionaldehyde and 3-phenyl-3-ketopropionaldehyde absorb at 335–345 mμ. The benzaldehyde-type anils which were reported by Topliss[4] and of which one example from 5-chlorosalicylaldehyde was prepared, absorb less strongly at 250–300 mμ (ϵ 10,000–25,000). Compound XIII shows a maximum at 356 mμ (ϵ 30,100). Since small amounts of dimethylformamide were used to aid in dissolving the enol–anils, data below 254 mμ were not obtained.

As mentioned before, 2,6-disubstituted 3-oxoalkyl-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxides could be converted to isomeric enol–anils by treatment with base, and ring closure of enol–anils to isomeric 1,2,4-benzothiadiazines could be effected by acid treatment or by heating insolution. The experiment to be described started with 3,4-dihydro-2-methyl-3-(2-oxopropyl)-6-trifluoro-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (V, R_1 and R_4 = CH_3; R_5 = CF_3; R_6 and R_7 = H) but is typical of several similar interconversions studied. In this instance, a 3.5×10^{-4} M stock solution of the 1,2,4-benzothiadiazine in ethanol was prepared. A portion of this solution was adjusted to 3.5×10^{-5} M and an ultraviolet spectrum was taken which was typical for this compound class. A portion of stock solution containing 0.30 mg. of compound was treated with 1.0 ml. of 0.1 N aqueous NaOH and, after 2 min., with 2.0 ml. of 0.1 N aqueous HCl and then diluted. The final solution was 3.5×10^{-5} M in treated compound, 4×10^{-3} M in NaCl, and 4×10^{-3} M in HCl, all in 88% aqueous ethanol. The spectrum of this material showed the typical enol–anil maximum at 352 mμ. After 30 hr. at room temperature, rescanning gave a spectrum virtually superimposable with the spectrum obtained from the diluted stock solution. This is good evidence for lack of hydrolysis during the manipulations since the spectrum of the aniline which would result from hydrolysis is significantly different. Also, acid-catalyzed ring closures of enol–anil followed by base-catalyzed reopenings were executed in an analogous manner.

Pharmacology[15]

All of the compounds listed in Tables I–III were evaluated for diuretic activity. Two testing methods, oral and intravenous, were used although not all compounds were evaluated in each test. In the first, compounds were administered intravenously to pentobarbital-anesthetized dogs at doses of 1 and 10 γ/kg. Total urine was collected every 10 min. from cannulated ureters according to the classical procedure and analyzed for Na^+, K^+, and Cl^-. In the second method, the compounds were administered orally at varying doses to groups of 5 or 6 trained unanesthetized female dogs. Control experiments were conducted with the same groups of animals which received either no drug or trichlormethiazide. Urine was collected at 0.5-hr. intervals by catheterization and analyzed for electrolyte concentration.

The compounds listed in Table I were evaluated by the second (oral) method only. Relative diuretic potency is given in the table with trichlormethiazide = 1. The diuretic activity of the first four compounds suggests that incorporation of 3-ketoalkyl groups was not desirable. The data for the 2-substituted materials indicate the remarkable increase in diuretic activity with 2-methylation noted already by other workers.[3,7] Also, extension of the alkylene chain between carbonyl and ring was beneficial in terms of potency.

The hydrazones listed in Table II exhibited little or no diuretic activity when evaluated orally by the method outlined above. However, Ross and Cafruny found

(15) The data reported here were supplied by Dr. Murray Finkelstein and Mr. Patrick Nufer, Pharmacology Department, Lakeside Laboratories.

that several of these compounds exhibit a unique blocking action on the diuretic activity of the "thiazides".[16] This is especially true of the hydrazones generated from 1-hydrazinophthalazine.[17] The 2-methyl oximes listed in Table II are potent diuretics which approach trichlormethiazide in activity but do not differ greatly from the precursor ketones.

The compounds of Table III were evaluated by the intravenous method outlined and the diuretic activity of the more potent agents was confirmed in an oral test. The data listed in the table are for relative diuretic potency with trichlormethiazide = +4 at both doses. Three of the materials were roughly similar in milligram potency to trichlormethiazide in this preparation. Ring closure *in vivo* to a more typical "thiazide" structure is a likely possibility which has not been fully studied. The data also suggest that the structural requirements for high diuretic activity for the enol anils parallel those of the more typical ring-closed compounds.

Experimental[18]

Preparation of Intermediates.—Aldehydes and acetals used were obtained from commercial sources or synthesized by known procedures. 5-Substituted 2,4-disulfamylanilines, 5-chloro-2,4-bis(dimethyl- or methylsulfamyl)anilines, 6-substituted 3-oxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxides, some 2-alkylated-6-substituted 3-oxo-3,4-dihydro-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxides, and some 5-substituted 2-alkylsulfamyl-4-sulfamylanilines are known compounds which were prepared by methods reported in the chemical literature.[3,6b] In several cases literature reports appeared subsequent to our work but similar preparative methods were employed. 1-Hydrazinophthalazine, 4-hydrazino-2H-1,2,3-benzothiadiazine 1,1-dioxide,[11] and O-benzylhydroxylamine are also known compounds which were prepared by published syntheses.

2-Allyl-6-chloro-3,4-dihydro-3-oxo-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide.—This compound was prepared from 2-unsubstituted material (VIII, R_5 = Cl) according to the general method of Close[7] in 81% yield and melted at 278–279°.

Anal. Calcd. for $C_{10}H_{10}ClN_3O_5S_2$: Cl, 10.07; S, 18.21. Found: Cl, 10.25; S, 18.23.

2-Allylsulfamyl-5-chloro-4-sulfamylaniline Monohydrate.—Alkaline hydrolysis of the above product according to the general method of Close[7] provided 67% of product, m.p. 75–77°.

Anal. Calcd. for $C_9H_{14}ClN_3O_5S_2$: Cl, 10.32; S, 18.70. Found: Cl, 10.23; S, 18.71.

Extended drying under vacuum at 100° afforded an amorphous solid.

Anal. Calcd. for $C_9H_{12}ClN_3O_4S_2$: Cl, 10.89. Found: Cl, 10.98.

2-Benzyl-3,4-dihydro-3-oxo-6-trifluoromethyl-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide.—Benzylation of 2-unsubstituted material (VIII, R_5 = CF_3) essentially by the general method of Close[7] gave the product in 40% yield, m.p. 228–230°.

Anal. Calcd. for $C_{15}H_{12}F_3N_3O_5S_2$: N, 9.65; S, 14.73. Found: N, 9.68; S, 14.49.

2-Benzylsulfamyl-4-sulfamyl-5-trifluoromethylaniline.—Alkaline hydrolysis of the above compound by Close's[7] general method afforded a 63% yield of product, m.p. 188–192°.

Anal. Calcd. for $C_{14}H_{14}F_3N_3O_4S_2$: N, 10.26; S, 15.66. Found: N 10.19; S, 15.46.

6-Substituted 3-Oxoalkyl-3,4-dihydro-2H-1,2,4-Benzothiadiazine-7-sulfonamide 1,1-Dioxides (V, R_4 = CH_3, C_6H_5, or OC_2H_5).—Materials prepared are listed in Table I. Typically, the starting 2,4-disulfamylaniline, a slight excess of aldehyde or acetal and concentrated HCl were heated in dimethylformamide for about 15 min. The solvent was removed by distillation, and the residue was crystallized and recrystallized from aqueous ethanol to provide the products in 30–90% yields. Frequently, decolorizing carbon was used. Similar ring closures are reported in profusion in the chemical literature.[3]

3-Oxoalkyl-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide Oximes (VI, Z = OH or $OCH_2C_6H_5$).—The appropriate starting ketone, an equivalent amount of O-benzylhydroxylamine hydrochloride or an excess of hydroxylamine hydrochloride and pyridine in ethanol were refluxed briefly and precipitation of pure product was induced by dilution with water or cooling. The yields were 63–89%.

6-Substituted 3-Oxoalkyl-3,4-dihydro-2H-1,2,4-Benzothiadiazine-7-sulfonamide 1,1-Dioxide Hydrazones.—Equivalent amounts of ketone and 1-hydrazinophthalazine or 4-hydrazino-2H-1,2,3-benzothiadiazine 1,1-dioxide were refluxed for about 0.5 hr. in ethanol with a small amount of acetic acid. The pure product separated on cooling to afford 60–85% yields.

Chlorothiazide from 6-Chloro-3,4-dihydro-3-(2-oxopropyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide.—A mixture of the ketone (7.08 g., 0.020 mole), 1.3 g. (0.020 mole) of N,N-dimethylhydrazine, and 3 drops of glacial acetic acid in 150 ml. ethanol was refluxed for 15 min. A solid formed during heating which, after cooling, was collected and dried to afford 3.5 g. (60%) of chlorothiazide, m.p. 347–349° dec. (lit.[19] m.p. 342–343° dec.). Infrared spectra of this product and authentic chlorothiazide were superimposable.

Anal. Calcd. for $C_7H_6ClN_3O_4S_2$: Cl, 11.99; S, 21.69. Found: Cl, 12.01; S, 21.88.

Enol anils listed in Table III were prepared by closely related methods which are specifically described for the following typical examples.

2-Allylsulfamyl-4-sulfamyl-5-chloro-N-(3-hydroxy-2-butenylidene)aniline (VII, R_5 = Cl; R_1 = $CH_2CH=CH_2$; R_4 = CH_3; R_2, R_3, R_6, and R_7 = H).—2-Allylsulfamyl-5-chloro-4-sulfamylaniline monohydrate (6.9 g., 0.020 mole) was dissolved in 14 ml. of 3-ketopropionaldehyde dimethylacetal at room temperature and, after filtration, 6 drops of 1 *N* HCl was added to the viscous solution. After stirring for 20 hr., a heavy suspension had formed which was diluted with 150 ml. of ethanol and filtered. The collected material was washed with ethanol and dried to afford 6.2 g. (78%) of product.

This product (100 mg.) was heated at 90–100° for 3 hr. in 5 ml. of 10% NaOH. After cooling and adjustment to pH 6 with acetic acid, a solid separated which was collected, washed with water, and dried. This material melted at 76–78°, amounted to 80 mg. (93%), and was identified as 2-allylsulfamyl-5-chloro-4-sulfamylaniline monohydrate based on superimposable infrared spectra and undepressed mixture melting points.

2-Methylsulfamyl-4-sulfamyl-5-trifluoromethyl-N-(2-hydroxycyclohexen-1-ylmethylidene)aniline (VII, R_5 = CF_3; R_3 = CH_3; R_2-R_4 = $(CH_2)_4$; R_6 and R_7 = H).—2-Methylsulfamyl-4-sulfamyl-5-trifluoromethylaniline (3.3 g., 0.010 mole) and 2.6 g. (0.020 mole) of freshly distilled 2-formylcyclohexanone were dissolved in 15 ml. of ethanol and 3 drops of concentrated HCl was added. After standing overnight, a solid formed. The mixture was diluted with ethanol and the solid was collected, washed with ethanol, and dried to yield 2.5 g. (56%) of product.

2-Allylsulfamyl-5-chloro-4-sulfamyl-N-(3-hydroxy-3-phenyl-2-propenylidene)aniline (VII, R_5 = Cl; R_1 = $CH_2CH=CH_2$; R_4 = C_6H_5; R_2, R_3, R_6, and R_7 = H).—2-Allylsulfamyl-5-chloro-4-sulfamylaniline monohydrate (3.4 g., 0.010 mole) and 3.4 g. (0.020 mole) of sodio-3-phenyl-3-ketopropionaldehyde were slurried together in 50 ml. of ethanol, and 5 ml. of concentrated HCl was added with stirring. After 3 min., about 20 ml. of water was added. A bright yellow solid formed which was collected, washed with aqueous ethanol, and dried to afford 2.1 g. (46%) of product.

(16) C. R. Ross and E. J. Cafruny, *J. Pharmacol. Experti. Therap.*, **140**, 125 (1963).

(17) (a) Pharmacologic and toxicologic studies with this compound class will be reported elsewhere. (b) After *in vitro* hydrolysis of compounds of this type under various acidic conditions, neither 1-hydrazinophthalazine or intact "3-ketoalkylthiazides" could be found. Rather, phthalazone and 5-substituted 2,4-disulfamylanilines were isolated after vigorous acid treatment.

(18) Melting points are corrected. Infrared spectra were obtained as Nujol mulls on a Beckman, Model IR5 spectrophotometer. Ultraviolet spectra were recorded from solutions in small amounts of dimethylformamide diluted with water or ethanol at a 1-cm. path length using a Beckman, Model DK2A spectrophotometer.

(19) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960).

Acknowledgment.—We wish to thank Drs. C. I. Judd and J. H. Biel for especially helpful discussions and encouragement. Mr. E. Kluchesky is also thanked for his capable direction of the analytical services. We are indebted to Mr. D. Gauger of the Pharmacology Department for his technical work.

Behavioral Stimulants. 4-Oxazolidinones

JOHN B. BICKING, SARA F. KWONG, MICHAEL H. FISHER, AND WILLIAM H. NICHOLSON

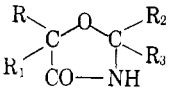
Merck Sharp and Dohme Research Laboratories, Division of Merck and Company, Inc., West Point, Pennsylvania

Received June 9, 1964

4-Oxazolidinones were synthesized by the acid-catalyzed condensation of α-hydroxyamides with acetone and other low molecular weight ketones. A number were found to have stimulant activity in animal operant behavior tests. One of the most active compounds, 2,2-dimethyl-5-styryl-4-oxazolidinone, has undergone extensive pharmacological and clinical testing.

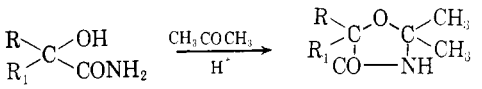
Although central nervous system (CNS) depressant activity is ordinarily associated with compounds which may be classed as cyclic amides (barbiturates, hydantoins, oxazolidinediones), stimulant and convulsant activity have been found in a number of compounds of this class.[1] 2-Imino-5-phenyl-4-oxazolidinone has recently been introduced into therapy as a CNS stimulant.[2]

Certain 4-oxazolidinones of the type I were found in these laboratories to possess stimulant properties of a magnitude and type that prompted us to prepare a series of these compounds for study.



I

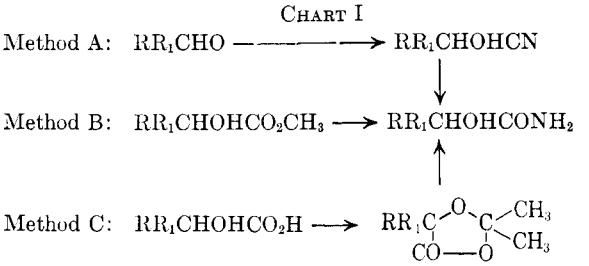
In Table I are listed 2,2-dimethyl-4-oxazolidinones prepared by the acid-catalyzed condensation of α-hydroxyamides with acetone, following the method described by Fischer, *et al.*[3] Chemical[3,4] and infrared[4,5] spectral evidence for the cyclic (oxazolidinone) struc-



ture of the condensation products of ketones and aldehydes with α-hydroxyamides has been presented.

The three methods used for the preparation of the required α-hydroxyamides are outlined in Chart I. Method A consisted of the preparation of aldehyde cyanohydrins by either of two methods and the hydrolysis of these, directly, without purification, to the α-hydroxyamides which are listed in Table II. Method B involved the ammonolysis of methyl esters of α-hydroxy acids. In method C, α-hydroxy acids were condensed with acetone to give 2,2-dimethyl-1,3-dioxolan-4-ones which were converted by ammonolysis to the α-hydroxyamides.

CHART I



When 2,2-dimethyl-5-styryl-4-oxazolidinone (IIb) was found to have outstanding stimulant activity, the condensation of the intermediate 2-hydroxy-4-phenyl-3-butenamide (IIa)[6,7] with ketones other than acetone and with benzaldehyde was studied. The resulting 4-oxazolidinones are listed in Table III. Ethyl methyl ketone was not markedly less reactive than acetone. Only one of the two possible racemates was obtained crystalline from the reaction mixture. Diethyl ketone reacted sluggishly to give the oxazolidinone in low yield. Fractional crystallization of the product from the condensation of IIa with acetylacetone gave the two racemic forms of 2-acetonyl-2-methyl-5-styryl-4-oxazolidinone.

The 4-oxazolidinones are colorless, crystalline compounds with a high degree of thermal stability, several having been purified by vacuum distillation. Their infrared spectra exhibit the characteristic[5] carbonyl absorption band in the range 1708–1722 cm.$^{-1}$ (KBr pellet). The oxazolidinones in contact with hot dilute mineral acids are rapidly hydrolyzed to the component α-hydroxyamides.

The expected derivatives of IIb were obtained by hydrogenation and bromination of the double bond. The N-methyl derivative, 2,2,3-trimethyl-5-styryl-4-oxazolidinone, was obtained by reaction of the sodio derivative of IIb with methyl iodide and was readily characterized by its infrared carbonyl absorption band at 1710 cm.$^{-1}$. The low-melting O-methyl derivative, obtained by the reaction of IIb with methyl iodide in the presence of silver oxide, was unstable and an entirely satisfactory analysis could not be obtained.

(1) P. K. Knoefel [*J. Pharmacol. Exptl. Therap.*, **84**, 26 (1945)] has reviewed the stimulant and convulsant barbituric acids.

(2) (a) L. Schmidt, *Arzneimittel-Forsch.*, **6**, 423 (1956); (b) G. A. Lienart and W. Janke, *ibid.*, **7**, 436 (1957).

(3) H. O. L. Fischer, G. Dangschat, and H. Stettiner, *Ber.*, **65**, 1032 (1932).

(4) W. Davies, T. H. Ramsay, and E. R. Stone, *J. Chem. Soc.*, 2633 (1949).

(5) K. Eichenberger, E. Ganz, and J. Druey, *Helv. Chim. Acta*, **38**, 284 (1955).

(6) R. Fittig and M. Ginsburg, *Ann.*, **299**, 23 (1898).

(7) Each α-hydroxyamide is designated by a Roman numeral followed by the letter a; the derived 2,2-dimethyl-4-oxazolidinone is designated by the same numeral followed by b.