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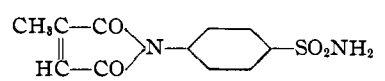
Synthesis of Lipophilic Chemotherapeuticals. V. N^4-Acyl-sulfanilamides[1a]

BY F. BERGMANN AND L. HASKELBERG

Sulfanilamide and its simple derivatives which have been studied very extensively during the last years, are assumed by several authors[1b] to be chemotherapeutical agents in the proper sense of the word, acting directly on the cells of the microorganisms to be affected. It seemed desirable, therefore, to study their influence on the "fatty" bacilli of the tuberculosis and leprosy type, after having made the molecules lipophilic. The idea, which has been expressed in the first part of this series,[2] that only lipophilic chemotherapeuticals can be expected to act upon "acid-fast" bacilli, has recently been applied by Crossley and co-workers[3] to the sulfanilamide group; these authors studied the N^1-acyl derivatives, which contain the acyl radicals in the sulfonamide group. In addition to such substances, we have prepared and studied a certain number of N^4-acyl-sulfanilamides, containing the acyl residues on the basic amino nitrogen. Such substances, as far as we are aware, have not been prepared hitherto with the exception of the acetyl compound,[4] the chloroacetyl derivative[5] and certain representatives recently described in a patent.[6] We used the radicals of high molecular fatty acids, of unsaturated and of halogen substituted acids, as previous studies in other series had shown these residues to be advantageous to our purpose. In Table I the substances we have prepared are listed.

We have also studied the influence of the molecular size on the activity and prepared to this effect the coupling products of sulfanilamide with dibasic acids. This study has been instigated by the well-known trypanocidal properties of Germanin (Bayer 205) as compared with the inactivity of the base, of which two molecules are coupled by phosgene to form the highly active preparation. Using maleic and succinic anhydride, respectively, such experiments have been performed before by Miller, Rock and Moore[7]; in this paper, the condensation reactions (2:1) are described between sulfanilamide and isophthaloyl chloride, adipoyl chloride and sebacoyl chloride, respectively. As with succinic anhydride, with phthalic anhydride, tetrachlorophthalic anhydride and diphenic anhydride, condensation occurred in the ratio of 1:1, the products obtained being monobasic acids of the general formula $H_2NO_2SC_6H_4NHCORCOOH$; this has been found in the case of the phthalic acid derivative by Schering-Kahlbaum.[7a] Citraconic anhydride behaves differently, as a non-acidic substance has been isolated, to which we ascribe the structure



of *p*-citraconimido-benzene-sulfanilamide.

This paper reports exclusively on the chemical part of our work; a description of the related chemotherapeutical experiments will be given elsewhere.

Experimental Part

Preparation of N^4-Acyl-sulfanilamides

Method 1. Trichloroacetyl Derivative.—The mixture of sulfanilamide (8.6 g.) with chloroform (50 cc.) and pyridine (4 g.) was cooled to 0° and treated with a solution of trichloroacetyl chloride (9.1 g.) in chloroform (25 cc.). After twelve hours of standing at room temperature, the reaction product was filtered off and recrystallized from 50% acetic acid as leaflets, m. p. 250°; if the solution is cooled very slowly, strongly birefringent rhombohedra are obtained, yield, 80%.

In most cases, the reaction could be carried out analogously with approximately the same yield. With stearoyl chloride, the product had to be isolated by evaporating the solution after shaking with water and drying with fused calcium chloride. With dibromoundecanoyl chloride, the analogous treatment of the mother liquor of the first crystallizate gave an additional crop of the desired product.

Method 2. Undecenoyl Derivatives.—Sulfanilamide (8.6 g.) was dissolved, by heating, in a mixture of glacial acetic acid (45 cc.) and saturated aqueous sodium acetate solution (45 cc.). The solution was cooled to −5° and,

(1a) The original manuscript was received on May 29, 1940. The minor alterations required unfortunately resulted in serious delay largely because of difficulties of communication.

(1b) See, *e. g.*, recently, A. T. Fuller, L. Colebrook and W. R. Maxted, *J. Path. Bact.*, **51**, 105 (1940); *Chem. Abs.*, **34**, 7436 (1940).

(2) E. Bergmann and Haskelberg, *J. Chem. Soc.*, 1 (1939).

(3) Crossley, Northey and Hultquist, THIS JOURNAL, **61** 2950 (1939).

(4) Gelmo, *J. prakt. Chem.*, [2] **77**, 371 (1908).

(5) Jacobs and Heidelberger, THIS JOURNAL, **39**, 2429 (1917).

(6) I. G. Farbenindustrie, British Patent 474,428; French Patent 820,546; U. S. Patent 2,169,971; *Chem. Zentr.*, **109**, I, 1829 (1938); *Chem. Abs.*, **32**, 2958 (1938); **34**, 1134 (1940).

(7) Miller, Rock and Moore, THIS JOURNAL, **61**, 1198 (1939); compare also L. Vargha, *Chem. Abs.*, **34**, 3703 (1940).

(7a) Schering-Kahlbaum, British Patent 502,558, see also Rosicky, French Patent 843,415; *Chem. Abs.* **34**, 6770 (1940); L. Vargha, **ref. 7.**

TABLE I

N^4-ACYL-SULFANILAMIDES

Acyl residue	Method of prepn.[a]	Recryst. from	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Chloroacetyl	1	Water or HAc	214							
Dichloroacetyl	1, 2	70% Alc.	218	$C_8H_8O_3N_2Cl_2S$	34.0	2.8	10.0	34.1	2.2	10.9
Trichloroacetyl	1	50% HAc	205	$C_8H_7O_3N_2Cl_3S$	30.4	2.2	..	30.2	2.1	..
Bromoacetyl	1	50% HAc, alc.	218 dec.	$C_8H_9O_3N_2BrS$	32.8	3.0	..	33.1	3.0	..
Trichloroacroyl	2	80% formic acid	258	$C_9H_7O_3N_2Cl_3S$	32.9	2.1	8.6	34.4	2.4	8.5
Stearoyl[b]	1	Alcohol	245	$C_{24}H_{42}O_3N_2S$	65.7	9.6	..	65.3	9.7	..
Oleyl	1	Gl. HAc	204	$C_{24}H_{40}O_3N_2S$	66.1	9.2	..	65.8	8.4	..
Stearoloyl[c]	1	Gl. HAc	189	$C_{24}H_{38}O_3N_2S$	66.3	8.7	..	65.8	8.7	..
Undecanoyl	1	Alcohol	205 dec.	$C_{17}H_{28}O_3N_2S$	60.0	8.2	..	60.6	8.8	..
Undecenoyl	1, 2	Alcohol	194–6	$C_{17}H_{26}O_3N_2S$	..	..	8.3	..	..	9.1
Dibromoundecanoyl	1, 2	80% HAc, PrOH	173–5	$C_{17}H_{26}O_3N_2SBr_2$	40.9	5.2	5.6	40.9	5.3	5.8
Cinnamoyl	1	Ethyl malonate	255–7	$C_{15}H_{14}O_3N_2S$	59.6	4.6	..	57.1	4.6	..
trans-α,β-Dibromocinnamoyl	2	Amyl alc.	266	$C_{15}H_{12}O_3N_2Br_2S$	39.1	2.6	6.1	39.6	2.9	5.9
Phenylpropioloyl	1	Gl. HAc, *i*-PrOH	254	$C_{15}H_{12}O_3N_2S$	60.0	4.0	..	59.7	4.2	..

[a] See Experimental Part. [b] By I. G. Farbenindustrie, the m. p. of this substance is erroneously given as 201°. [c] $CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO$—.

while stirring, undecenoyl chloride (10.1 g.) added. After twelve hours of standing at room temperature, the reaction product was filtered and recrystallized from glacial acetic acid or alcohol, m. p. 194–196°; yield, 70%. In general, it was not worth while to extract a further amount from the original mother liquor.

Acid Chlorides.—The provenience of the halogenated aliphatic chlorides and of the C_{11} chlorides has been indicated in previous papers.[8] Stearoyl, oleoyl and cinnamoyl chlorides were obtained from the pure acids by means of thionyl chloride; they had b. p. 215° (15 mm.); 160–165 (1 mm.) and 130° (11 mm.), respectively. **Stearolic acid** was prepared according to Kino[9] and its acid **chloride** in the following way. The acid (10 g.) was heated with thionyl chloride (10 cc.) at 70–80°, until the evolution of hydrochloric acid ceased. Distillation *in vacuo* gave the pure chloride of b. p. 210° (15 mm.); d^{22} 0.9504; $n^{22}D$ 1.4663.

Phenylpropioloyl Chloride.—Phenylpropiolic acid (15 g.)[10] was gently boiled for three hours with thionyl chloride (27 cc.). The excess thionyl chloride was evaporated and the residue distilled *in vacuo:* b. p. 103–105° (3.5 mm.); yield, quantitative.

***trans*-α,β-Dibromocinnamoyl Chloride.**—The acid (38 g.)[11] was heated with thionyl chloride (140 g.) for three hours on the water-bath. From the solution, the thionyl chloride was removed at ordinary pressure and the acid chloride distilled *in vacuo:* b. p. 205–208° (7 mm.); yield, 35.2 g.

N^4,$N^{4'}$-Isophthaloyl-bis-sulfanilamide.—Sulfanilamide (17.2 g.) was dissolved in a hot mixture of glacial acetic acid (90 cc.) and saturated aqueous sodium acetate solution (90 cc.) and at 0° allowed to react with isophthaloyl chloride (9.1 g.).[12] After twelve hours of standing at room temperature, the reaction product was filtered, washed with water, alcohol and ether and recrystallized from pyridine, m. p. above 360°. *Anal.* Calcd. for $C_{20}H_{18}O_6N_4S_2$: C, 50.6; H, 3.8; N, 11.8. Found: C, 49.3; H, 4.1; N, 11.2%. In the same way was obtained: **N^4,$N^{4'}$-adipoyl-bis-sulfanilamide** with adipoyl chloride (9.1 g.; b. p. 125° (14 mm.));[13] recrystallization from aqueous pyridine. *Anal.* Calcd. for $C_{18}H_{22}O_6N_4S_2$: C, 47.6; H, 4.8. Found: C, 47.5; H, 5.4.

Also **N^4,$N^{4'}$-sebacoyl-bis-sulfanilamide** with sebacoyl **chloride** (11.9 g.; b. p. 177–180° (20 mm.));[14] recrystallization from water and pyridine (1:2). *Anal.* Calcd. for $C_{22}H_{30}O_6N_4S_2$: C, 51.7; H, 5.0; N, 11.0. Found: C, 50.9; H, 5.7; N, 10.5. The yields were quantitative, both melting points above 300°.

***p*-Sulfamyl-phthalanilic Acid.**—An intimate mixture of sulfanilamide (8.6 g.) and phthalic anhydride (7.2 g.) was heated for one hour at 150°. The reaction product crystallized from glacial acetic acid in leaflets, m. p. 338°. *Anal.* Calcd. for $C_{14}H_{12}O_5N_2S$: C, 52.5; H, 3.7; N, 8.8. Found: C, 52.3; H, 3.7; N, 9.1.

Analogously, ***p*-sulfamyl-tetrachlorophthalanilic acid** was prepared, starting with tetrachlorophthalic anhydride (15.6 g.), and recrystallized from glacial acetic acid, xylene or most conveniently from acetic anhydride; needles, which decompose at 322°. *Anal.* Calcd. for $C_{14}H_8O_5N_2Cl_4S$: C, 36.7; H, 1.7; N, 6.1. Found: C, 36.2; H, 2.0; N, 6.4. The same procedure followed with **succinic anhydride,** gave in good yield, *p*-sulfamyl-succinanilic acid, m. p. 212.5–213.5°.[7]

With diphenic acid anhydride no reaction occurred under the above conditions. But ***p*-sulfamyl-diphenanilic acid** was easily obtained, when sulfanilamide (17.2 g.) and diphenic anhydride (22.4 g.) were boiled for one hour in propyl alcohol (100 cc.). The reaction product separated on cooling and was recrystallized from the same solvent, m. p. 278–279° (decompn.); yield, 35 g. *Anal.* Calcd. for $C_{20}H_{16}O_5N_2S$: C, 60.6; H, 4.0. Found: C, 60.3; H, 4.1.

(8) Part III, THIS JOURNAL, **63**, 1432 (1941); Part IV, *J. Soc. Chem. Ind.*, **60**, in press (1941).

(9) Kino, *Chem. Zentr.*, **107**, I, 2531 (1936); compare Overbeck, *Ann.*, **140**, 49, 61 (1866).

(10) Curtius and Kenngott, *J. prakt. Chem.*, [2] **112**, 319 (1926). See Schlenk and E. Bergmann, *Ann.*, **463**, 82 (1928).

(11) See E. Bergmann, *J. Chem. Soc.*, 406 (1936).

(12) B. p. 162° (15 mm.); m. p. 42°. Compare H. Meyer, *Monatsh.*, **22**, 436 (1901).

(13) Blaise and Koehler, *Bull. soc. chim.*, [4] **5**, 683 (1909).

(14) H. Meyer, *Monatsh.*, **22**, 421 (1901); Auger, *Ann. Chim.*, [6] **22**, 361 (1891).

p-Citraconimido-benzene-sulfonamide.—When citraconic anhydride (23.4 g.) and sulfanilamide (34.4 g.) were mixed at room temperature (25°), the temperature rose spontaneously to 60°. After one hour of heating on the water-bath, the product was recrystallized from water; m. p. 210–213°. *Anal.* Calcd. for $C_{11}H_{10}O_4N_2S$: C, 49.6; H, 3.8. Found: C, 50.0; H, 4.0.

Summary

Fourteen N^4-acyl-sulfanilamides have been prepared, the acyl residues being expected to make the molecule lipophilic. The condensation of sulfanilamide with isophthaloyl chloride, sebacoyl chloride, adipoyl chloride, phthalic anhydride, tetrachlorophthalic anhydride, diphenic anhydride, succinic and citraconic anhydride is also reported.

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Synthesis of Lipophilic Chemotherapeuticals. VI. Lipophilic Substitutions in Azo-dyes

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The efficacy of a pharmaceutically active substance can be increased, following the terminology of P. Ehrlich, by changing the toxophoric or the haptophoric group of the substance. Thus an increase in the selective aptitude of a compound for fixation on a parasite or bacterium cell may make more obvious even feeble chemotherapeutical effects. This possibility which we indicated in the first paper of this series,[1] has now been investigated for 4-benzene-azo-naphthylamine-(1). This azo-dye is known to have chemotherapeutical value.[2]

In order to give the dye a higher affinity for the "lipoidic" micro-organisms like the tubercle or leprosy bacilli, we have tried to increase its lipophilic character. As in our previous papers, we have introduced into the amino group various acyl radicals, especially those of long-chain fatty and halogenated acids, respectively. Table I describes these derivatives, all of which were previously unknown.

The trichloroacetyl derivative showed a slight but definite curative activity for tuberculosis (in guinea pigs) and for leprosy (in Syrian hamsters). This interesting result explains why we have taken the N-trichloroacetyl-4-(benzene-azo)-naphthylamine-(1) as a starting point for further syntheses. We have, for example, prepared the trichloroacetyl derivatives of the azo-dyes from α-naphthylamine and diazotized *o*-chloroaniline, *p*-chloroaniline and ethyl *p*-aminobenzoate. We have also prepared and tested the undecenoyl derivative of the latter azo-dye. The details of the chemotherapeutical experiments with the substances included in Table I will be published elsewhere.

We have also prepared analogous acyl derivatives of the isomeric 1-(benzene-azo)-2-naphthylamine. The substances prepared are given in Table II. The trichloroacetyl derivative of ethyl 2-aminonaphthalene-(1-azo-1')-benzoate-4' was definitely active against leprosy in hamsters.

In a third series of experiments, which we are also continuing, we have omitted the naphthalene nucleus from the molecules and substituted for it a benzene ring. Thus, we have prepared the trichloroacetyl derivatives of the following azo-dyes: 4-amino-azobenzene, 4-amino-2-methyl-azobenzene, 4-amino-3-methyl-azobenzene and 4-amino-3-methoxy-azobenzene.

Experimental

Acid Chlorides.—The preparations of the uncommon acid chlorides which we used have been described in previous communications[3]; acetylsulfaniloyl chloride was obtained according to "Organic Syntheses."[4]

Azo-dyes.—4-Benzene-azo-naphthylamine-(1) was obtained by the method of Griess,[5] and the isomeric 1-benzene-azo-naphthylamine-(2)[6] according to the directions of Bamberger and Schieffelin.[7] The properties of 4'-chlorobenzene-1'-azo-4-naphthylamine-(1) were found to be in accordance with the data given by Bamberger and Grob.[8] A much higher melting point (141°) was observed for 2'-chlorobenzene-(1'-azo)-4-naphthylamine-(1) than

(1) E. Bergmann and L. Haskelberg, *J. Chem. Soc.*, 1 (1939).

(2) See, *e. g.*, Dyson, "The Chemistry of Chemotherapy," Ernest Benn Ltd., London, 1928, p. 82.

(3) Parts III and IV (in press).

(4) "Organic Syntheses," Collective Volume I, New York, 1932, p. 8.

(5) Griess, *Ann.*, **137**, 60 (1866).

(6) For its structure see E. Bergmann and A. Weizmann, *Trans. Faraday Soc.*, **32**, 1318 (1936).

(7) Bamberger and Schieffelin, *Ber.*, **22**, 1376 (1889).

(8) Bamberger and Grob, *ibid.*, **35**, 78 (1902).