ganic salts were removed by filtration, the filtrate dried over potassium carbonate, and the product collected by distillation; b.p. 83–86° (1.2 mm.), yield 25.9 g. (71.2%), $n_D^{25}$ 1.4972.

*Anal.* Calcd. for $C_6H_{14}N_2O$: N, 10.78. Found: N, 11.03.

*N-Benzyl-4-hydroxypiperidine* (XVI). A mixture consisting of 50.0 g. (0.5 mole) of 4-hydroxypiperidine, 50.0 g. (0.5 mole) of triethylamine, 62.5 g. (0.5 mole) of benzyl chloride and 250 cc. of dry toluene was refluxed for 4 hr. The triethylamine hydrochloride was filtered off, the filtrate concentrated, and the product collected by distillation, b.p. 122–123° (0.7 mm.); yield 65.0 g. (69%), $n_D^{25}$ 1.5514.

*Anal.* Calcd. for $C_{12}H_{17}NO$: C, 75.34; H, 8.96; N, 7.32 Found: C, 74.62; H, 8.77; N, 6.98.

*Acknowledgment.* We are indebted to Dr. H. L. Friedman for his many valuable suggestions and Dr. H. L. Daiell for his continued interest and support of this study.

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# *Notes* A department for short papers of immediate interest.

## Sulfonamides and Some Related Materials[1]

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In connection with the investigation of the effect of acyl substituents on the therapeutic activity of sulfonamide-related materials, acyl derivatives of sulfanilamide, sulfathiazole, 2-amino-5-thiazolyl-*p*-nitrophenyl sulfide,[2] and 2-amino-5-thiazolyl-*p*-nitrophenyl sulfone[2] were required (Tables I and II). Synthesis was accomplished conveniently by reaction of the amino compound with the appropriate anhydride (diglycolic,[3] thiodiacetic,[3] benzylsuccinic, and tetrachlorophthalic) and in most cases the desired product crystallized out of the reaction medium. In the reactions with thiodiacetic anhydride it was essential to use a substantial molar excess of the anhydride in order to avoid formation of oily or colored products which led to difficulties on purification.

The benzylsuccinyl derivatives (Compounds II and V) made from benzylsuccinic anhydride[4] are considered to be the β-amides in accordance with the Anschutz Rule.[5] This assignment of structure is supported further by the fact that high yields of pure products are obtained.

The aminophenyl compounds (VIII and X) were made by ammoniacal iron acid reduction of the corresponding nitrophenyl derivatives.

Convenient laboratory methods were devised for making diglycolic and thiodiacetic anhydrides.

### EXPERIMENTAL[6]

*Diglycolic anhydride.*[7] In a 500-ml. flask fitted with a column equivalent to eight theoretical plates there were placed 49 g. of diglycolic acid (0.37 mole), 139 ml. of acetic anhydride (1.48 moles) and 3 drops of phosphoric acid. The solution was heated sufficiently to maintain a slow rate of distillation of acetic acid. When the vapor temperature at the top of the column reached about 127°, heating was increased and about 25 ml. of acetic anhydride was distilled forward. The flask was fitted with a 1 × 13 cm. still head packed with 1–16″ glass helices. The remaining acetic anhydride was distilled at 100 mm. absolute pressure. Then the diglycolic anhydride was distilled at 140° (35 mm.). Yield, 33.2 g. (78%). A sample recrystallized from benzene melted at 91–93°.

*Thiodiacetic anhydride.*[8] A mixture of 64.8 g. (0.4 mole) of thiodiacetic acid (assaying 92.5%), 18.4 g. (0.134 mole) of phosphorus trichloride, and 80 ml. of chloroform was warmed at 55–57° with stirring until no more hydrogen chloride was evolved. Then the mixture was refluxed for 1 hr., 9.2 g. (0.067 mole) of phosphorus trichloride was added, and refluxing was continued for one more hour. The hot chloroform solution was decanted through a filter, the residue on the filter was washed with a small amount of chloro-

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(1) Part of a presentation at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960.

(2) L. L. Bambas, *J. Am. Chem. Soc.*, **67**, 671 (1945).

(3) Some related diacyl *N,N'*-diaminodiphenyl sulfones were described by L. P. Kyrides, U. S. Patents **2,399,600** (April 30, 1946) [*Chem. Abstr.*, **40**, 4180 (1946)] and **2,413,833**-**2,413,835** (January 7, 1947) [*Chem. Abstr.*, **41**, 2749–50 (1947)].

(4) J. Binapfl, U. S. Patent **2,121,183** (June 21, 1938) [*Chem. Abstr.*, **32**, $6259^7$ (1938)]; German Patent **607,380** (January 2, 1935) [*Chem. Abstr.*, **29**, $1834^9$ (1935)].

(5) R. Anschutz, C. Hahn, and P. Walter, *Ann.*, **354**, 136 (1907), showed the β-amide was obtained in the reaction of phenylsuccinic anhydride with aniline.

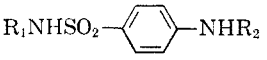
(6) All melting points are corrected.

(7) Preparation from diglycolic acid with acetyl chloride was described by R. Anschutz, *Ann.*, **259**, 190 (1890) and with phosphorus pentasulfide by R. Anschutz and F. Biernaux, *Ann.*, **273**, 64 (1893).

(8) Preparation by reaction of thiodiacetic acid with acetyl chloride was described by R. Anschutz and F. Biernaux, *Ann.*, **273**, 68 (1893), and by direct distillation of thiodiacetic acid by L. C. Lappas and G. L. Jenkins, *J. Am. Pharm. Assoc.*, **41**, 257 (1952). In our work, the acetic anhydride method shown above for diglycolic anhydride gave poor results with thiodiacetic acid; the thiodiacetic anhydride could not be distilled out of the reaction mixture without decomposition and crystallization proved difficult.

TABLE I

$N^4$-ACYLSULFANILAMIDES

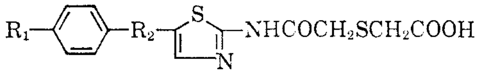


| Compound | $R_1$ | $R_2$ | Empirical Formula | Mol. Wt. | Yield, % | M.P. | Nitrogen Calcd. | Nitrogen Found | Neut. Equiv. Calcd. | Neut. Equiv. Found |
|---|---|---|---|---|---|---|---|---|---|---|
| I | H | TD[a] | $C_{10}H_{12}N_2O_5S_2$ | 304 | 87[b] | 181–182 | 9.21 | 9.2 | | |
| II | H | BS[c] | $C_{17}H_{18}N_2O_5S$ | 462 | 92[b] | 158–159[d] | 7.73 | 7.61 | | |
| III | 2-T[e] | TD | $C_{13}H_{13}N_3O_5S_3$ | 387 | 100[b] | 165–166 | | | 194 | 194 |
| IV | 2-T | DG[f] | $C_{13}H_{13}N_3O_6S_2$ | 371 | 96[b] | 179–180 | | | 186 | 185 |
| V | 2-T | BS | $C_{20}H_{19}N_3O_5S_2$ | 446 | 91 | 205–206 | 9.44 | 9.36 | | |
| VI | 2-T | TCP[g] | $C_{17}H_9Cl_4N_3O_5S_2$ | 541 | 74 | 205 | 7.8 | 7.3 | | |

[a] TD = thiodiacetyl, —$COCH_2SCH_2COOH$. [b] Recrystallized from water. [c] BS = benzylsuccinyl, —$COCH_2CH(CH_2C_6H_5)COOH$. [d] Solidifies above 165° and then melts at 241–242° (probably the imide). [e] 2-T = 2-thiazolyl. [f] DG = diglycolyl, — $COCH_2OCH_2COOH$. [g] TCP = $o$-$COC_6Cl_4COOH$. Tetrachlorophthalic anhydride purchased from Niagara Alkali Co.

TABLE II

2-ACYLAMINO-5-THIAZOLYLPHENYL SULFONES AND SULFIDES



| Compound | $R_1$ | $R_2$ | Empirical Formula | Mol. Wt. | Yield, % | M.P. | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|
| VII | $NO_2$ | —S— | $C_{13}H_{11}N_3O_5S_3$ | 385 | 81 | 228–231 | 10.91 | 10.61 |
| VIII | $NH_2$ | —S— | $C_{13}H_{13}N_3O_3S_3$ | 355 | 74 | 187–188[a] | 11.8 | 12.1 |
| IX | $NO_2$ | —$SO_2$— | $C_{13}H_{11}N_3O_7S_3$ | 417 | 82 | 212–214 | 10.07 | 9.99 |
| X | $NH_2$ | —$SO_2$— | $C_{13}H_{13}N_3O_5S_3$ | 387 | 64 | 221–222[a] | 10.85 | 10.54 |

[a] Recrystallized from ethanol.

form, and the filtrate was cooled to 10°. Thiodiacetic anhydride was obtained in the form of colorless needles. Yield, 31 g. (58.7%).

The chloroform filtrate from the previous batch was used for making a second batch with the same charges and procedure described above; the yield of thiodiacetic anhydride was 40 g. (75.8%).

*Methyl hydrogen thiodiacetate.*[9] A mixture of 34.8 g. of dimethyl thiodiacetate[10] (0.20 mole) and 30.0 g. of thiodiacetic acid (0.20 mole) was heated with stirring for 7 hr. at 175°. The mixture then was distilled giving 12.2 g. of unchanged dimethyl thiodiacetate and 15.2 g. of methyl hydrogen thiodiacetate; yield of half ester, 46.3% based on thiodiacetic acid charged.

Methyl hydrogen thiodiacetate and dimethyl thiodiacetate also were made as follows: A mixture of 135 g. of thiodiacetic acid (0.90 mole) and 122 ml. of methanol (3.0 moles) was heated at 50° for 6 hr. The methanol and products then were distilled, giving 61.3 g. (38.6%) of dimethyl thiodiacetate, b.p. 140–143° (25 mm.). (*Anal.* Calcd. for $C_6H_{10}O_4S$ (178.21): S, 18.0. Found: S, 18.2.) and 55.5 g. (37.8%) of methyl hydrogen thiodiacetate, b.p., 178–185° (25 mm.).

*Anal.* Calcd. for $C_5H_8O_4S$ (164.18): S, 19.5. Found: S, 21.0.

*Methyl 2-(chloroformylmethylthio)acetate.* A mixture of 55.5 g. of methyl hydrogen thiodiacetate (0.338 mole) and 50 ml. of thionyl chloride (0.69 mole) was allowed to stand for 12 hr. at about 25°. The excess thionyl chloride and the acid chloride were distilled; b.p. 133° (24 mm.); yield, 53.9 g. (82%).

*Anal.* Calcd. for $C_5H_7ClO_3S$ (182.63): Cl, 19.4. Found: Cl, 18.8.

*2-[5-(p-Nitrophenylthio)-2-thiazolylcarbamoylmethylthio]-acetic acid* (Compound VII). A slurry of 168 g. (0.66 mole) of 2-amino-5-thiazolyl-$p$-nitrophenyl sulfide,[11] 2000 ml. of acetone and 121 g. (0.92 mole) of thiodiacetic anhydride was refluxed for 15 hr. Then the mixture was cooled to 15°, the solid product filtered off, washed with acetone, and dried. Yield, 207 g. (80.9%).

*2-[5-p-Aminophenylthio-2-thiazolylcarbamoylmethylthio]-acetic acid.* (Compound VIII). To a slurry of 128.5 g. (0.33 mole) of the nitroamide (Compound VII), 2800 ml. of water, and 926 g. (3.33 moles) of ferrous sulfate heptahydrate there was added 665 ml. (10 moles) of 28.5% ammonium hydroxide solution. Then the batch was filtered, the iron filter cake was reslurried in dilute ammonia and again filtered, and the combined filtrates were acidified with hydrochloric acid solution. The solid precipitated product was filtered off and dried. Yield, 97 g. (73.6%).

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(9) G. T. Morgan and E. Walton, *J. Chem. Soc.*, 903 (1936), used a similar method for preparation of methyl hydrogen sebacate by refluxing dimethyl sebacate and sebacic acid.

(10) Prepared efficiently by esterification of thiodiacetic acid with methanol using sulfuric acid or hydrochloric acid catalyst. We also made this ester from thiodiacetic anhydride and methanol, b.p. 134–138° (21 mm.). This ester was made previously by J. Schurz and G. Kromer, *Chem. Ber.*, 88, 1633 (1955), from methyl chloroacetate and sodium sulfide and by R. Anschutz and F. Biernaux, *Ann.*, 273, 69 (1893), from the diacid chloride.

(11) Ref. 2, p. 671.