The compound also could be obtained in an analytically pure but non-crystalline condition by rapidly precipitating it from dioxane solution with ligroin. The substance after darkening and partially melting at 265° melted with decomposition at about 330°.

*Anal.* Calcd. for $C_{25}H_{20}O_2N_2$: N, 7.06; C, 75.74; H, 5.07. Found: N, 7.12; C, 75.50; H, 5.18.

**3 - Amino - 10 - methyl - 1,2 - benzanthracene.**—3-Hydroxy-10-methyl-1,2-benzanthracene, m. p. 192.5–193.5° vac., was synthesized by the method of Fieser and Hershberg[10] in 11% yield from 2-(4'-methoxy-1'-naphthylmethyl)-benzoic acid by way of 3-methoxy-1,2-benzanthrone prepared by hydrogen fluoride ring closure.[11] It was found expedient to conduct small-scale syntheses and it may be noted that some of the 3-methoxy-10-methyl-1,2-benzanthracene preparations required purification through the picrate. A mixture of 2.1 g. of the hydroxy compound, 12 cc. of dioxane, 20 cc. of concentrated ammonia solution and 10 g. of sodium bisulfite in 20 cc. of water was heated in a sealed tube at 175–185° for sixteen hours. The yellow, remarkably clean, crystalline product was dissolved in hot ethanol. After concentration and dilution with water, 1.59 g. (70%) of yellow needles, m. p. 185–187° vac., were obtained. One portion (1.09 g.) on recrystallization from benzene–hexane gave 0.90 g. of amine, m. p. 188–189° in an evacuated capillary. The remainder was purified through the sulfate and crystallized from ether-petroleum ether as yellow needles (265 mg.), m. p. 187.5–188.5° vac. A sample after several recrystallizations melted at 189–189.5° vac. (188–189° in an open capillary).

*Anal.* Calcd. for $C_{19}H_{15}N$: N, 5.44. Found: N, 5.25.

**10 - Methyl - 1,2 - benzanthryl - 3 - isocyanate.**—Following the described procedure, 1.02 g. of amine gave 0.76 g. (68%) of isocyanate as yellow needles, m. p. 149.5–150°, from ether–petroleum ether.

*Anal.* Calcd. for $C_{20}H_{13}ON$: N, 4.94; C, 84.78; H, 4.62. Found: N, 4.79; C, 84.96; H, 4.65.

The isocyanate was characterized by the formation of the ethyl carbamate which was obtained as colorless needles, m. p. 201–201.5°, from ether.

*Anal.* Calcd. for $C_{22}H_{19}O_2N$: N, 4.25. Found: N, 4.12.

**10-Methyl-1,2-benzanthryl-3-urea** was prepared in the usual manner and was crystallized with difficulty from dioxane as poorly formed needles, m. p. 348–350° vac.

*Anal.* Calcd. for $C_{20}H_{16}ON_2$: N, 9.30. Found: N, 8.89.

The **ethyl ester of 10-methyl-1,2-benzanthryl-3-carbamidoacetic acid** was synthesized by the described procedure and obtained from dioxane–ligroin as almost colorless needles, m. p. 213–214° vac.

*Anal.* Calcd. for $C_{24}H_{22}O_4N_2$: N, 7.24; C, 74.59; H, 5.72. Found: N, 7.24; C, 74.53; H, 5.70.

**Acknowledgments.**—The author wishes to thank the International Cancer Research Foundation for a grant supporting the research and to express his appreciation of the interest and advice of Professor L. F. Fieser.

## Summary

3,4-Benzpyrenyl-5-isocyanate and 10-methyl-1,2-benzanthryl-3-isocyanate have been synthesized from the corresponding amines and characterized by the formation of ethyl carbamates and substituted urea derivatives. The isocyanates were coupled with glycine ethyl ester to form compounds required for studies of the protein conjugates prepared from the isocyanates. The isocyanates, amino acid conjugates and the newly synthesized 3-amino-10-methyl-1,2-benzanthracene are being tested for carcinogenic activity.

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(10) Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).
(11) Fieser and Hershberg, *ibid.*, **61**, 1272 (1939).

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[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION, SHARP AND DOHME, INC.]

# Sulfonamido Derivatives of Thiazoles

BY JAMES M. SPRAGUE AND L. W. KISSINGER

The success of sulfapyridine in combating bacterial infections, particularly pneumococcal infections, has led to the preparation and study of other heterocyclic derivatives of sulfanilamide. The recent interest in thiazole derivatives[1] prompts us to report on a series of sulfonamidothiazoles which we have prepared and tested for their chemotherapeutic activity.[2]

(1) Fosbinder and Walter, THIS JOURNAL, **61**, 2032 (1939); Lott, *et al.*, *ibid.*, **61**, 3593 (1939); **62**, 1873 (1940); Roblin, *et al.*, *ibid.*, **62**, 2002 (1940); Barlow and Homburger, *Proc. Soc. Exptl. Biol. Med.*, **43**, 317 (1940); Long, *et al.*, *ibid.*, **43**, 324–328 (1940).
(2) *Cf.* Northey, *Chem. Rev.*, **27**, 85 (1940).

## Experimental Part[3]

The 2-aminothiazoles were prepared by procedures reported in the literature; 2-amino-4-ethyl-5-methylthiazole and 2-amino-4,5,6,7-tetrahydrobenzothiazole, which were prepared from α-bromo-diethyl ketone and α-bromocyclohexanone, respectively, do not appear in the literature previously. The properties and analyses of these compounds are recorded in Table I.

**2-Sulfonamidothiazoles.**—In general, these compounds were prepared by the slow addition of a slight excess of the appropriate sulfonyl chloride to a solution of a 2-aminothiazole in pyridine. After the addition was com-

(3) All melting points are uncorrected.

TABLE I

SULFONAMIDO-THIAZOLES

| ( )-Thiazole | M. p., °C. (uncor.) | Activity[f] Anti streptoccal | Anti pneumococcal | Formula | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|
| 2-Sulfanilamido-[a,b,c] | 195.5–196.5 | ++ | + | | | |
| 2-Sulfanilamido-4-methyl-[a,b,c] | 237–238 | ++ | + | | | |
| 2-N⁴-Caproylsulfanilamido-4-methyl | 171–172 | ++ | 0 | $C_{16}H_{21}N_3O_3S_2$ | 11.44 | 11.29 |
| 2-N⁴-Acetylsulfanilmethylamido-4-methyl-[i] | 237–239 | | | $C_{13}H_{15}N_3O_3S_2$ | 12.91 | 12.83 |
| 2-Sulfanilmethylamido-4-methyl-[e,j] | 203–204 | ± | ± | $C_{11}H_{13}N_3O_2S_2$ | 14.84 | 14.53 |
| 2-*p*-Nitrobenzenesulfonamido-4-methyl-[g] | 199.5–200 | +++ | ± | $C_{10}H_9N_3O_4S_2$ | 14.01 | 13.85 |
| 2-*o*-Nitrobenzenesulfonamido-4-methyl-[g] | 189–190 | 0 | 0 | $C_{10}H_9N_3O_4S_2$ | 14.01 | 14.03 |
| 2-Benzenesulfonamido-4-methyl-[h] | 161–162 | 0 | 0 | $C_{10}H_{10}N_2O_2S_2$ | 11.05 | 11.01 |
| 2-N⁴-Acetylsulfanilamido-4-phenyl- | 227–229 | | | $C_{17}H_{15}N_3O_3S_2$ | 11.25 | 11.30 |
| 2-Sulfanilamido-4-phenyl-[e] | 205–206 190–191[e] | + | ± | $C_{15}H_{13}N_3O_2S_2$ | 12.68 | 12.48 |
| 2-N⁴-Acetylsulfanilamido-4-methyl-5-carbethoxy-[e] | 246–248 | | | $C_{15}H_{17}N_3O_5S_2$ | 10.96 | 10.80 |
| 2-Sulfanilamido-4-methyl-5-carbethoxy-[e,k] | 194–196 | + | −[d] | $C_{13}H_{15}N_3O_4S_2$ | 12.31 | 12.37 |
| 2-Sulfanilamido-4,5-dihydro-[e] | 204–205 | + | ± | $C_9H_{11}N_3O_2S_2$ | 16.33 | 16.14 |
| 2-N⁴-Acetylsulfanilamido-4-ethyl-5-methyl | 230–231 | | | $C_{14}H_{17}N_3O_3S_2$ | 12.49 | 12.28 |
| 2-Sulfanilamido-4-ethyl-5-methyl | 199–200 | ++ | ± | $C_{12}H_{15}N_3O_2S_2$ | 14.14 | 14.10 |
| 2-N⁴-Acetylsulfanilamido-6-methylbenzo- | 297–299 | | | $C_{16}H_{15}N_3O_3S_2$ | 11.63 | 11.45 |
| 2-Sulfanilamido-6-methylbenzo- | 282.5–284 | ± | 0 | $C_{14}H_{13}N_3O_2S_2$ | 13.15 | 13.03 |
| 2-N⁴-Acetylsulfanilamido-4,5,6,7-tetrahydrobenzo- | 277–278 | | | $C_{15}H_{17}N_3O_3S_2$ | 11.96 | 11.73 |
| 2-Sulfanilamido-4,5,6,7-tetrahydrobenzo- | 249–250 | ± | 0 | $C_{13}H_{15}N_3O_2S_2$ | 13.57 | 13.48 |
| 2-Amino-4,5,6,7-tetrahydrobenzo·HCl | 249–250 | | | $C_7H_{11}N_2SCl$ | 14.69 | 14.65 |
| 2-Amino-4-ethyl-5-methyl- | 70–71 | | | $C_6H_{10}N_2S$ | 19.70 | 19.63 |
| Sulfapyridine | | ++ | ++ | | | |
| Sulfanilamide | | ++ | + | | | |

[a] Fosbinder and Walter, THIS JOURNAL, **61**, 2032 (1939). [b] Lott and Bergeim, *ibid.*, 61, 3593 (1939). [c] British Patent 517,272. [d] Toxic at the 20-mg. dose. [e] 2-Sulfanilamido-2-thiazoline. [f] *Cf.* reference 2. [g] Prepared from two moles of 2-amino-4-methylthiazole and one mole of *o*-nitrobenzenesulfonyl chloride in acetone solution at room temperature. [h] A dibenzenesulfonyl derivative (m. p. 147–148°; N, found 7.09%, calcd. 7.10%) was obtained from the reaction of benzenesulfonyl chloride with 2-amino-4-methylthiazole in aqueous bicarbonate, carbonate or sodium hydroxide solution. On warming with alkali the dibenzenesulfonyl derivative was converted to 2-benzenesulfonamido-4-methylthiazole. *p*-Acetylaminobenzenesulfonyl chloride also gave a disulfonyl derivative (m. p. 145–147°) which yielded 2-N⁴-acetylsulfanilamido-4-methylthiazole on warming with dilute alkali. [i] Prepared by the methylation of 2-N⁴-acetylsulfanilamido-4-methylthiazole in alkaline solution with dimethyl sulfate. [j] The hydrochloride (m. p. 245°) separated on chilling the solution from the acid hydrolysis of the acetyl derivative. [k] The hydrochloride (60%; m. p. 237–239°) separated from the solution after acid hydrolysis of the acetyl derivative. 2-Sulfanilamido-4-methylthiazole (21%) was obtained from the filtrate by neutralization.

plete, the reaction mixture was heated on a steam-bath for thirty minutes to one hour and then poured into several volumes of cold water or dilute hydrochloric acid. The crude product was separated, dissolved in dilute aqueous ammonia and the solution decolorized with charcoal ("Darco"). The product was precipitated by neutralizing the ammonia solution and recrystallized from alcohol or alcohol and water.

The condensation of *p*-acetylaminobenzenesulfonyl chloride with 2-methylamino-4-methylthiazole in pyridine gave a 40% yield of a product isomeric with that obtained by the methylation of 2-N⁴-acetylsulfanilamido-4-methylthiazole. After recrystallization from 50% alcohol, it melted at 172–173° (N calcd. 12.91; found 12.82). On chilling the solution from the acid hydrolysis of this substance, a 57% yield of sulfanilic acid separated and from the filtrate, 55% of the 2-methylamino-4-methylthiazole was recovered by making the solution strongly alkaline and extracting with ether.

**Hydrolysis.**—The acid hydrolysis of the N⁴-acetylsulfanilamidothiazoles was carried out by suspending the crude acetyl compound in 2 *N* hydrochloric acid (10 cc. per g.) and warming the suspension, with stirring, on a steam-bath until all the solid had dissolved. The cooled solution was neutralized with concentrated aqueous ammonia. The crude product was redissolved in very dilute ammonia solution and decolorized with charcoal ("Darco"). The product obtained on neutralization of this solution was recrystallized from alcohol or alcohol and water.

For the alkaline hydrolysis, the crude acetyl derivatives were suspended or dissolved in 10% sodium hydroxide (10 cc. per g.) and warmed on a steam-bath for one to two hours or, in the case of the disulfonyl derivatives, for thirty minutes after solution was complete. The product was obtained by neutralization of the cooled solution and purified as above. The sulfanilamido derivatives of 4-phenylthiazole and 6-methylbenzothiazole separated from the hot alkaline solution during hydrolysis as the crystalline sodium salts.

Because of the insolubility of the hydrochloride of 2-sulfanilamido-4-phenylthiazole, a complete solution was not obtained during the acid hydrolysis of the corresponding acetyl derivative. The hydrochloride (m. p. 250–254°) was filtered from the hot solution and the 2-sulfanilamido-4-phenylthiazole obtained by shaking the hydrochloride with bicarbonate solution. After purification it melted at 190–191°. However, when the hydrolysis was carried out in alkali the final product melted at 205–206°. These two forms of 2-sulfanilamido-4-phenylthiazole were indistinguishable by analysis and by pharmacological tests.

**2-Sulfanilamido-2-thiazoline.**—When equal molar quantities of *p*-acetylaminobenzenesulfonyl chloride and 2-amino-2-thiazoline were condensed in pyridine according to the general procedure, the product consisted mainly of an alkali-insoluble disulfonyl derivative. When two equivalents of the sulfonyl chloride were used, an 89% yield of the disulfonyl compound was obtained. After recrystallization from alcohol and water it melted at 162–163°.

*Anal.* Calcd. for $C_{19}H_{20}O_6N_4S_3$: N, 11.30. Found: N, 11.29.

2-Sulfanilamido-2-thiazoline was obtained from the disulfonyl compound by either acid or alkaline hydrolysis and, after recrystallization from alcohol, it melted at 204–205°.

Thirteen of these sulfonamidothiazole derivatives were tested[4] against experimental streptococcal and pneumococcal infections in a standard stock strain of white mice. In the antistreptococcal tests the mice were injected intraperitoneally with one-thousand lethal doses of a virulent strain of β-hemolytic streptococci at the time of oral administration of 5 mg. of the compound. Three additional doses of 5 mg. each were administered at twenty-four, forty-eight and seventy-two hours. The antipneumococcal activity was determined by intraperitoneal injection with one-hundred lethal doses of type I pneumococci at the time of the first dose of compound. Additional doses were administered orally at seven, twenty-four, forty-eight, seventy-two and ninety-six hours. Each dose was 20 mg.

The relative chemotherapeutic effects of these compounds are recorded in Table I.

(4) We are indebted to Dr. Bettylee Hampil and Mr. G. W. Webster for the testing of these compounds.

## Summary

Thirteen 2-sulfanilamido-thiazoles have been prepared and tested for their chemotherapeutic effect against experimental streptococcal and pneumococcal infections in mice.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

# Coumarano-coumaranes

BY JOSEPH B. NIEDERL AND RICHARD H. NAGEL[1]

With the elucidation of the structures of the crystalline condensation products of catechol and hydroquinone with α- and γ-diketones successfully accomplished,[2] the study of the structures of the condensation products of the other remaining isomeric dihydric phenol, resorcinol, and diketones was undertaken and is reported in the following.

The condensation systems studied included an aliphatic α-diketone, diacetyl, and an aromatic α-diketone, benzil. Fusions of the latter diketone with resorcinol under rather strenuous conditions have been previously reported,[3] but the structural as well as the empirical formulas advanced differ widely from the empirical and structural formulas assigned to the condensation product of benzil and resorcinol formed under the mild reaction conditions described herein. Guided by the experimental findings in mono-ketone resorcinol condensations[4] in which it was shown that resorcinol may undergo double alkylation with the formation of the corresponding alkylated phenolic coumarane it became evident that an analogous "coumarane" structure may also be assigned to the crystalline condensation products obtainable from both aliphatic and aromatic α-diketones and resorcinol.

Thus diacetyl and resorcinol yielded the 6′-hydroxy-coumarano-2′,3′:3,2-(6-hydroxy-2,3-dimethyl)-coumarane (I) of which a crystalline diacetate (Ia) and di-propionate (Ib) was prepared. Benzil and resorcinol gave the corresponding crystalline phenyl substituted coumarano-coumarane, the 6′-hydroxy-coumarano-2′,3′: 3,2-

(1) Taken from a portion of the thesis presented by Richard H. Nagel to the Graduate School of New York University in partial fulfillment of the requirements for the degree of doctor of philosophy.

(2) J. B. Niederl and R. H. Nagel, THIS JOURNAL, **62**, 3070 (1940); **63**, 307 (1941).

(3) J. von Liebig, *J. prakt. Chem.*, [2] **72**, 135 (1905); [2] **74**, 379 (1906); *Ann.*, **360**, 183 (1908).

(4) J. B. Niederl and V. Niederl, THIS JOURNAL, **61**, 348 (1939).