Experimental[14]

4-Chloro-6-nitrosoresorcinol.—4-Chlororesorcinol (14.4 g., 0.1 mole) was dissolved in a solution of sodium ethoxide prepared from 2.3 g. (0.1 g. atom) of sodium and 100 ml. of anhydrous ethanol. The resulting solution was cooled to 0° and treated with a solution of 10.3 g. (0.1 mole) of butyl nitrite in 10 ml. of anhydrous ethanol. The dark reaction mixture was stirred for 3 hr. at 0° then poured into 300 ml. of water. Neutralization of the dark solution with hydrochloric acid gave a yellow precipitate which was recrystallized from aqueous ethanol to give 12 g. (69%) of yellow crystals which slowly decomposed without melting upon heating; $\lambda_{max}^{CH_3OH}$ 308 mμ (ε 18,000); λ_{max}^{Nujol} 2.85, 2.98, 3.16, 6.20, 6.41 μ.

Anal. Calcd. for $C_6H_4ClNO_3 \cdot H_2O$: C, 37.7; H, 3.2; N, 7.3; H_2O, 9.4. Found: C, 37.8; H, 3.3; N, 7.0; H_2O, 9.2.

2-Amino-5-chloro-6-hydroxybenzoxazole.—A solution of cyanogen bromide in methanol was prepared by slowly adding 17.6 g. (0.11 mole) of bromine to 5.4 g. (0.11 mole) of sodium cyanide in 200 ml. of methanol. The air in the flask was displaced with nitrogen and a solution of 4-amino-6-chlororesorcinol [prepared by shaking at room temperature a solution of 17.3 g. (0.1 mole) of 4-chloro-6-nitrosoresorcinol in 200 ml. of methanol with hydrogen under a pressure of 2.8 kg./cm.² and 2 g. of 10% palladium-charcoal catalyst until 0.2 mole of hydrogen was absorbed] was added rapidly with stirring. The reaction mixture was heated quickly to reflux and allowed to cool to room temperature. The solution was neutralized with sodium bicarbonate solution, and most of the methanol was removed by distillation under reduced pressure. The black precipitate was purified by several recrystallizations from methanol after treatment with Norit A to give 6.2 g. (33.7% yield) of colorless crystals, m.p. 215–217° dec.; $\lambda_{max}^{CH_3OH}$ 242 and 302 mμ (ε 11,000 and 8,1000); $\lambda_{max}^{0.1\ N\ HCl}$ 235 and 292 mμ (ε 9,500 and 8,600); $\lambda_{max}^{0.1\ N\ NaOH}$ 315 and 323 mμ (ε 19,500 and 19,600); λ_{max}^{Nujol} 2.98, 3.01, 5.99, 6.11, 6.37, 6.71 μ.

Anal. Calcd. for $C_7H_5ClN_2O_2$: C, 45.5; H, 2.7; Cl, 19.2; N, 15.2. Found: C, 45.7; H, 2.6; Cl, 19.2; N, 15.1.

5-Chloro-6-hydroxy-2-benzoxazolinone (VI). 1. From 4-Amino-6-chlororesorcinol.—A solution of 4-amino-6-chlororesorcinol was prepared as described above, using ethyl acetate in place of methanol. This solution was transferred under nitrogen to a flask containing 18 g. (0.22 mole) of sodium acetate in 100 ml. of ethyl acetate. The mixture was stirred and treated rapidly with a solution of 9.8 g. (0.10 mole) of phosgene in 20 ml. of ethyl acetate. The reaction mixture was heated to reflux and then allowed to cool to room temperature. Water was added, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic solution was washed with dilute sodium bicarbonate solution, then with dilute hydrochloric acid and finally with water. The solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give 15 g. of crude red product which was purified by several recrystallizations from methanol after treatment with Darco to give colorless crystals (6.0 g., 32.3%), m.p. 245–247° $\lambda_{max}^{CH_3OH}$ 232 and 300 mμ (ε 5,700 and 7,300); $\lambda_{max}^{0.1\ N\ HCl}$ 229 sh and 293 mμ (ε 5,100 and 6,000); $\lambda_{max}^{0.1\ N\ NaOH}$ 238 and 321 mμ (ε 11,100 and 7,200); λ_{max}^{Nujol} 3.06, 5.59, 5.68, 6.07, 6.67, 6.78 μ.

Anal. Calcd. for $C_7H_4ClNO_3$: C, 45.4; H, 2.2; N, 7.5. Found: C, 45.1; H, 2.2; N, 7.3.

2. From 2-Amino-5-chloro-6-hydroxybenzoxazole.—A solution of 1.4 g. of 2-amino-5-chloro-6-hydroxybenzoxazole (IV) in 50 ml. of 2 *N* hydrochloric acid was refluxed for 5 hr. The solid was collected by filtration, washed with water and purified by recrystallization from a mixture of acetone and benzene to give 0.6 g. of product which was shown to be identical with the material obtained from the phosgene method by melting point, mixture melting point and ultraviolet and infrared spectra.

2-Amino-5-chloro-6-methoxybenzoxazole (VII).—A suspension of 5.0 g. (0.027 mole) of 2-amino-5-chloro-6-hydroxybenzoxazole (IV) in 25 ml. of water was cooled to 0–5° and treated with a solution of 1.2 g. (0.03 mole) of sodium hydroxide in 25 ml. of water to give a dark blue solution to which was added slowly 4.0 g. (0.03 mole) of dimethyl sulfate. The ice bath was removed and stirring was continued until the mixture was neutral to litmus. The precipitate was collected, washed with water and purified by crystallization from a mixture of acetone and benzene to give 3.0 g. (56.0% yield) of colorless crystals which decomposed from 195–215°; $\lambda_{max}^{CH_3OH}$ 245 and 302 mμ (ε 11,900 and 8,100); λ_{max}^{Nujol} 2.89, 5.87, 6.36, 6.79 μ.

Anal. Calcd. for $C_8H_7ClN_2O_2$: C, 48.4; H, 3.6; N, 14.1. Found: C, 48.2; H, 3.6; N, 14.1.

5-Chloro-6-methoxy-2-benzoxazolinone (VIII).—A solution of 1.0 g. of 2-amino-5-chloro-6-methoxybenzoxazole (VII) in 25 ml. of 2 *N* hydrochloric acid was refluxed for 4 hr. The precipitate was collected and purified by three recrystallizations from methanol to give 0.25 g. (26.0%), m.p. 225–227°; $\lambda_{max}^{CH_3OH}$ 235 and 298 mμ (ε 6,600 and 6,860); λ_{max}^{Nujol} 3.11, 5.30, 5.60, 6.10, 6.18, 6.70 μ.

Anal. Calcd. for $C_8H_6ClNO_3$: C, 48.1; H, 3.0; N, 7.0. Found: C, 48.0; H, 3.1; N, 7.0.

Acknowledgment.—We wish to thank Mrs. Mary C. Christie for determining the ultraviolet and infrared spectra and for certain of the nitrogen analyses.

(14) Melting points are corrected and were determined on a Thomas–Hoover capillary apparatus. Infrared spectra were determined on a Perkin Elmer Model 21 spectrophotometer and ultraviolet spectra on a Cary Model 14 spectrophotometer.

Thio Derivatives of 2,3-Dihydro-4H-1,3-benzoxazin-4-one. Synthesis and Pharmacological Properties

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A series of 2,3-dihydro-4H-1,3-benzoxazin-4-one-2-thio derivatives has been prepared either by condensation of salicylamide with S-substituted 3-thiopropionaldehyde or thioacetaldehyde acetals or by treating 2-(2-chloroethyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (chlorthenoxazine) with alkali salts of mercaptans. The pharmacological screening of the most active members of the series, 2,3-dihydro-2-[2-(methylthio)ethyl]-4H-1,3-benzoxazin-4-one (1) and 2,3-dihydro-2-[2-(phenylsulfinyl)ethyl]-4H-1,3-benzoxazin-4-one (8), has shown that they may be classified as interesting antiinflammatory and antipyretic agents of very low toxicity.

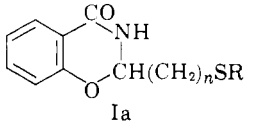
2-Substituted 2,3-dihydro-4H-1,3-benzoxazin-4-ones have not often been tested for pharmacological properties and the results of those tests have proved of little interest. Kaufmann[2] found no pharmacological activity for 2,3-dihydro-2-(trichloromethyl)-4H-1,3-benzoxazin-4-one, while Horrom,[3] who synthetized a series of mono- and disubstituted benzoxazinones of this class, reported slight analgesic activity for some of these com-

(1) Research Laboratories of Zambon S.p.A., Milan-Bresso, Italy.

(2) H. P. Kaufmann, *Arch. Pharm.*, **265**, 226 (1927).

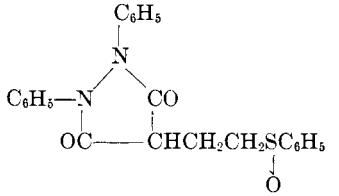
(3) B. W. Horrom and H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 721 (1950).

pounds in dogs and hypnotic activity in mice. Recently, however, antiinflammatory properties have been observed for a new halogen derivative, 2-(2-chloroethyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (chlorthenoxazine).[4,5,6] These findings prompted us to further investigate the benzoxazinone structure and to prepare a series of derivatives of the general formula (Ia), where R = alkyl, alkylaryl, phenyl, and



Ia

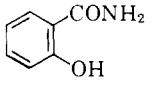
n = 1 or 2. Furthermore, in view of the interesting properties exhibited by 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione[7] the corresponding



sulfoxides Ib and sulfones Ic of Ia have been prepared.

The compounds Ia, where n = 2, were prepared by the reaction sequence

$$CH_2{=}CHCHO \xrightarrow[C_2H_5OH]{HCl} CH_2ClCH_2CH(OC_2H_5)_2 \xrightarrow[KOH]{RSH} RSCH_2CH_2CH(OC_2H_5)_2$$



$$+ (C_2H_5O)_2CHCH_2CH_2SR \xrightarrow{HCl} \text{Ia}$$

S-Substituted 3-thiopropionaldehyde diethyl acetals were prepared readily from 3-chloropropionaldehyde diethyl acetal by reaction with the corresponding mercaptans in ethanolic sodium ethoxide solution. Some of these thio derivatives of aldehydes, as 3-(phenylthio)-propionaldehyde diethyl acetal, are not reported in the literature. The subsequent condensation of salicylamide with S-substituted 3-thiopropionaldehyde diethyl acetals was accomplished by bubbling in a nonpolar solvent at 50–60°, a stream of dry hydrogen chloride in the presence of glacial acetic acid (Method A). The products Ia, where R = aryl and alkylaryl and n = 2, are solids at room temperature, whereas those where R = alkyl exhibit, on lengthening of the alkyl chain, a tendency to become liquids. The compounds Ia were prepared also by another procedure, *i.e.*, by treating chlorthenoxazine with sodium or potassium salts of the corresponding mercaptans using ethanol as a solvent (Method B).

In addition to the compounds Ia, 2,3-dihydro-2-[(phenylthio)methyl]-4H-1,3-benzoxazin-4-one was prepared by treating, under the same conditions, salicylamide with (phenylthio)acetaldehyde dimethyl acetal which, in turn, was synthetized from chloroacetaldehyde dimethyl acetal and sodium phenylmercaptide. Compounds Ib and Ic were obtained by oxidizing the compounds of formula Ia with hydrogen peroxide. It is essential to facilitate this reaction by using a suitable solvent: in fact, the stoichiometric quantities of hydrogen peroxide to obtain sulfoxides (Ib) gave, in acetic acid, mixtures of sulfoxides (Ib) and sulfones (Ic), as well as starting products which proved to be difficult to separate. With ethanol as a solvent prevalently sulfoxides (Ib) were obtained, even when excesses over the stoichiometric quantities of hydrogen peroxide were used (Method C). Sulfones (Ic) were obtained in glacial acetic acid using the theoretical quantities or a slight excess of hydrogen peroxide (Method D).

Numerous attempts were made to obtain from the compounds Ia the corresponding sulfonium salts by treating the thioalkyl derivatives with methyl iodide and aryl derivatives with dimethyl sulfate.[8] In the first case generally trimethylsulfonium iodide was obtained, because of the known reversibility of this reaction.[9] In the second case the yield consisted of brown products extremely difficult to purify.

Experimental

ω-Thioaldehydes Acetals, $RS(CH_2)_nCH(OR)_2$.—Example: 3-(Phenylthio)propionaldehyde diethyl acetal. To a solution of 33.1 g. (0.3 mole) of thiophenol in 400 ml. of absolute ethanol an ethanolic solution of sodium ethoxide prepared by treating 6.9 g. (0.3 g. atom) of sodium with 150 ml. of absolute ethanol, was added. To the mixture, heated to 50°, 50 g. (0.3 mole) of 3-chloropropionaldehyde diethyl acetal was added gradually; the mixture was refluxed gently for 2 hr., cooled and the separated sodium chloride filtered off. The solvent was distilled off and the residue dissolved in ether, a small quantity of salt was filtered and, after removing the ether, the residue was fractionated yielding 75 g. (94%) of distillate, b.p. 148–149° (0.4 mm.).

Preparation of Derivatives Ia (Method A).—The acetal of an S-substituted-ω-thioaldehyde (0.05 mole), 0.05 mole of salicylamide and 6 moles of glacial acetic acid were placed in 75 ml. of chloroform. The mixture was heated to 50° and dry hydrogen chloride bubbled through for 5 min. At the end of this reaction, the clear solution was extracted repeatedly with 10% sodium hydroxide solution, washed to neutrality and dried over calcium chloride. The solvent was removed and the residual product, if solid, crystallized from suitable solvents; if liquid, it was fractionated *in vacuo* (see Table I).

(Method B).—2-(2-Chloroethyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (1 mole) was dissolved in 2 l. of absolute ethanol containing 1 mole of a sodium mercaptide. The mixture was stirred, heated to boiling, and then maintained under reflux until no longer alkaline. It was cooled, sodium chloride filtered off, and the alcoholic solution evaporated to dryness. The residue was dissolved in chloroform and the solution washed with a 10% sodium hydroxide solution and then with water. After drying over calcium chloride and evaporation, the residue, if solid, was crystallized from suitable solvents; if liquid, it was fractionated (see Table I).

Preparation of Sulfoxides (Ib) (Method C).—The thio derivative (Ia) (0.07 mole) was dissolved in boiling ethanol (100 ml.). Hydrogen peroxide (30%, 16 ml., 0.14 mole) was added, the mixture heated under reflux for 4 hr. and cooled in a refrigerator overnight. The separated precipitate was crystallized repeatedly from a suitable solvent (see Table I).

Preparation of Sulfones (Ic) (Method D).—The thio derivative (Ia) (0.07 mole) was dissolved in a mixture of 80 ml. of glacial acetic acid and 12 ml. of acetic anhydride. Hydrogen peroxide (30%, 24.4 ml., 0.21 mole) was added and the mixture heated on a steam bath for 1 hr. It was left in a refrigerator overnight and the crystalline precipitate was collected. The sulfone was crystallized repeatedly from suitable solvents (see Table I).

(4) R. Kadatz, *Arzneimittel-Forsch.*, **7**, 651 (1957).

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(6) W. Schneider and H. Tronnier, *ibid.*, **7**, 659 (1957).

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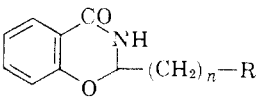
(8) H. Gilman, in "Organic Chemistry," J. Wiley and Sons, Inc., New York, N. Y., 1949, Vol. I, p. 867.

(9) J. Goerdeler, "Methoden zur Herstellung und Umwandlung von Sulfoniumverbindungen," in "Methoden der Organischen Chemie" (Houben-Weyl), E. Müller, ed., Georg Thieme Verlag, Stuttgart, 1955, Vol. 9, p. 180.

TABLE I



Compound	n	R	Method	Yield, %	M.p. or b.p. °C.	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Oxygen Calcd.	Oxygen Found	Sulfur Calcd.	Sulfur Found
1	2	$-SCH_3$	B	81	48–49[a]	160 (0.2) $C_{11}H_{13}NO_2S$	59.17	58.93	5.87	6.03	6.27	6.16	14.33	14.48	14.36	14.05
2	2	$-SC_2H_5$	B	65	172–175	(0.5) $C_{12}H_{15}NO_2S$					5.90	5.98			13.51	13.42
3	2	$-SC_3H_7$	B	64	159	(0.1) $C_{13}H_{17}NO_2S$					5.57	5.18			12.75	12.30
4	1	$-SC_6H_5$	A	68	112–113[a]	$C_{15}H_{13}NO_2S$	66.40	66.79	4.83	5.04	5.16	5.31	11.79	11.50	11.82	11.69
5	2	$-SC_6H_5$	A & B	A = 65 B = 82	126.5[a]	$C_{16}H_{15}NO_2S$	67.33	67.04	5.30	5.60	4.91	4.81			11.23	11.00
6	2	$-SCH_2C_6H_5$	B	78	64–65[a]	$C_{17}H_{17}NO_2S$	68.20	68.33	5.72	5.79	4.68	4.80	10.69	10.79	10.71	10.55
7	2	$-SOCH_3$	C	45	99–100[b]	$C_{11}H_{13}NO_3S$	55.22	55.70	5.48	5.40	5.85	5.65	20.06	20.41	13.40	13.33
8	2	$-SOC_6H_5$	C	53	166–167[a]	$C_{16}H_{15}NO_3S$	63.75	63.24	5.02	4.88	4.60	4.80	15.92	15.96	10.64	10.68
9	2	$-SOCH_2C_6H_5$	C	48	145–146[b]	$C_{17}H_{17}NO_3S$	64.74	65.04	5.43	5.59	4.44	4.58	15.22	15.53	10.17	9.98
10	2	$-SO_2C_6H_5$	D	62	172–173[a]	$C_{16}H_{15}NO_4S$	60.54	60.58	4.78	5.06	4.41	4.51	20.16	20.24	10.10	9.88
11	2	$-SO_2CH_2C_6H_5$	D	58	194–195[a]	$C_{17}H_{17}NO_4S$	61.61	61.81	5.17	5.23	4.22	4.31	19.31	19.10	9.67	9.54

Solvent of crystallization: [a] 95% ethanol; [b] 50% ethanol.

TABLE II

ORAL ANTIPYRETIC ACTIVITY IN RATS (5 PER GROUP) MADE HYPERTHERMIC BY PARENTERAL ADMINISTRATION OF YEAST.

Compound and dose	mg./kg.	Mean results, representing the difference in temperature between the treated animals and controls, min. after the treatment: 90	180	270
Acetylsalicylic acid	300	1.3	2.1	1.5
Chlorthenoxazine	300	1.2	1.7	1.2
Compound 5	300	0.4	0.6	1.1
Compound 8	300	0.9	1.2	1
Compound 10	300	0.7	0.9	0.8
Compound 1	300	1.3	1.9	1.7

TABLE III

ANTIINFLAMMATORY ACTIVITY OF SOME OF THE COMPOUNDS TESTED SHOWN IN COMPARISON TO CHLORTHENOXAZINE AND SALICYLAMIDE.

Compound and dose	mg./kg.	Number of implants	Route	Granuloma Mean dry weight, mg.	Reduction, %
Controls		20		77	
Chlorthenoxazine	400	14	i.p.	39	50
Salicylamide	400	16	i.p.	46	41
Compound 5	400	14	i.p.	59	24
Compound 8	400	22	i.p.	42	46
Compound 10	400	16	i.p.	51	34
Compound 1	400	16	i.p.	56	28

Pharmacology.—Antipyretic activity was studied in rats made hyperthermic by subcutaneous administration of 1 ml./100 g. of a 12% suspension of yeast.[10] The animals were given the test compounds 10 hr. later by gastric tube. Table II shows the most interesting results obtained. Compounds 1 and 8 proved the most active derivatives investigated, the former being even more active than chlorthenoxazine. No effect of the test compounds on the temperature of normal animals was observed.

(10) J. H. Burn, in "Biological Standardization," Oxford Medical Publ., London, 1952, p. 313.

TABLE IV

INFLUENCE OF TEST COMPOUNDS ON THE FORMALIN ASCITES IN RATS

Compound and dose mg./kg.	Inhibition of the ascites at 4 hour: No. of animals	% reduction	at 8 hour: No. of animals	% reduction
Phenylbutazone 100	8	37	8	41
Chlorthenoxazine 300	8	26	8	7
Compound 8 300	8	53	8	15
Compound 1 300	8	29	8	38

Antiinflammatory activity was estimated by the cotton pellet granuloma test.[11] Pellets of 50 mg. were implanted in the dorsal region of rats weighing between 120 and 150 g. Immediately after the implantation the animals were given the derivatives, by intraperitoneal administration twice daily for 3 days. The animals were sacrificed 24 hr. after the last dose and the pellets removed, oven dried for 12 hr. at 80° and weighed. The results obtained are summarized in Table III showing that the sulfoxide derivative (8) approaches very closely the activity exhibited by chlorthenoxazine.

In a further series of experiments, compounds 8 and 1 were compared with phenylbutazone and chlorthenoxazine for possible inhibitory activity on ascites induced in rats of about 300 g. weight by intraperitoneal introduction of 1 ml./animal of a 1.5% formalin solution.[12] The animals were pretreated orally with the test compounds, then killed between 4 and 8 hr. after the administration of formalin and the ascitic liquid was measured immediately. Table IV shows the per cent reduction in the weight of the liquid in respect to controls. In the present assay compound 1 proved more active than chlorthenoxazine. It is of interest to note the substantial inhibitory action of compound 8 at 4 hr.; as for chlorthenoxazine this effect is markedly reduced at 8 hr.

In view of these observations and considering the low toxicity exhibited by the above compounds, further pharmacological screening of compounds 8 and 1 could prove rewarding and possibly lead to their evaluation as therapeutic agents.

(11) R. Meier, W. Scholer, and P. Desaulles, *Experientia*, **6**, 469 (1950).

(12) G. Tedeschi, G. Wilhelmi, and E. Martin, *Minerva Medica*, **49**, 681 (1958).