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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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

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).

that recorded in the literature (129°).[9] Because of this discrepancy the preparation of this dye-stuff is described below in detail. The m. p. of 2'-chlorobenzene-(1'-azo-1)-naphthylamine-(2) was slightly higher (158°) than the recorded[9] m. p. (151°).

2'-Chlorobenzene-(1'-azo-4)-naphthylamine-(1).—The solution obtained by diazotization of 25.4 g. of *o*-chloroaniline in a mixture of 60 cc. of concentrated hydrochloric acid and 200 cc. water by 180 cc. of 2 *N* sodium nitrite, was added to 28.6 g. of α-naphthylamine which had been dissolved in 160 cc. of alcohol and precipitated in finely divided form by addition of 60 cc. of water. The dyestuff hydrochloride precipitated at once as a violet-brown mass which after twelve hours of standing was treated with 120 cc. of saturated aqueous sodium acetate solution. The reaction product was filtered and recrystallized from alcohol; red needles, m. p. 141°.

Anal. Calcd. for $C_{16}H_{12}N_3Cl$: C, 68.3; H, 4.3. Found: C, 68.7; H, 4.4.

4'-Carbethoxy-benzene-(1'-azo-4)-naphthylamine-(1).—16.5 grams of ethyl *p*-aminobenzoate dissolved in a mixture of 30 cc. of concentrated hydrochloric acid and 50 cc. of water was diazotized with 7 g. of sodium nitrite in 30 cc. of water. When the resulting solution was added to 14.3 g. of α-naphthylamine in 100 cc. of alcohol, the dark violet hydrochloride of the desired azo-dye separated, which was collected, dissolved in boiling alcohol and treated with the double volume alcoholic ammonia solution. From alcohol or butyl alcohol brown needles with green metallic luster; on exposure to the air, they disintegrate into a dark red powder; m. p. 164°.

Anal. Calcd. for $C_{19}H_{17}O_2N_3$: C, 71.5; H, 5.3; N, 13.2. Found: C, 72.0; H, 5.1; N, 13.6.

2-Amino-naphthalene-(1-azo-1')-benzene-4'-carboxylic Acid.[10]—13.7 grams of *p*-aminobenzoic acid, dissolved in a hot mixture of 50 cc. of water and 30 cc. of concentrated hydrochloric acid was diazotized at 50° with 7 g. of sodium nitrite in 28 cc. of water and added to a solution of 14.7 g. of β-naphthylamine in 250 cc. of alcohol. The dyestuff precipitated in well-crystallized form; it was collected, washed with water, triturated with glacial acetic acid and recrystallized from butyl alcohol as bright red needles, m. p. 265°. When the acid was dissolved in the equivalent amount of hot 10% sodium carbonate solution, the sodium salt, on cooling, separated in the form of orange-red leaflets.

The corresponding **ethyl ester** was obtained exactly in the same way, using 16.5 g. of ethyl *p*-aminobenzoate as starting material; crimson-red crystals, m. p. 183°.

Anal. Calcd. for $C_{19}H_{17}O_2N_3$: C, 71.5; H, 5.3. Found: C, 71.5; H, 5.1.

For the preparation of the **amide** the conditions were slightly different: 8 g. of *p*-amino-benzamide[11] in a mixture of 17 g. of concentrated hydrochloric acid and 100 cc. of water was diazotized at ice temperature with 29.3 cc. of 2 *N* sodium nitrite solution and the reaction product mixed with 8.4 g. of β-naphthylamine dissolved in 150 cc. of alcohol. The reaction product separated spontaneously and was recrystallized from ethyl or butyl alcohol as brown needles, which give a red powder; m. p. 243–244°.

Anal. Calcd. for $C_{17}H_{14}ON_4$: C, 70.3; H, 5.0. Found: C, 69.3; H, 4.7.

For the preparation of the **azo-benzene derivatives** we adopted in general the method of K. H. Meyer,[12] consisting in the treatment of diazoaminobenzene with an appropriate amine (aniline, *o*-toluidine, *m*-toluidine) in presence of its hydrochloride. In this way, from 15 g. of diazoaminobenzene with 39 g. of aniline and 9 g. of aniline hydrochloride, the hydrochloride of 4-aminoazobenzene formed within one hour at 40° and twenty-four hours at room temperature. It was filtered, washed with dilute hydrochloric acid and treated in boiling alcohol (45 cc.) with an excess of aqueous ammonia and recrystallized from isopropyl alcohol. Analogously, 40 g. of diazoaminobenzene gave with 100 g. of *m*-toluidine (*o*-toluidine) and 4 g. of its hydrochloride 22 g. of 4-amino-2-methyl-azobenzene; crystallized from benzene-light petroleum; m. p. 76°[13] (22 g. 4-amino-3-methylazobenzene, from the same solvent, m. p. 101°[14]). For the preparation of 4-amino-3-methoxyazobenzene, the classical method proved preferable, but gave also poor results: from 7.6 g. of aniline, diazotized as usual, and 10 g. of *o*-anisidine, a dye-stuff hydrochloride was obtained, which, after the above treatment with ammonia and recrystallization from benzene-light petroleum, gave 4.5 g. of the desired dyestuff, m. p. 110°.[15]

Acylation Experiments. Method No. 1.—Trichloroacetyl derivative of 4'-carbethoxy-benzene-(1'-azo-1)-naphthylamine-(2): to 6.2 g. of the dyestuff dissolved in a mixture of 50 cc. of anhydrous chloroform and 1.6 g. of anhydrous pyridine at 0°, was added slowly 1.6 g. of trichloroacetyl chloride dissolved in 25 cc. of chloroform. After twelve hours of standing, the reaction product was collected and recrystallized from glacial acetic acid as orange-red needles, m. p. 206°. Owing to the variations in solubility, sometimes a part of the solvent had to be distilled off before the reaction product was collected (III, VIII, XXVIII, XXVII) or the solution had even to be brought to dryness (IV, X, XVIII, XIX, XX, XXI,[16] XXII, XXVI). In these cases, it is preferable to remove the pyridine hydrochloride formed by washing with dilute sulfuric acid and water and to dry before removing the solvent.

Method No. 2.—Trichloroacetyl derivative (XXIX) of 2-amino-naphthalene-(1-azo-1')-benzene-4-carbonamide: 5.8 g. of the dyestuff was dissolved in 100 cc. of benzene and after addition of 4 g. of trichloroacetyl chloride and 2.6 g. of anhydrous potassium carbonate boiled for four hours. The boiling solution was filtered, evaporated *in vacuo* and the residue washed with water and after drying recrystallized from glacial acetic acid, m. p. 230° (decomposition); crimson-red needles. In some cases the condensation product crystallizes from the filtered solution, on cooling (XVII).

(9) Troeger and Schaefer, *J. prakt. Chem.*, [2] **113**, 268 (1926); Troeger and Bertram, *ibid.*, [2] **114**, 269 (1926).

(10) Briefly described by Woroshzow, *Ann. chim.*, [9], **7**, 91 (1917); O. Fischer, *J. prakt. Chem.*, [2] **107**, 34 (1924); Beilstein, Supplementary Volume XVI, p. 333.

(11) Beilstein and Reichenbach, *Ann.*, **132**, 144 (1864).

(12) K. H. Meyer, *Ber.*, **54**, 2273 (1921).

(13) Mehner, *J. prakt. Chem.*, [2] **65**, 407 (1902).

(14) Mehner, *ibid.*, [2] **65**, 420 (1902). There the m. p. is stated to be 118–119°.

(15) Jacobson and Hoenigsberger, *Ber.*, **36**, 4096 (1903).

(16) Here it was preferable to boil the solution for two hours.

Finally, the new acyl derivatives, which have not been included in the two tables, will be briefly described here.

N-Trichloroacetyl-2'-chlorobenzene-(1'-azo-4)-naphthylamine-(1).—The mixture of 28.1 g. of the dye-stuff

TABLE I

N-ACYL-4-(BENZENE-AZO)-NAPHTHYLAMINES-(1)

	Acyl	Method of prepn.[b]	Recrystallized from	Remarks	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	Acetyl	Ac_2O[c]	Alc.	Orange-red ndls.	241	$C_{18}H_{15}ON_3$	74.7	74.6	5.2	5.1
II	Chloroacetyl	2	BuOH, EtOH	Orange-brown ndls.	221	$C_{18}H_{14}ON_3Cl$	66.9	67.1	4.3	4.5
III	Dichloroacetyl	1	HAc, BuOH	Brown-yel. ndls.	214	$C_{18}H_{13}ON_3Cl_2$	60.5	61.1	3.6	4.1
IV	Trichloroacetyl	1, 2	Alc., ligroin	Dark-red rhomb., in air lt.-br. powder	153.5	$C_{18}H_{12}ON_3Cl_3$	55.2	55.1 55.3	3.0	3.9 3.9
V	Trichloroacroyl	2	BuOH	Brick red	143–144	$C_{19}H_{12}ON_3Cl_3$	56.4	57.2	3.0	2.8
VI	Undecanoyl	1	Alc.	Dark-red; br.-red powder	150	$C_{27}H_{33}ON_3$	78.0	77.6	7.9	7.0
VII	Undecenoyl	1	Bz., lt. petr.	Orange-red ndls.	84	$C_{27}H_{31}ON_3$[h]	78.4	78.5	7.5	6.8
VIII	Dibromoundecanoyl	1	Alc.		111–112	$C_{27}H_{31}ON_3Br_2$	56.5	56.3 56.7	5.4	4.9 4.8
IX	Cinnamoyl	2	BuOH	Orange-yel.	236–237	$C_{25}H_{19}ON_3$	79.6	79.6	5.0	5.0
X	Phenylpropioloyl	1	BuOH	Orange-yel. ndls.	221	$C_{25}H_{17}ON_3$[i]	80.0	79.5	4.5	4.9
XI	*trans*-α,β-Dibromocinnamoyl	1	BuOH	Orange-brown	215	$C_{25}H_{17}ON_3Br_2$[j]	56.1	55.9	3.2	3.2
XII	Phthaloyl[a]	Melt[d]	BuOH	Orange ndls.	224–225	$C_{24}H_{15}O_2N_3$	76.4	76.1	4.0	4.8
XIII	Tetrachlorophthaloyl[a]	Melt[e]	Bromobz.		296	$C_{24}H_{11}O_2N_3Cl_4$	56.1	55.6	2.1	2.0
XIV	Toluenesulfonyl	1[f]	Alc., Bz.	Orange-red ndls.	209	$C_{23}H_{19}O_2N_3S$	68.8	69.4	4.7	4.7
XV	Acetylsulfaniloyl-	1[g]	PrOH	Yel.-brown	270	$C_{24}H_{20}O_3N_4S$	64.9	4.5	6.43	4.7

[a] The products obtained were the N-substituted phthalimides. [b] For the significance of the figures see experimental part. [c] The dye was boiled for 1 hour with three times its weight acetic anhydride; the acetyl derivative crystallized spontaneously. [d] From equivalent amounts of the azo-dye and the anhydride; 3 hours at 120°. [e] From equivalent amounts of the azo-dye and the anhydride; 1 hour at 100°, then 2 hours at 130°. [f] Here benzene was used instead of chloroform. [g] Here acetone was used instead of chloroform, and the reaction product isolated by diluting with ice-water. [h] N, calcd. 10.2, found 10.7. [i] N, calcd. 11.2, found 11.3. [j] N, calcd. 7.8, found 7.7.

TABLE II

DERIVATIVES OF 1-BENZENE-AZO-2-NAPHTHYLAMINE

Number	Diazotized amine[a]	Acyl residue	Method of prepn.[b]	Recrystallized from	Remarks	Formula	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XVa	Aniline	Dichloroacetyl	1	BuOH	Brown-yel.	$C_{18}H_{13}ON_3Cl_2$	214	60.5	61.7	3.6	4.1	..	..
XVI	Aniline	Trichloroacetyl	2	Alc.	Lt.-red ndls.	$C_{18}H_{12}ON_3Cl_3$	130	55.2	54.9	3.1	3.1	..	..
XVII	Aniline	Trichloroacroyl	2	Gl. HAc	Dark-red, violet-blue luster—in air, brown powder	$C_{19}H_{12}ON_3Cl_3$	174	56.4	56.6	3.0	2.8	..	..
XVIII	Aniline	Undecenoyl	1	Alc.; benzine	Orange-red ndls.	$C_{27}H_{31}ON_3$	82–84	78.4	78.4	7.5	7.7	10.1	10.0
XIX	Aniline	Undecanoyl	1	Alc.	Orange-red ndls.	$C_{27}H_{33}ON_3$	98	78.0	77.8	7.9	8.3	10.1	10.2
XX	Aniline	Phenylpropioloyl	1	*i*-PrOH	Orange-red ndls.	$C_{25}H_{17}ON_3$	170	80.0	80.1	4.5	4.8	..	..
XXI	Aniline	Acetylsulfaniloyl	1	BuOH		$C_{24}H_{20}O_3N_4S$	206–207	64.9	64.8	4.5	4.5	12.6	12.9
XXII	*o*-Chloroaniline	Trichloroacetyl	1	Bz.+light petr.[c]	Needles	$C_{18}H_{11}ON_3Cl_4$	171	50.8	49.3	2.6	2.4	..	..
XXIII	*p*-Aminobenzoic acid	Trichloroacetyl	Na salt + acid chloride[d]	BuAc	Needles	$C_{19}H_{12}O_3N_3Cl_3$	246	52.4	53.0	2.8	3.0	9.7	9.7
XXIV	Ethyl *p*-aminobenzoate	Undecenoyl	1	MeOH	Orange-red	$C_{30}H_{35}O_3N_3$	106	74.2	74.2	7.2	7.1	8.7	8.8
XXV	Ethyl *p*-aminobenzoate	Undecanoyl	1	Alc., PrOH		$C_{30}H_{37}O_3N_3$	110–111	73.9	73.5	7.7	8.0	8.6	9.3
XXVI	Ethyl *p*-aminobenzoate	Dibromoundecanoyl	1	PrOH		$C_{30}H_{35}O_3N_3Br_2$	124	55.8	55.5	5.4	5.7	6.5	6.5
XXVII	Ethyl *p*-aminobenzoate	Trichloroacetyl	1	Gl. HAc, BuOH	Red ndls.	$C_{21}H_{16}O_3N_3Cl_3$	206	54.4	53.2	3.5	3.4	..	..
XXVIII	Ethyl *p*-aminobenzoate	Trichloroacroyl	1	Bz., BuOH	Orange-red ndls.	$C_{22}H_{16}O_3N_3Cl_3$	193	55.6	55.8	3.4	3.6	8.8	9.2
XXIX	*p*-Aminobenzamide	Trichloroacetyl	2	Gl. HAc	Crimson-red ndls.	$C_{19}H_{13}O_2N_4Cl_3$	230 dec.	52.4	51.9	3.0	3.6	..	..

[a] Coupled with β-naphthylamine. [b] For the significance of the figures, see Experimental Part. [c] From butyl alcohol, a solvate, m. p. 133°, was obtained. [d] 30 g. of the sodium salt of the azo-dye and 20 g. of trichloroacetyl chloride were boiled in 200 cc. of xylene for two hours. The reaction product was filtered, washed with cold water, dried and recrystallized as indicated.

in 100 cc. of chloroform and 8 cc. of pyridine, and 18 g. of trichloroacetyl chloride in 50 cc. of chloroform was heated, after twelve hours of standing, for one hour on the water-bath. A small precipitate of the dyestuff hydrochloride[17] was rejected, the solution evaporated after the treatment suggested above and the residue triturated with alcohol and recrystallized from the same solvent as brown-violet needles, m. p. 125°.

Anal. Calcd. for $C_{15}H_{11}ON_3Cl_4$: C, 50.8; H, 2.6. Found: C, 50.3; H, 2.8.

N-Trichloroacetyl-4'-chlorobenzene-(1'-azo-4)-naphthylamine-(1).—Exactly the same procedure gave the desired product, which, after recrystallization from glacial acetic acid and from butyl alcohol, melted at 184°.

Anal. Calcd. for $C_{18}H_{11}ON_3Cl_4$: C, 50.8; H, 2.6. Found: C, 50.8; H, 2.2.

N-Trichloroacetyl-4'-carbethoxybenzene-(1'-azo-4)-naphthylamine-(1).—Sixteen grams of the dyestuff in 200 cc. of chloroform containing 6 g. of pyridine was treated at ice temperature with 6 g. of trichloroacetyl chloride in 50 cc. of chloroform. The chloroform solution was washed with water, evaporated and the reaction product was collected and recrystallized from acetic acid or butyl alcohol as orange-red leaflets, m. p. 149°.

Anal. Calcd. for $C_{21}H_{16}O_3N_3Cl_3$: C, 54.6; H, 3.5. Found: C, 53.9; H, 3.42.

N-Undecenoyl-4'-carbethoxy-(1'-azo-4)-naphthylamine-(1).—Method no. 1 was applied, as usual. The reaction product crystallized spontaneously and formed withering, orange-red crystals, after recrystallization from alcohol, m. p. 164–165°.

Anal. Calcd. for $C_{30}H_{35}O_3N_3$: C, 74.2; H, 7.2; N, 8.7. Found: C, 75.0; H, 7.9; N, 8.8.

N-Trichloroacetyl-4-aminoazobenzene.—Method no. 1: the small precipitate formed was 4-aminoazobenzene hydrochloride; the reaction product was obtained by evaporation of the (washed and dried) solution; from alcohol, brown crystals, m. p. 149°; yield, 10.5 g. from 0.1 mole of the components.

(17) With strongly basic dyestuffs, such hydrochlorides form sometimes even in presence of pyridine.

Anal. Calcd. for $C_{14}H_{10}ON_3Cl_3$: C, 49.3; H, 3.0. Found: C, 48.8; H, 2.8.

Analogously, the **N-trichloroacetyl derivative** was obtained of **4-amino-2-methylazobenzene,** orange-red crystals from alcohol, m. p. 137°; yield, 6 g. from 0.05 mole of the components (*Anal.* Calcd. for $C_{15}H_{12}ON_3Cl_3$: C, 50.7; H, 3.4. Found: C, 49.9; H, 3.6) and of **4-amino-3-methoxyazobenzene,** brown needles from alcohol, m. p. 132°; yield, 2.5 g. from 0.02 mole of the components (*Anal.* Calcd. for $C_{15}H_{12}O_2N_3Cl_3$: C, 48.5; H, 3.2. Found: C, 48.3; H, 3.7). In all these cases, the trichloroacetyl compounds were soluble in chloroform.

De-acetylation Experiments with the Acetylsulfaniloyl Derivatives XV and XXI.—While we found no method to deacetylate the acetylsulfaniloyl compound of 4-(benzene-azo)-naphthylamine-(1), the original azo-dye being the sole product of the reaction,[18] the isomer 1-(benzene-azo)-naphthylamine-(2) derivative was converted into **N-sulfaniloyl-1-(benzene-azo)-naphthylamine-(2)** in the following way. It was boiled (2 g.) for two hours with 40 cc. of 15% alcoholic hydrochloric acid; the solution was evaporated *in vacuo,* and the residue treated with alcoholic ammonia solution and recrystallized from glacial acetic acid as dark-red needles, m. p. 221–222°.

Anal. Calcd. for $C_{22}H_{18}O_2N_4S$: C, 65.7; H, 4.4. Found: C, 64.9; H, 4.2.

Summary

Fifteen acyl derivatives of 4-(benzene-azo)-naphthylamine-1 have been described. As the N-trichloro-acetyl derivative showed a slight curative effect on tuberculosis and leprosy, its molecular structure has been systematically varied and the activity of the new products tested. Twenty-four new acyl derivatives of twelve azo-dyes have been prepared for this purpose.

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(18) Similar observations have been made recently by Fosbinder and Walter, THIS JOURNAL, **61**, 2032 (1939), and by Winterbottom, *ibid.*, **62**, 160 (1940).