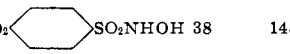
TABLE II

N⁴-ACYLSULFANILHYDROXAMIDES

| No. | Acyl group | Yield, % | M. p., °C.,[a] dec. | Antistrep. activity | Formula | Nitrogen, % Calcd. | Nitrogen, % Found | | Sulfur, % Calcd. | Sulfur, % Found | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[b,c] | H | 80 | 170.5–173 | ++ | $C_6H_8O_3N_2S$ | 14.90 | | | 17.02 | 17.19 | 17.11 |
| 2[b,d] | $CH_3CO$ | 44–68 | 194–196 | + | $C_8H_{10}O_4N_2S$ | 12.17 | 12.05 | 12.09 | 13.92 | 13.96 | 14.07 |
| 3[d] | $CH_3CH_2CO$ | 44 | 174–178 | + | $C_9H_{12}O_4N_2S$ | 11.48 | 11.42 | 11.41 | 13.12 | 13.28 | |
| 4[d] | $CH_3(CH_2)_2CO$ | 79 | 172–178 | +++ | $C_{10}H_{14}O_4N_2S$ | 10.85 | 10.85 | 10.78 | 12.40 | 12.26 | 12.43 |
| 5[d] | $CH_3(CH_2)_3CO$ | 80 | 178–179.5 | ++++ | $C_{11}H_{16}O_4N_2S$ | 10.29 | 10.32 | 10.34 | 11.76 | 11.90 | 11.87 |
| 6[d] | $CH_3(CH_2)_4CO$ | 75 | 175–179 | ++++ | $C_{12}H_{18}O_4N_2S$ | 9.79 | 9.82 | 9.89 | 11.19 | 11.29 | 11.25 |
| 7[d] | $CH_3(CH_2)_5CO$ | 65 | 166–169 | ++++ | $C_{13}H_{20}O_4N_2S$ | 9.33 | 9.27 | 9.39 | 10.67 | 10.67 | 10.60 |
| 8[d] | $CH_3(CH_2)_6CO$ | .. | 160–163 | +++ | $C_{14}H_{22}O_4N_2S$ | 8.91 | 8.84 | 8.75 | 10.19 | 10.34 | 10.20 |
| 9[d] | $CH_3(CH_2)_7CO$ | 50 | 168–172 | + | $C_{15}H_{24}O_4N_2S$ | 8.54 | 8.46 | 8.44 | 9.76 | 10.01 | 9.92 |
| 10[d] | $(CH_3)_2CHCO$ | 70 | 172–176 | + | $C_{10}H_{14}O_4N_2S$ | 10.85 | 10.60 | | | | |
| 11[d] | $(CH_3)_2CHCH_2CO$ | 75 | 168.5–173 | + | $C_{11}H_{16}O_4N_2S$ | 10.29 | 10.45 | 10.42 | 11.76 | 11.92 | |
| 12[d] | $(CH_3)_2CH(CH_2)_2CO$ | 55 | 153–157 | + | $C_{12}H_{18}O_4N_2S$ | 9.79 | 9.70 | 9.80 | 11.19 | 11.15 | |
| 13[e] | $HOOCCH_2CH_2CO$ | 50 | 170–174 | 0 | $C_{10}H_{12}O_6N_2S$ | 9.72 | 9.73 | 9.66 | | | |
| 14[e] | HOOCCH=CHCO | 63 | 184–185 | 0 | $C_{10}H_{10}O_6N_2S$ | 9.79 | 9.62 | 9.57 | | | |
| 15[f] |  | 38 | 145–149 | ++ | $C_6H_6O_5N_2S$ | | | | | | |

[a] These compounds start to darken slightly on top, in the melting point tube, a few degrees before this range is reached, and then bubble up the tube as a brown liquid at the range indicated. [b] Previously reported by Kharasch and Reinmuth.[2] [c] Recrystallized from water as glistening prismatic plates. [d] Recrystallized from dilute ethanol, usually as glistening crystals. Slightly soluble in water. [e] Recrystallized from water as small glistening platelets. Decomposed with vigorous effervescence. [f] Recrystallized from alcohol. Too unstable for satisfactory analysis as it decomposes during the process. Appreciably soluble in water.

sodium salt of 4-*n*-hexanaminobenzenesulfinic acid, 4.9 g. (74% yield), was obtained when the solution was poured into a large volume of acetone. Neutralization of the sodium salt with dilute sulfuric acid gave the free acid, which upon crystallization from dilute ethanol, as feathery needles, melted at 113–116°.

*Anal.* Calcd. for $C_{12}H_{17}O_3NS$: N, 5.49. Found: N, 5.35.

The identity of the product was further established by the reduction of 4-*n*-hexanaminobenzenesulfonyl chloride with sodium sulfite.[5] The resulting 4-*n*-hexanaminobenzenesulfinic acid, m. p. 113–116°, gave no depression in melting point when mixed with the above product.

(5) "Organic Syntheses," Coll. Vol. I, p. 7.


## Summary

The preparation, properties and some reactions of a series of N⁴-acyl derivatives of sulfanilhydroxyamide are described, together with the preliminary results of their chemotherapeutic activity against experimental streptococcic infections in mice.

Certain of the aliphatic acyl derivatives have been found to possess unusual activity as antistreptococcal agents. The dicarboxylic acid derivatives are less effective in this respect.


GLENOLDEN, PENNSYLVANIA RECEIVED MAY 11, 1940

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

# The Preparation of Some Amino Sulfonamides

BY ELLIS MILLER, JAMES M. SPRAGUE, L. W. KISSINGER AND LANE F. MCBURNEY

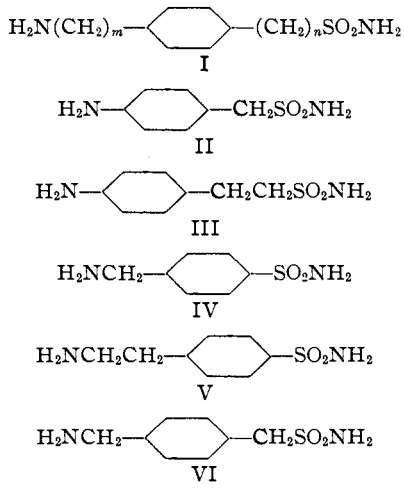
The results of many studies[1] on the chemotherapy of experimental streptococcal infections indicate that the maximum therapeutic effect is obtained with those compounds which have a nitrogen and sulfur attached to a benzene nucleus in the 1,4 positions. Although the results of variations in the structure of sulfanilamide and related compounds support this conclusion, it has not been shown definitely that it is necessary for the nitrogen and sulfur to be attached directly to an aromatic nucleus. However, Shaeffer[2] has reported that β-(*p*-sulfamylphenyl)-alanine has a greater antistreptococcal activity than sulfanilamide.

In order to determine the effect upon therapeutic value of the separation of the amino group and the sulfonamide group from the benzene nucleus, several compounds of the general structure I have been synthesized.

II and III were prepared by the catalytic re-

(1) Fourneau, *et al.*, *Compt. rend. soc. biol.*, **122**, 258 (1936); Butler, *et al.*, *Biochem. J.*, **32**, 1101 (1938); Crossley, *et al.*, THIS JOURNAL, **60**, 2217 (1938); for a review, *cf.* Marshall, *Physiol. Rev.*, **19**, 252 (1939).

(2) Shaeffer, *Proc. Soc. Expil. Biol. Med.*, **37**, 648 (1938).




duction of the corresponding nitro sulfonamides; IV and V by the hydrolysis of the acetyl derivatives which in turn had been prepared from the sulfonyl chlorides obtained by the action of chlorosulfonic acid upon the N-acetyl derivatives of benzylamine and phenethylamine, respectively. IV and VI were prepared more readily by the catalytic reduction of *p*-cyanobenzene- and *p*-cyanophenylmethane-sulfonamides.

Although these compounds approach the structure of the aliphatic sulfonamides, it was desirable to determine the chemotherapeutic activity of the aminoalkanesulfonamides, $H_2N(CH_2)_xSO_2NH_2$. For this purpose the hydrochlorides, of 2-aminoethanesulfonamide, 3-amino-1-propanesulfonamide and 4-amino-1-butanesulfonamide have been prepared. The last two compounds were prepared in the following manner: β-chloropropionitrile or γ-chlorobutyronitrile was condensed with thiourea and the resulting isothiourea converted, by chlorination, to the corresponding cyanoalkanesulfonyl chloride. From the sulfonyl chloride, the cyanoalkanesulfonamide was prepared and reduced catalytically, in alcoholic hydrogen chloride solution, to the hydrochloride of the aminoalkanesulfonamide. Attempts to prepare aminoethanesulfonamide from chloroacetonitrile in an analogous manner were unsuccessful. The S-cyanomethylisothiourea which was obtained from chloroacetonitrile did not yield a sulfonyl chloride on chlorination.[3] However, 2-aminoethanesulfonamide was prepared easily and in excellent yields from 2-phthalimidoethanesulfonamide, $C_6H_4(CO)_2NCH_2CH_2SO_2NH_2$, by the method of Ing and Manske[4] for the preparation of amines from phthalimide derivatives.[5]

When tested[6] against experimental streptococcal infections in mice, after the administration of a single dose of the compound, these amino sulfonamides did not exhibit any significant protective action. These results indicate that, in the sulfanilamide structure, the separation of either the amino group or the sulfonamide group from the benzene nucleus or the substitution of an aliphatic chain for the benzene nucleus results in compounds of definitely inferior chemotherapeutic activity.

## Experimental Part[7]

***p* - Aminophenylmethanesulfonamide II.**—*p* - Nitrophenylmethanesulfonamide[8] was converted to this amino compound by catalytic reduction, in alcohol solution, at atmospheric pressure. Platinum oxide or Raney nickel catalyst was used. The yield was good with either catalyst. However, the nickel catalyst gave a product which was more readily purified.

**2 - *p* - Nitrophenylethanesulfonamide.**—*p* - Nitrophenethyl chloride[9] was condensed with thiourea in alcohol solution and the resulting crude isothiourea salt chlorinated[10] in water solution below 18°. A 96% yield of crude 2-*p*-nitrophenylethanesulfonyl chloride, m. p. 74–80°, was obtained. After recrystallization from benzene, it melted at 81.5–83°. The crude sulfonyl chloride was added slowly to concentrated aqueous ammonia and the amide which precipitated was recrystallized from dilute alcohol, m. p. 120.5–122°, yield 51%.

**2 - *p* - Aminophenylethanesulfonamide III.**—This compound was obtained by the catalytic reduction of the above nitro amide in alcohol solution using Raney nickel catalyst. It was recrystallized from alcohol, m. p. 181–182°.

***p* - (β - Acetylaminoethyl) - benzenesulfonamide.**—To 340 g. of chlorosulfonic acid, cooled to −10° in an ice–salt-bath, 25 g. (0.15 mole) of N-acetylphenethylamine[11] was added slowly with stirring. After the addition, the reaction mixture was stirred for two hours in the slowly melting ice-bath, then removed and allowed to stand at room temperature for thirty minutes. It was then poured into ice and water and the solid removed by filtration. After drying, this crude sulfonyl chloride can be recrystallized from benzene although considerable decomposition takes place, m. p. 142.5–144°. The crude, moist sulfonyl chloride was treated with aqueous ammonia and the amide obtained by removing the excess ammonia under di-

(3) This is similar to the behavior of the isothioureas from chloroacetic acid and ethyl chloroacetate. Sprague and Johnson, THIS JOURNAL, **59**, 2439 (1937).

(4) Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

(5) Christiansen, U. S. Patent 2,184,279, *C. A.*, **34**, 2536 (1940), has recently described the preparation of 2-aminoethanesulfonamide through the same intermediate compounds.

(6) We are indebted to Messrs. G. W. Webster and Harry J. Pratt for the pharmacological results.

(7) All melting points are uncorrected.

(8) Mohr, *Ann.*, **221**, 218 (1883).

(9) Barger, *J. Chem. Soc.*, **95**, 2194 (1909); Von Braun, *Ber.*, **45**, 1277 (1912); Von Braun and Bartsch, *ibid.*, **46**, 3050 (1913).

(10) For the general procedure for the preparation of alkanesulfonyl chlorides, see Johnson and Sprague, THIS JOURNAL, **58**, 1349 (1936); **59**, 1837, 2439 (1937).

(11) Carothers and Jones, *ibid.*, **47**, 3057 (1925).

minished pressure. The yield of crude amide (m. p. 164–166°) was 60% based upon the N-acetylphenylethylamine. The amide was recrystallized from water, m. p. 168–169°.

That the sulfonyl chloride group which was introduced by the chlorosulfonic acid occupied the para position was shown by a dichromate oxidation of the amide to *p*-sulfamylbenzoic acid, m. p. 290–290.5°. This showed no depression of the melting point when mixed with an authentic sample of this acid prepared from *p*-toluenesulfonamide.[12]

***p*-(β-Aminoethyl)-benzenesulfonamide V.**—The crude acetyl derivative (15.8 g.) was refluxed for eight hours with 1:3 hydrochloric acid and the solution evaporated to dryness. The residue was washed with cold alcohol and dried, 13.5 g., m. p. 223–228°. This hydrochloride was recrystallized from hot alcohol by the addition of ether, m. p. 229–231°. The base was obtained by the addition of saturated sodium carbonate solution to a concentrated solution of the hydrochloride in water. After recrystallization from alcohol by addition of petroleum ether, it melted at 147.5–149°.

***p*-Cyanobenzenesulfonamide.**[13]—A solution of 17.2 g. (0.1 mole) of sulfanilamide in 130 cc. of 2 *N* hydrochloric acid was cooled to 0° and a cold solution of 7.0 g. of sodium nitrite in 45 cc. of water added during a period of ten minutes. This diazotized solution was poured with vigorous stirring into a solution of 26 g. of crystalline copper sulfate and 21.7 g. of sodium cyanide in 140 cc. of water. After standing for two hours, the mixture was heated to 70° for ten minutes and then chilled. The brown solid was removed, dried and extracted with 400 cc. of a 5% solution of alcohol in benzene. On evaporating the extract, 14 g. of a tan crystalline product was obtained, m. p. 162–165°. On recrystallization from water, after decolorizing with charcoal, 10.9 g. of pale yellow *p*-cyanobenzenesulfonamide was obtained, m. p. 166–167°, yield 59.5%.

***p*-Aminomethylbenzenesulfonamide IV.**—*p*-Cyanobenzenesulfonamide was reduced catalytically in alcoholic hydrochloric acid solution using palladium–charcoal catalyst.[14] The yield of pure hydrochloride, after recrystallizing from 95% alcohol, was 81%, m. p. 248–249°. The *p*-aminomethylbenzenesulfonamide was obtained from the hydrochloride by addition of ammonia to the aqueous solution and was recrystallized from alcohol, m. p. 151–152°. With acetic anhydride, the acetyl derivative was obtained, m. p. 172–173°. This N-acetyl derivative was also prepared in a 20% yield from N-acetylbenzyl amine by the action of chlorosulfonic acid followed by ammonia in a manner similar to the procedure described for N-acetylphenethylamine.

***p*-Cyanophenylmethanesulfonamide.**—Thirty-two grams of *p*-cyanobenzyl chloride[15] was condensed with thiourea in alcohol and the isothiourea chlorinated[10] to give *p*-cyanophenylmethanesulfonyl chloride. The crude yield was 80%, m. p. 98–99°. This sulfonyl chloride can be recrystallized from benzene, m. p. 102–103°. The crude sulfonyl chloride was treated with ammonia and the amide (29 g., m. p. 208–210°), recrystallized from 50% alcohol, m. p. 216–217°.

***p*-Aminomethylphenylmethanesulfonamide VI.**—The hydrochloride of this compound was obtained by reduction of the cyanophenylmethanesulfonamide in alcoholic hydrochloric acid solution using either platinum oxide or palladium–charcoal catalyst. The platinum oxide gave a more rapid reduction. The hydrochloride melted at 278–280° with decomposition. The base was obtained from the hydrochloride by the addition of ammonia to the water solution. After recrystallizing from alcohol by the addition of isopropyl ether, it melted at 160.5–162°.

**3-Cyano-1-propanesulfonamide.**—γ-Chlorobutyronitrile[16] (0.1 mole) was condensed with thiourea, with or without alcohol as solvent, to give S-γ-cyanopropylisothiourea hydrochloride. This was a crystalline solid, m. p. 125–127° (from alcohol). Analysis and tests showed the presence of some bromine which was derived from the trimethylene chlorobromide used in the preparation of the chlorobutyronitrile. The picrate analyzed correctly. On chlorination[10] of a water solution of the hydrochloride below 15°, a yellow oil was obtained. This was taken up in ether, washed and dried. On removing the ether completely 13.6 g. (80%) of an oil having the properties of a sulfonyl chloride was obtained. This material could not be distilled without decomposition. An ether solution of the crude sulfonyl chloride was added to a saturated solution of dry ammonia in alcohol. The ammonium chloride was removed and the solution concentrated under diminished pressure below 30°. The residue was extracted with ethyl acetate and the extract evaporated to dryness. The residue solidified to a crystalline mass (11.9–13.5 g., m. p. 63–66°) containing a small amount of oil which was removed by washing with a cold 1:1 alcohol–ether solution. After recrystallizing from ethyl acetate and ether, the 3-cyano-1-propane sulfonamide melted at 65–66°. The yield was 50%.

**4-Amino-1-butanesulfonamide Hydrochloride.**—The cyanopropylsulfonamide was hydrogenated in alcoholic hydrogen chloride solution using platinum oxide catalyst. With palladium–charcoal as the catalyst the reduction was very slow. After reduction was complete the alcohol was brought to boiling to redissolve the precipitated hydrochloride and filtered from the catalyst. The residue obtained on evaporating the alcohol filtrate was triturated with cold alcohol and filtered. The yield of white hydrochloride was 92%, m. p. 126–128°. After recrystallizing from 90% alcohol, it melted at 127–129° and was analytically pure. The benzoyl derivative was prepared and recrystallized from water and alcohol, m. p. 154–155°.

**3-Amino-1-propanesulfonamide.**—This compound was obtained from β-chloropropionitrile[17] through a series of reactions analogous to that just described using γ-chlorobutyronitrile. However, the yields were lower when β-chloropropionitrile was used.

A small portion of the crude 2-cyanoethanesulfonyl chloride was distilled without decomposition, b. p. 135–136° (5–6 mm.).

**2-Phthalimidoethanesulfonamide.**[5]—Twenty-one grams (0.1 mole) of β-chloroethylphthalimide,[18] 10 g. of thiourea

(12) Remsen, *Ann.*, **178**, 297 (1875).

(13) Remsen, Hartman and Muckenfuss, *Am. Chem. J.*, **18**, 159 (1896).

(14) Hartung, THIS JOURNAL, **50**, 3372 (1928).

(15) Barkenbus and Holtzclaw, *ibid.*, **47**, 2189 (1925).

(16) "Organic Syntheses," Coll. Vol. I, 1932, p. 150.

(17) Chapman and Stephen, *J. Chem. Soc.*, **127**, 888 (1925).

(18) Wenker, THIS JOURNAL, **59**, 422 (1937).

TABLE I

| Compound | M. p., °C. | Yield, % (pure) | Formula | Nitrogen, % Calcd. | Nitrogen, % Found | Chlorine, % Calcd. | Chlorine, % Found |
|---|---|---|---|---|---|---|---|
| *p*-Aminophenylmethanesulfonamide | 171–172 | 70–86 | $C_7H_{10}O_2N_2S$ | 15.04 | 14.97 | | |
| 2-*p*-Nitrophenylethanesulfonamide | 120.5–122 | 51 | $C_8H_{10}O_4N_2S$ | 12.17 | 12.18 | | |
| 2-*p*-Aminophenylethanesulfonamide | 181–182 | 67 | $C_8H_{12}O_2N_2S$ | 13.99 | 14.01 | | |
| *p*-(β-Acetylaminoethyl)-benzenesulfonyl chloride | 142.5–144 | 35 | $C_{10}H_{12}O_3NSCl$ | 5.35 | 5.22 | | |
| *p*-(β-Acetylaminoethyl)-benzenesulfonamide | 168–169 | 50 | $C_{10}H_{14}O_3N_2S$ | 11.56 | 11.57 | | |
| *p*-(β-Aminoethyl)-benzenesulfonamide·HCl | 228–230 | 80 | $C_8H_{13}O_2N_2SCl$ | 11.83 | 11.76 | 14.99 | 14.78 |
| *p*-(β-Aminoethyl)-benzenesulfonamide | 147.5–149 | 55 | $C_8H_{12}O_2N_2S$ | 14.00 | 13.95 | | |
| *p*-Aminomethylbenzenesulfonamide | 151–152 | 50 | $C_7H_{10}O_2N_2S$ | 15.04 | 15.07 | | |
| *p*-Aminomethylbenzenesulfonamide·HCl | 249–250 | 81 | $C_7H_{11}O_2N_2SCl$ | 12.58 | 12.59 | 15.93 | 16.00 |
| *p*-(Acetylaminomethyl)-benzenesulfonamide | 172–173 | 81 | $C_9H_{12}O_3N_2S$ | 12.27 | 12.29 | | |
| *p*-Cyanophenylmethanesulfonyl chloride | 102–103 | 65 | $C_8H_6O_2NSCl$ | 6.49 | 6.48 | 16.45 | 16.46 |
| *p*-Cyanophenylmethanesulfonamide | 216–217 | 60 | $C_8H_8O_2N_2S$ | 14.28 | 14.32 | | |
| *p*-Aminomethylphenylmethanesulfonamide·HCl | 278–280 | 80 | $C_8H_{13}O_2N_2SCl$ | 11.84 | 11.98 | 14.99 | 14.95 |
| *p*-Aminomethylphenylmethanesulfonamide | 160.5–162 | | $C_8H_{12}O_2N_2S$ | 14.00 | 14.04 | | |
| 3-Cyano-1-propanesulfonamide | 65–66 | 50 | $C_4H_8O_2N_2S$ | 18.90 | 18.89 | | |
| 4-Amino-1-butanesulfonamide·HCl | 127–129 | 92 | $C_4H_{13}O_2N_2SCl$ | 14.85 | 14.71 | 18.80 | 18.90 |
| 4-Benzoylamino-1-butanesulfonamide | 154–155 | | $C_{11}H_{16}O_3N_2S$ | 10.93 | 10.87 | | |
| 2-Phthalimidoethanesulfonyl chloride[5] | 157.5–158.5 | 80 | $C_{10}H_8O_4NSCl$ | 5.12 | 5.14 | 12.96 | 13.07 |
| 2-Phthalimidoethanesulfonamide[5] | 207–208 | 60 | $C_{10}H_{10}O_4N_2S$ | 11.02 | 11.06 | | |
| 2-Aminoethanesulfonamide·HCl[5] | 131–133 | 76 | $C_2H_9O_2N_2SCl$ | 17.43 | 17.35 | 22.07 | 22.01 |
| β-Benzoylaminoethanesulfonamide | 165–166 | .. | $C_9H_{12}O_3N_2S$ | 12.28 | 12.12 | | |
| S-*p*-Cyanobenzylisothiourea·HCl | 204–205 | .. | $C_9H_{10}N_3SCl$ | 18.45 | 18.57 | 15.58 | 15.69 |
| S-γ-Cyanopropylisothiourea·HCl | 125–127 | .. | $C_5H_{10}O_3SCl$ | 23.38 | 22.94 | 19.74 | 19.70 |
| S-γ-Cyanopropylisothiourea picrate | 163.5–164.5 | 75 | $C_{11}H_{12}O_7N_6S$ | 22.57 | 22.43 | | |
| S-β-Phthalimidoethylisothiourea·HCl | 243–245 | .. | $C_{11}H_{12}O_2N_3SCl$ | 14.70 | 14.63 | | |
| S-Cyanomethylisothiourea·HCl | (decompn.) | 82 | $C_3H_6N_3SCl$ | 27.70 | 27.51 | 23.39 | 23.38 |
| S-β-Cyanoethylisothiourea·HCl | 165–166 | 80 | $C_4H_8N_3SCl$ | 25.38 | 25.32 | 21.41 | 21.40 |
| 2-Cyanoethanesulfonamide | 94–95 | 25 | $C_3H_6O_2N_2$ | 20.89 | 20.59 | | |
| 3-Amino-1-propanesulfonamide·HCl | 159–160 | 60 | $C_3H_{11}O_2N_2SCl$ | 16.04 | 16.13 | 20.31 | 20.24 |

and 10 cc. of alcohol were heated together on a steam-bath or in an oil-bath at 100–110° for forty to sixty hours. The mixture was then dissolved in water (600 cc.), filtered from any unreacted material and chlorinated[10] at a temperature between 5 and 10°. The yield of crude, dry 2-phthalimidoethanesulfonyl chloride was 25 g. (93%), m. p. 152–155°. This sulfonyl chloride can be recrystallized from a benzene–petroleum ether solution, m. p. 157.5–158.5°.

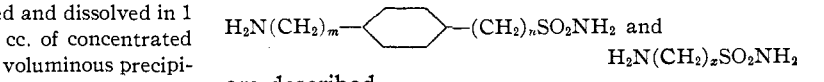
The crude sulfonyl chloride was added to 300 cc. of cold concentrated aqueous ammonia and stirred for thirty minutes. After the excess ammonia had been removed under diminished pressure, the solution was evaporated on a steam-bath until completely dry and no further odor of ammonia was detectable. The residue was triturated with cold water and the insoluble amide removed by filtration. The total yield of crude amide was 15.85 g., m. p. 201–206°. For analysis, it was recrystallized from water, m. p. 207–208°.

**2-Aminoethanesulfonamide Hydrochloride.**[5]—The crude 2-phthalimidoethanesulfonamide (15.8 g.) was suspended in 200 cc. of hot alcohol and 10.5 cc. of 42% hydrazine hydrate added. After refluxing for a few minutes the amide dissolved completely and the insoluble intermediate[4] began to precipitate. After forty-five minutes, the mixture was cooled, the precipitate removed and dissolved in 1 liter of hot water. On addition of 12 cc. of concentrated hydrochloric acid to this hot solution a voluminous precipitate of phthalhydrazide formed. After cooling, the mixture was filtered, the filtrate concentrated and any further phthalhydrazide removed. On evaporating to dryness, a crystalline solid was obtained. After washing with cold alcohol, the yield of the crude hydrochloride of 2-aminoethanesulfonamide was 9.0 g., m. p. 125–130°. This crystallized from 95% alcohol in large prisms, m. p. 130.5–132°; yield 7.8 g. (76.5%). The benzoyl derivative was prepared and recrystallized from 50% alcohol, m. p. 165–166°.

**S-Cyanomethylisothiourea Hydrochloride.**—A solution of 7.6 g. of thiourea and 9 g. of chloroacetonitrile[19] in 175 cc. of acetone was allowed to stand at room temperature for two to four days. A colorless oil separated and gradually crystallized. The crystals were removed and washed with ether, yield 82%. On plunging into a hot bath, this material melted around 95–105° to a clear oil. The oil rapidly changed to a solid which did not melt below 350°. With slow heating no melting was observed. The analysis and properties of this material agree with the isothiourea structure. On chlorination of an aqueous solution, no sulfonyl chloride was produced and the sulfur was converted to sulfate.[3]

## Summary

1. A number of compounds of the general types



and



are described.

(19) Steinkopf, *Ber.*, **41**, 2541 (1908).

2. These compounds did not exhibit any significant protective action against experimental streptococcic infections in mice.

GLENOLDEN, PENNSYLVANIA RECEIVED MAY 16, 1940

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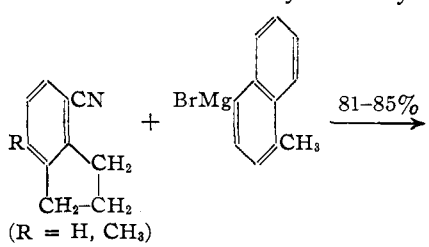
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

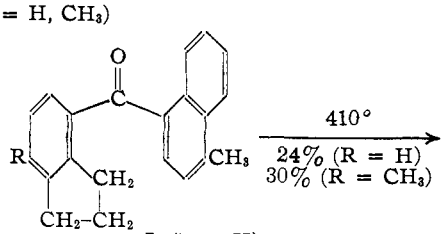
# New Methyl and Dimethyl Derivatives of Cholanthrene

BY LOUIS F. FIESER AND DOUGLAS M. BOWEN

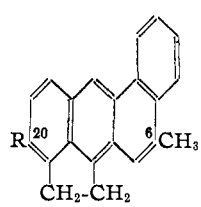
Information concerning the influence of alkyl substitution on the carcinogenic properties of cholanthrene is available with respect to only three positions.[1] 20-Methylcholanthrene, the only one of the twelve possible monomethyl isomers hitherto known, corresponds closely with the parent hydrocarbon in potency, while the 15,20- and 16,20-dimethyl homologs show diminished activity associated with the presence of the added substituent in the five-membered ring. It is of interest to study the effect of attaching alkyl groups elsewhere in the molecule, particularly for comparison with the results obtained in the 1,2-benzanthracene series where all twelve monomethyl derivatives are now known.

In one series of experiments we investigated the introduction of methyl at position 6 via the Elbs reaction. 4-Methyl-1-naphthylmagnesium bromide condensed smoothly with 4-cyanohydrindene




I (R = H)
II (R = CH₃)




III (R = H), IV (R = CH₃)

and its 7-methyl derivative and after hydrolysis of the ketimines the ketones I and II were obtained easily in a crystalline condition. Pyrolysis of the monomethyl compound I gave a hydrocarbon mixture probably containing some cholanthrene and affording a pure methyl homolog in low yield only after considerable processing by adsorption and crystallization. 6-Methylcholanthrene (III) has a relatively high melting point (209°), which facilitated its characterization as to purity. Although some cleavage of the methyl group probably occurred, as indicated by the character of the reaction mixture, the retention of the alkyl radical at position 6 was much better than observed with other substituents. The methoxyl group was found to be completely eliminated from this position,[2] and although chlorine was in part retained the yield of 6-chloro compound was only 1.2%.[2] The Elbs reaction proceeded even better in the case of the dimethyl compound II, and 6,20-dimethylcholanthrene (IV) was produced in an easily purified condition and in yield comparable with that of the parent hydrocarbon.[3,4] The methyl group appearing at the 20-position seems to favor the condensation.

A second series of experiments was concerned with substitution at position 22. 6-Methyl-4-cyanohydrindene (X), required as an intermediate for application of the Elbs synthesis, was obtained by the following process starting with acetyl *p*-toluidine (V).

Using the method of Cohen and Raper[5] with some modifications, this was converted into 4-bromo-3-chlorotoluene (VII). Since a preliminary trial of the condensation of a comparable Grignard derivative with the γ-chloropropyl ester of *p*-toluenesulfonic acid gave unpromising results, the desired three-carbon side chain was introduced via the aldehyde. The reaction of 4-methyl-2-chlorophenylmagnesium bromide with ethyl ortho-

(1) For literature and summary of the biological data, see Fieser, *Am. J. Cancer*, **34**, 37 (1938).

(2) Fieser and Desreux, THIS JOURNAL, **60**, 2255 (1938).

(3) Fieser and Seligman, *ibid.*, **57**, 2174 (1935).

(4) Bachmann, *J. Org. Chem.*, **3**, 434 (1938).

(5) Cohen and Raper, *J. Chem. Soc.*, **85**, 1269 (1904).