[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Central Nervous System Depressants. The Preparation of Some 2-Aryl-4-metathiazanones

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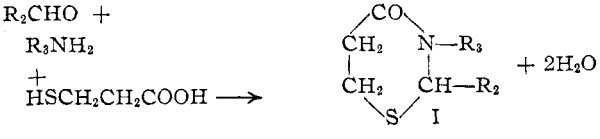
It has been found that β-mercaptopropionic acid reacts readily with ammonia or primary amines and aryl aldehydes to give 2- and 2,3-substituted-4-metathiazanones. The condensation with a variety of substituted benzaldehydes, pyridyl and thienyl carboxaldehydes, ammonia, alkyl and aralkylamines is reported. The preparation of the corresponding 4-metathiazanone-1-dioxides is also described. In determining the pharmacological profile of most of the compounds reported, it was found that several members of the series showed interesting paralyzing and anticonvulsant activities. One of the compounds, 2-(4-chlorophenyl)-3-methyl-4-metathiazanone-1-dioxide,[1] in clinical testing, has been found to be an effective and promising skeletal muscle relaxant.

In connection with our studies dealing with the addition of sulfhydryl compounds to Schiff bases,[2] it was of interest to see whether β-mercaptopropionic acid would react with aldehydes and amines (or Schiff bases) to yield substituted metathiazanone derivatives according to the equation



Most of the 4-metathiazanones (1,3-thiazin-4-ones) described in the literature contain a 2-imino group, having been prepared from thiourea and β-chloropropionic acid derivatives. During the past few years some 2-alkyl- and 2-aryl-5,6-benzo-4-metathiazanones have been reported. In 1953, Böhme and Schmidt[3] demonstrated that thiosalicylamide condenses readily with aldehydes or ketones in alcoholic solution in the presence of dry hydrogen chloride. For example, with benzaldehyde the product is 5,6-benzo-2-phenyl-4-metathiazanone. The same product was obtained later by Boudet[4] from the reaction of thiosalicylamide with benzylidene chloride in pyridine solution.

Our initial attempts to synthesize 2,3-disubstituted 4-metathiazanones starting with aniline, benzaldehyde (or benzylideneaniline) and β-mercaptopropionic acid were unsuccessful. This is in contrast to our experience with thioglycolic acid which reacts readily with benzylideneaniline to give the cyclic amide, 2,3-diphenyl-4-thiazolidone.[5]

Under similar conditions, with ammonium carbonate as a source of ammonia, benzaldehyde and β-mercaptopropionic acid in refluxing benzene, the condensation proceeded smoothly with elimination of two moles of water to give 2-phenyl-4-metathiazanone (I, $R_2 = C_6H_5$, $R_3 = H$). Further investigation indicated that the reaction is quite general for ammonia as well as for aliphatic primary amines. For example, with methylamine and benzaldehyde the product is 3-methyl-2-phenyl-4-metathiazanone (I, $R_2 = C_6H_5$, $R_3 = CH_3$). The reaction probably involves the initial formation of an azomethine, addition of the sulfhydryl group to the C=N linkage followed by dehydration to give the cyclic amide.

(1) Investigated clinically under the code number Win 4692.

(2) See for example, A. R. Surrey and R. A. Cutler, THIS JOURNAL, **76**, 578 (1954).

(3) H. Böhme and W. Schmidt, *Arch. Pharm.*, **286**, 330 (1953).

(4) R. Boudet, *Bull. soc. chim. France*, 1518 (1955).

(5) A. R. Surrey, THIS JOURNAL, **69**, 2911 (1947).

A variety of substituted benzaldehydes as well as 2- and 3-pyridyl- and 2-thienylcarboxaldehydes have been employed. In Table I are listed most of the 2-aryl-4-metathiazanones prepared in the present work, and others are reported later in the Experimental part. In most cases no attempt was made to isolate the intermediate Schiff bases. However, better yields than those reported in Table I probably could be obtained if the starting material was a purified Schiff base. With 4-chlorobenzylidenemethylamine the yield of 2-(4-chlorophenyl)-3-methyl-4-metathiazanone was 63% as compared to 11% when 4-chlorobenzaldehyde and methylamine were used directly with β-mercaptopropionic acid.

In general, the amount of water collected during the reaction with a reflux time of about 24 hours varied from 75 to 100% of theoretical. In some cases refluxing for as long as 72 hours did not appreciably change the quantity of water collected. The use of an excess of β-mercaptopropionic acid appears to have a favorable effect upon the yields. This is shown in the preparation of 3-benzyl-2-phenyl-4-metathiazanone.

A mixture of benzaldehyde and benzylamine in benzene was refluxed for 1.5 hours and an equivalent amount of β-mercaptopropionic acid was then added. After refluxing the mixture for 48 hours, 83% of the theoretical amount of water was collected. At the end of this time there was no further evidence of water being evolved. A 30% excess of β-mercaptopropionic acid was added and refluxing was continued for an additional 24 hours at which time the total water collected was 92% of theory.

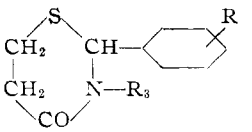
At room temperature the formation of metathiazanones proceeds slowly. When equivalent quantities of benzaldehyde, methylamine and β-mercaptopropionic acid in benzene solution were stirred at 25° for one week and then allowed to stand for an additional week, the product, 3-methyl-2-phenyl-4-metathiazanone, was obtained in 22% yield.

Most of the 2-aryl-4-metathiazanones were converted to the corresponding 1-dioxides by oxidation in acetic acid solution with potassium permanganate. The yields of products (Table II) were generally very satisfactory.

Pharmacology.—The compounds in the present series were tested for paralyzing, anticonvulsant and hypothermic activities in mice. The results indicated that the simple 2-aryl-4-metathiazanones

TABLE I

2-ARYL-4-METATHIAZANONES

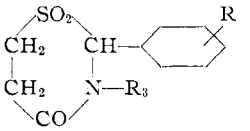


R	R_3	Yield, %	M.p., °C.	Formula	Sulfur, % Calcd.	Sulfur, % Found	Chlorine, % Calcd.	Chlorine, % Found
H	H	34	179.3–180.7	$C_{10}H_{11}NOS$	16.58	16.34	7.25	7.18
4-OCH_3	H	39	193.2–193.8	$C_{11}H_{13}NO_2S$	14.36	14.44	6.28	6.30
4-Cl	H	25	174.9–175.7	$C_{10}H_{10}ClNOS$	14.08	14.19	15.57	15.20
4-Br	H	34	184.3–185.5	$C_{10}H_{10}BrNOS$	11.78	11.86	29.36[h]	29.25[h]
2,4-Cl_2	H	25	166.9–168.7	$C_{10}H_9Cl_2NOS$	12.23	12.32	27.05	27.50
3,4-Cl_2	H	36	149.3–151.1	$C_{10}H_9Cl_2NOS$	12.23	12.15	27 05	27.20
H	CH_3	74	95.2–96.2	$C_{11}H_{13}NOS$	15.46	15.50	6.75	6.97
4-*i*-Pr	CH_3	28	110.0–112.1	$C_{14}H_{19}NOS$	12.86	12.72	67.44[i]	67.41[i]
							7.68[j]	7.74[j]
4-OCH_3	CH_3	59	67.2–69.6[a]	$C_{12}H_{15}NO_2S$	13.51	13.35	5.90[k]	6.12[k]
2-Cl	CH_3	39	76.4–79.6[b]	$C_{11}H_{12}ClNOS$	54.67[i]	54.70[i]	14.68	14.54
					5.01[j]	4.86[j]		
3-Cl	CH_3	59	57.2–60.6[c]	$C_{11}H_{12}ClNOS$	54.67[i]	54.45[i]	14.68	14.72
					5.01[j]	5.04[j]		
4-Cl	CH_3	11	[d]	$C_{11}H_{12}ClNOS$	13.27	13.24	14.67	14.43
2,4-Cl_2	CH_3	65	117.8–122.3	$C_{11}H_{11}Cl_2NOS$	11.61	11.36	25.67	25.50
3,4-Cl_2	CH_3	70	81.8–83.2	$C_{11}H_{11}Cl_2NOS$	11.61	11.99	25.67	25.50
4-Cl	C_2H_5	37	106.0–107.7	$C_{12}H_{14}ClNOS$	5.48[k]	5.14[k]	13.86	13.90
3,4-Cl_2	C_2H_5	37	63.2–67.4[e]	$C_{12}H_{13}Cl_2NOS$	11.17	10.73	24.43	24.33
4-Cl	C_3H_7	25	[f]	$C_{13}H_{16}ClNOS$	11.87	12.04	13.13	12.98
H	$C_6H_5CH_2$	31	82.9–84.5	$C_{17}H_{17}NOS$	11.31	11.41	4.94[k]	5.18[k]
H	$C_6H_5(CH_2)_2$	45	75.4–83.8	$C_{18}H_{19}NOS$	10.78	10.93	4.71[k]	4.76[k]

[a] B.p. 176–179° (0.5 mm.), $n^{25}D$ 1.5937. [b] B.p. 156–158° (0.5 mm.), $n^{25}D$ 1.6072. [c] B.p. 178–180° (0.1 mm.), $n^{25}D$ 1.6060. [d] B.p. 172–175° (0.2 mm.), $n^{25}D$ 1.6072. [e] B.p. 150–158° (0.5 mm.), $n^{25}D$ 1.6044. [f] B.p. 164–167° (0.2 mm.). [h] Bromine, %. [i] Carbon, %. [j] Hydrogen, %. [k] Nitrogen, %.

TABLE II

2-ARYL-4-METATHIAZANONE-1-DIOXIDES



R	R_3	Yield, %	M.p., °C.	Formula	Sulfur, % Calcd.	Sulfur, % Found	Chlorine, % Calcd.	Chlorine, % Found
H	H	27	153.9–155.5	$C_{10}H_{11}NO_3S$	14.23	13.94	6.21[b]	6.23[b]
4-Cl	H	95	173.0–173.6	$C_{10}H_{10}ClNO_3S$	12.34	12.20	13.65	13.41
4-Br	H	89	176.1–177.1	$C_{10}H_{10}BrNO_3S$	10.54	10.48	26.27[c]	25.95[c]
3,4-Cl_2	H	81	184.3–185.3	$C_{10}H_9Cl_2NO_3S$	10.90	11.19	24.10	24.15
H	CH_3	67	174.9–175.7[a]	$C_{11}H_{13}NO_3S$	13.40	13.27	5.85[b]	5.95[b]
4-$CH(CH_3)_2$	CH_3	67	152.9–157.3	$C_{14}H_{19}NO_3S$	11.39	11.18	59.75[d]	59.98[d]
							6.80[e]	6.80[e]
4-OCH_3	CH_3	60	132.4–133.4	$C_{12}H_{15}NO_4S$	11.92	11.78	5.20[b]	5.20[b]
2-Cl	CH_3	86	172.8–175.4	$C_{11}H_{12}ClNO_3S$	11.71	11.80	12.95	12.65
3-Cl	CH_3	75	153.4–156.2	$C_{11}H_{12}ClNO_3S$	11.71	11.75	12.95	12.96
4-Cl	CH_3	46	116.2–118.6	$C_{11}H_{12}ClNO_3S$	11.71	11.88	12.95	13.20
2,4-Cl_2	CH_3	79	135.4–137.7	$C_{11}H_{11}Cl_2NO_3S$	10.40	10.62	23.01	22.70
3,4-Cl_2	CH_3	61	122.5–126.1	$C_{11}H_{11}Cl_2NO_3S$	42.86[d]	42.70[d]	23.01	22.60
					3.60[e]	3.99[e]		
4-Cl	C_2H_5	66	157.6–159.8	$C_{12}H_{14}ClNO_3S$	4.87[b]	4.90[b]	12.32	12.47
3,4-Cl_2	C_2H_5	66	137.2–139.8	$C_{12}H_{13}Cl_2NO_3S$	9.95	9.99	22.01	22.04
4-Cl	C_3H_7	90	110.4–112.2	$C_{13}H_{16}ClNO_3S$	10.62	10.62	11.74	11.67
3,4-Cl_2	C_3H_7	55	85.8–91.4	$C_{13}H_{15}Cl_2NO_3S$	9.53	9.83	21.09	21.34
H	$C_6H_5CH_2$	61	158.4–161.2	$C_{17}H_{17}NO_3S$	10.17	10.04	64.73[d]	64.47[d]
							5.43[e]	4.95[e]
4-Cl	$C_6H_5CH_2$	41	180.0–187.4	$C_{17}H_{16}ClNO_3S$	9.16	9.23	10.14	9.94
4-Cl	$C_6H_5(CH_2)_2$	49	133.2–137.2	$C_{18}H_{18}ClNO_3S$	8.81	8.80	9.74	9.83
3,4-Cl_2	$C_6H_5(CH_2)_2$	50	149.8–151.8	$C_{18}H_{17}Cl_2NO_3S$	8.04	8.11	17.80	17.68

[a] Dimorphic form, m.p. 162.6–166.0°. [b] Nitrogen, %. [c] Bromine, %. [d] Carbon, %. [e] Hydrogen, %.

(I, R_2 = aryl, R_3 = H) were the most toxic and most active hypothermic agents, although they were devoid of paralyzing and anticonvulsant properties. The most effective paralyzing and anticonvulsant compounds were those containing an alkyl group in the 3-position and a chloro- or dichloro-substituted phenyl group in the 2-position of the metathiazanone ring.

A comparison of the 2-aryl-3-alkyl-4-metathiazanones with the corresponding 1-dioxides indicated that both types had similar pharmacological profiles but differed in oral absorption, toxicity and duration.

The 1-dioxides showed the maximal activity but had a somewhat shorter duration than the parent compounds. In general, the pharmacological profile found for those metathiazanone derivatives suggested a mephanesen-like type of action. One of the most active members of the present series, 2-(4-chlorophenyl)-3-methyl-4-metathiazanone-1-dioxide, in clinical testing, has been found to be an effective and promising skeletal muscle relaxant.

Detailed pharmacology of most of the compounds reported in the present work will be published elsewhere.

Acknowledgment.—We are indebted to Mr. M. E. Auerbach and Mr. K. D. Fleischer and staffs for the analytical data and corrected melting points, and to Dr. F. Coulston for pre-clinical studies in monkeys.

Experimental[6]

2-Aryl-3-alkyl-4-metathiazanones.—The preparation of these compounds is illustrated below.

3-Methyl-2-(3-pyridyl)-4-metathiazanone.—A solution of 43.2 g. of 3-pyridinecarboxaldehyde, 42.5 g. of β-mercaptopropionic acid and 14 g. of methylamine in 200 ml. of benzene was refluxed for 48 hours with a continuous separator connected to the reaction vessel for removal of water. After this time the theoretical amount of water was collected. The reaction mixture was cooled and washed with dilute ammonium hydroxide. The solid (53 g.) which separated from the benzene solution was collected, washed with water, dried and recrystallized from absolute ethyl alcohol to give 43.5 g. (52%) of product melting at 165.2–168.8°.

Anal. Calcd. for $C_{10}H_{12}N_2OS$: N, 13.45; C, 57.65; H, 5.81. Found: N, 13.43; C, 57.43; H, 6.35.

If no solid was obtained from the benzene solution after washing with ammonium hydroxide the solvent was removed *in vacuo* and the residue was vacuum distilled. In several instances the viscous distillates solidified on standing.

3-Methyl-2-(2-pyridyl)-4-metathiazanone was prepared in 20% yield after refluxing for 72 hours. The product was recrystallized several times from a mixture of benzene–hexane; m.p. 89.5–92° (uncor.).

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.65; H, 5.81; N, 13.45. Found: C, 58.16; H, 6.46; N, 13.16.

3-Methyl-2-(2-thienyl)-4-metathiazanone was prepared in 59% yield after refluxing for 72 hours. The product was recrystallized from Skellysolve C; m.p. 80.6–83.4°.

Anal. Calcd. for $C_9H_{11}NOS_2$: C, 50.67; H, 5.20. Found: C, 50.46; H, 5.50.

2-Aryl-4-metathiazanone-1-dioxides.—The following example illustrates the general procedure for the preparation of these compounds.

3-Methyl-2-(3-pyridyl)-4-metathiazanone 1-Dioxide.—A solution of 36.7 g. of potassium permanganate in 300 ml. of water was added dropwise to a well-stirred solution of 28.3 g. of 2-(3-pyridyl)-3-methyl-4-metathiazanone in 230 ml. of glacial acetic acid. The temperature was kept below 30° with external cooling. A concentrated aqueous sodium bisulfite solution then was added to remove the manganese dioxide. The reaction mixture was basified to a *p*H of 6 and extracted several times with chloroform. The solvent from the combined extracts was distilled *in vacuo* and the residue was triturated with hexane to give 12.5 g. of solid. After recrystallization from ethyl alcohol, 9 g. of product was obtained melting at 163.2–171.8°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S$: C, 49.98; H, 5.04; N, 11.66. Found: C, 50.30; H, 4.67; N, 11.46.

In many instances a solid product was obtained after addition of the bisulfite solution and was filtered off and purified by recrystallization. Only in the case of the 2-(pyridyl) compounds was it necessary to adjust the *p*H. Most of the sulfones were recrystallized from either ethyl or isopropyl alcohol.

3-Methyl-2-(2-pyridyl)-4-metathiazanone 1-dioxide was prepared in 37% yield. After recrystallization from isopropyl alcohol the product melted at 144.6–152.4°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S$: S, 13.34; N, 11.66. Found: S, 13.11; N, 11.61.

RENSSELAER, NEW YORK

(6) All melting points are corrected unless otherwise indicated.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Some Thiazolines and Thiazolidinones with Antituberculous Activity

BY R. H. MIZZONI AND P. C. EISMAN

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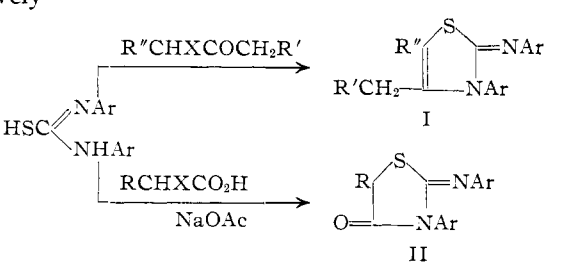
A series of 3-aryl-2-arylimino-4-substituted-4-thiazolines and 3-aryl-2-arylimino-4-thiazolidinones were prepared and evaluated as antituberculous agents. Some of the substances are active in this regard.

Appropriately substituted 1,3-bis-thiocarbanilides display a high order of antituberculous activity *in vitro* and in experimental animals.[1] It seemed desirable, therefore, to investigate this property among various cyclic modifications of the parent structure.

Two such modifications may be found in the 3-aryl-2-arylimino-4-thiazoline and 3-aryl-2-arylimino-4-thiazolidinone structures, I and II respectively



(1) C. F. Huebner, J. L. Marsh, R. H. Mizzoni, R. P. Mull, D. C. Schroeder, H. A. Troxell and C. R. Scholz, THIS JOURNAL, **75**, 2274 (1953); R. L. Mayer, P. C. Eisman and E. A. Konopka, *Proc. Soc. Exptl. Biol. Med.*, **89**, 88 (1955).