chloride to make the solution acidic to congo red paper. The yields were determined largely by the recovery which each recrystallization solvent permitted, as the condensation reaction itself was almost quantitative.

One derivative was prepared by using 2-hydroxy-3-diethylaminopropylamine as the side-chain.

Whenever the dihydrochloride was obtained as a hydrate, a sample of the anhydrous form (very hygroscopic) was prepared for characterization by heating the hydrate at 140°, or by recrystallizing it from an inert solvent containing thionyl chloride.

12-(3'-Diethylaminopropylamino)-benz[a]acridine Dihydrochloride.—This compound was prepared in a manner analogous to the procedure used for the corresponding benz[c]acridine derivatives. The yield after two recrystallizations from propanol–dibutyl ether was 31% of very small, yellow needles, m. p. 250–252° by the instantaneous method.

Anal. Calcd. for $C_{24}H_{29}N_3Cl_2$: C, 66.97; H, 6.79. Found: C, 67.06, 67.15; H, 6.75, 6.82.

Summary

A series of dialkylaminoalkylaminobenzacridines has been prepared for testing as antimalarials.

LAFAYETTE, INDIANA RECEIVED MARCH 30, 1946

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. The Preparation of Certain Derivatives of Sulfanilamide[1]

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Conflicting reports on the value of sulfanilamide in the treatment of malaria are to be found in the earlier literature; a review of some of these papers has been made by Sinton,[2] whose work indicated that sulfanilamide itself was of no value in human malaria, of little or no value in avian malaria, but did, however, have a definite effect upon *P. Knowlesi* in monkeys. Walker and Van Dyke[3] have shown that sulfathiazole, sulfadiazine and sulfanilamide, in this order, are effective against *P. lophurae* in ducklings. Coggeshall[4] and co-workers, employing sulfadiazine, showed it to be effective against all forms of human malaria.

When it thus became apparent that the sulfa drugs were effective against malaria, and when it appeared[5] that sulfadiazine was a causal prophylactic in avian malaria, investigations were undertaken with the object of finding a more active drug which might act as a causal prophylactic in man.

The present paper describes the preparation of twenty-two drugs which were synthesized for this purpose. Data concerning the activity of the compounds will be found elsewhere.[6]

The sulfanilamide derivatives were prepared by coupling N-acetylsulfanilyl chloride with the appropriate amine or amine salt, followed by hydrolysis, in some cases with acid and in others with base, to remove the acetyl group. The amines in some instances are known compounds, and were prepared by methods reported in the literature or were obtained from stock. In many instances the precursor of the desired amine was prepared by a known series of reactions, and this compound was converted to the desired amine by an appropriate method. In a few cases neither the amine nor any of its immediate precursors are reported in the literature, and methods of synthesis were devised for these compounds.

The coupling was carried out in pyridine solution at temperatures varying from 60 to 100°, and for times ranging from one to four hours in all cases except that of 3-chloro-4-dimethylaminosulfanilanilide (SN-5069). In this instance 2-chloro-N^1,N^1-dimethyl-*p*-phenylenediamine in ether solution was stirred and refluxed with N-acetylsulfanilyl chloride in the presence of anhydrous sodium carbonate for one and one-half hours. Coupling in pyridine was not used in this case because all attempts to isolate the free amine resulted in extensive decomposition; the reduction mixture from 2-chloro-4-nitro-N,N-dimethylaniline, therefore, was coupled directly with N-acetylsulfanilyl chloride as described above without isolating the 2-chloro-N^1,N^1-dimethyl-*p*-phenylenediamine.

N^1-(2-Hydroxy-3-camphanyl)-sulfanilamide was prepared by a Meerwein–Ponndorf reduction of α-(N-acetylsulfanilamido)-camphor, followed by acid hydrolysis. The α-(N-acetylsulfanilamido)-camphor was prepared in the usual manner by coupling α-aminocamphor with N-acetylsulfanilyl chloride in pyridine.

p-Aminobenzenesulfinic acid was prepared by the standard method[7,8] starting with N-acetylsulfanilyl chloride.

(1) This work was carried out under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Maryland.

(2) Sinton, Hutton and Shute, *Ann. Trop. Med.*, **33**, 37–44 (1939).

(3) Walker and Van Dyke, *Proc. Soc. Exptl. Biol. Med.*, **48**, 368 (1941); *C. A.*, **35**, 567 (1942).

(4) Coggeshall, Maier and Best, *J. Am. Med. Assoc.*, **117**, 1077 (1941).

(5) "Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, editor, Chapter V, in press.

(6) "Antimalarial Drugs, 1941–1945," published by the Survey of Antimalarial Drugs, in press. Drugs described herein are identified by the SN number used in this monograph.

(7) Smiles and Bere, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., p. 7.

(8) Tensen and Linquist, *Dansk. Tids. Farm.*, **14**, 129 (1940); *C. A.*, **35**, 3987 (1941).

Experimental

2,6-Dibromo-4-*t*-butylaniline.—Forty-three grams of bromine (14 ml., 0.27 mole) was added dropwise at room temperature to a stirred solution of 58 g. of 2-bromo-4-*t*-butylaniline[9] (0.26 mole) in 400 ml. of glacial acetic acid containing 10 ml. of water. Stirring was continued at room temperature for an hour after the addition of bromine was complete. The mixture was poured into water, the excess bromine was destroyed with sodium bisulfite, and the mixture was extracted with benzene. The benzene extracts were washed with sodium bicarbonate solution until neutral, dried and the benzene was distilled. The residue was fractionated at reduced pressure to give 66 g. (83%) of 2,6-dibromo-4-*t*-butylaniline, b. p. 136–140° (2 mm.). A portion of the amine was converted to the hydrochloride. *Anal.* Calcd. for $C_{10}H_{14}NBr_2Cl$: Cl, 10.32. Found: Cl, 10.40.

2,6-Dibromo-4-*t*-amylaniline.—Eighty-seven grams of 4-*t*-amylaniline (Eastman Kodak Co.) (0.53 mole) dissolved in 250 ml. of glacial acetic acid containing 5 ml. of water, was brominated at 30–40° by dropwise addition of 171 g. of bromine (55 ml., 1.07 moles). Stirring was continued for twenty minutes after all the bromine had been added. The reaction mixture was poured into water, excess bromine was removed with sodium bisulfite and the mixture was then made basic with sodium hydroxide. The amine was extracted with benzene and washed with water. The extracts were dried, the benzene was distilled and the residue was subjected to steam distillation to remove the unbrominated and monobrominated amines (the dibromoamine does not distil with steam). The residue was extracted with ether, the extracts dried and the ether distilled. The residue was fractionated at reduced pressure to give 136 g. (79%) of 2,6-dibromo-4-*t*-amylaniline, b. p. 138–140° (0.5 mm.).

3-Trifluoromethylaniline.[10]—About 185 g. of 3-nitrobenzotrifluoride[11,12] (0.97 mole) was dissolved in enough ethanol to make a liter of solution. The solution was placed in a high-pressure hydrogenation bomb, 13 cc. of moist Raney nickel added, and the material reduced under 4000 p. s. i. pressure of hydrogen. The temperature rose to about 55° during the reaction. The mixture was filtered, the alcohol distilled, and the residue fractionated at reduced pressure to give 115 g. (74%) of 3-trifluoromethylaniline, b. p. 74–75° (10 mm.).

4-Nitrobenzotrifluoride.[13]—The method of Booth[12] for the preparation of substituted benzotrifluorides was adapted to the preparation of this compound. In a 125-ml. Claisen flask, fitted with a 115-ml. distilling flask as a receiver, were placed 60 g. of dry 4-nitrobenzotribromide[14] (0.20 mole) and 60 g. of sublimed antimony trifluoride (0.31 mole). The pressure was reduced to 30 mm. (water pump) and the flask was heated to 100° until the foaming ceased. The 4-nitrobenzotrifluoride was distilled from the reaction mixture by raising the bath temperature. This distillate was redistilled to give 27 g. (90%) of product, b. p. 121° (50 mm.).

4-Trifluoromethylaniline.[15]—Nineteen grams of 4-nitrobenzotrifluoride (0.1 mole) was dissolved in 50 ml. of ethanol and reduced in a low pressure Parr hydrogenator in the presence of Raney nickel. After hydrogenation was complete the mixture was filtered, and the alcohol was distilled. The residue was fractionated at reduced pressure to give 14 g. (80%) of 4-trifluoromethylaniline, b. p. 117° (40 mm.).

1-Nitro-3,5-di-(trifluoromethyl)-benzene[16] **and 1-Nitro-2,5-di-(trifluoromethyl)-benzene.**—In a flask equipped with a reflux condenser, a stirrer, and an addition funnel, was placed 299 g. of a mixture of *m*-di-(trifluoromethyl)-benzene and *p*-di-(trifluoromethyl)-benzene (1.4 moles).[17] The flask was cooled in an ice-bath and 596 g. of fuming sulfuric acid (30% sulfur trioxide) was added with stirring. To this mixture 358 g. of 100% nitric acid[18] was added, after which the ice-bath was removed and the temperature raised to 105–110° and held there for one hour with stirring. An additional 236 g. of fuming sulfuric acid and 165 g. of 100% nitric acid were then added in this order, and the temperature was raised to 110–120°. Stirring was continued at this temperature for two hours.

The reaction flask was cooled in an ice-bath, and the contents poured into four liters of ice water. The organic layer was drawn off in a separatory funnel, and the aqueous layer was extracted with ether. The organic layer and the extracts were combined and dried, the ether was removed, and the residual oil was distilled at reduced pressure to give 212 g. (58%) of a mixture of the two nitro compounds, b. p. 87–89° (18 mm.).

3,5-Di-(trifluoromethyl)-aniline[19] **and 2,5-Di-(trifluoromethyl)-aniline.**—The mixture of the two isomeric nitro compounds was reduced in small batches with hydrogen in the presence of Adams platinum catalyst.[20]

In a typical run 50 g. of the mixture of 1-nitro-3,5-di-(trifluoromethyl)-benzene and 1-nitro-2,5-di-(trifluoromethyl)-benzene (0.2 mole) was dissolved in 125 ml. of warm glacial acetic acid and added to 0.5 g. of catalyst which had been previously reduced in glacial acetic acid. The mixture was reduced in a low pressure Parr hydrogenator.

After the reduction was complete and the mixture had been filtered, the products of the several reductions (from a total of 157 g. of the isomeric nitro compounds) were combined and poured into a liter of cold water. The organic layer was separated, and the aqueous layer was neutralized and extracted with ether. The organic layer and ether extracts were combined and dried, the ether was removed, and the residue was distilled at reduced pressure to give 100 g. (68%) of a mixture of 3,5-di-(trifluoromethyl)-aniline and 2,5-di-(trifluoromethyl)-aniline, b. p. 78.5–79.5° (18 mm.).

3,5-Di-(trifluoromethyl)-aniline Hydrochloride.—In an Erlenmeyer flask was placed 100 g. of the mixture of 3,5-di-(trifluoromethyl)-aniline and 2,5-di-(trifluoromethyl)-aniline (0.46 mole). Sixty-one grams of acetic anhydride (0.60 mole) was then added in small portions with shaking. The acetyl derivatives crystallized immediately. After the reaction mixture had stood for one hour, it was poured into 400 ml. of cold water. The product was filtered and recrystallized from ethanol–water, which removed most of the color. The material was then dissolved in 250 ml.

(9) Gelzer, *Ber.*, **21**, 2941 (1888).

(10) This amine was prepared by Swarts (see ref. 11) by reduction of the corresponding nitro compound with zinc chloride and hydrochloric acid and by Booth (see ref. 12) by reduction of the nitro compound with tin and hydrochloric acid.

(11) Swarts, *Bull. acad. roy. sci. Belg.*, (3) **35**, 388 (1898).

(12) Booth, Elsey and Burchfield, THIS JOURNAL, **57**, 2066 (1935).

(13) This compound was prepared previously in small yields by Rouche, *Bull. Acad. roy. sci. Belg.*, **13**, 346 (1927); *C. A.*, **22**, 2149 (1928) and by H. Heyna, I. G. Farbenindustrie A.-G.: German Patent 637,318 (Oct. 27, 1936); *C. A.*, **31**, 706 (1937) by nitration of 3-acetaminobenzotrifluoride, followed by diazotization of the 3-amino-4-nitrobenzotrifluoride isomer and removal of the diazo group.

(14) Fisher, THIS JOURNAL, **56**, 2469 (1934).

(15) This amine was prepared previously by Heyna (see ref. 13) by reduction of the corresponding nitro compound with an unspecified reducing agent.

(16) This compound was prepared previously (I. G. Farbenindustrie A.-G., French Patent 745,293 (May 8, 1933); *C. A.*, **27**, P. 4414 (1933)) (see also ref. 46), but the directions for the nitration are not given in any detail in the patents.

(17) The starting material, a mixture of 60% *m*-di-(trifluoromethyl)-benzene and 40% *p*-di-(trifluoromethyl)-benzene, was obtained from Hooker Electrochemical Co., Niagara Falls, N. Y.

(18) The nitric acid was prepared from sodium nitrate and concd. sulfuric acid. The nitric acid, formed by warming this mixture in a flask equipped with a short column, was distilled at reduced pressure.

(19) This amine was prepared previously (see ref. 16 and 46) by reduction of the corresponding nitro compound with an unspecified reducing agent.

(20) Raney nickel catalyst was also tried, but was found unsatisfactory, since the reaction stopped with the formation of insoluble intermediate reduction products.

TABLE I

Compound	SN	Method of condensation: Medium[a]	Temp., °C.	Time, hr.	Hyd.[b]	Yield, %	M. p., °C.[c]	Composition, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Sulfanilamide derivatives											
N¹-(5-Chloro-4,6-dimethyl-2-pyrimidyl)-	6887	P	60–70	2	B	47	226 – 228	46.08	46.29	4.19	4.38
N¹-(5-Bromo-1-naphthyl)-	7157	P	70	2.5	A	75	116 – 117	50.95	50.67	3.44	3.50
N¹-(4-Bromo-1-naphthyl)-	7158	P	60	1	B	55	205 – 206		[e]		
N¹-(1-Bromo-2-naphthyl)-	7313	P	60	1	A	21	183 – 185		[f]		
N¹-(1-6-Dibromo-2-naphthyl)-	7771	P	60	1.5	A	64	206 – 206.5	42.14	42.15	2.65	3.37
N¹-(α-Camphoryl)-	8304	P	60–65	2	A	60	163 – 165	59.63	59.55	6.83	6.94
N¹-(2-Hydroxy-3-camphanyl)-	8350	[g]			A	71	158 – 159	59.25	59.30	7.46	7.49
N¹-(5-Quinolyl)-	8412	P	60–70	3	A	36	230 – 231	60.20	60.35	4.34	4.70
Sulfanilanilide derivatives											
Sulfanilanilide	276	P	60–70	2	A	53	197 – 198		[d]		
4′-Amino-3′,5′-dichloro-	4269	P	85–90	1	A	62	172 – 173	43.38	43.61	3.33	3.43
3′-Chloro-4′-dimethylamino-	5069	C	35	1.5	A	24	101 – 103.5	51.61	51.51	4.95	5.18
4′-*t*-Butyl-	5367	P	70–80	1	A	54	184 – 185	63.16	63.56	6.58	6.67
2′,6′-Dichloro-	5369	P	60–70	2	B	25	195 – 196	45.43	45.66	3.15	3.22
4′-*t*-Amyl-	5370	P	60–70	1	B	60	104 – 106	64.11	64.42	6.96	6.96
3′,5′-Dichloro-4′-dimethylamino-	5726	P	100	1	A	65	161 – 162	46.67	46.41	4.17	4.23
3′-Bromo-4′-*t*-butyl	6933	P	70–80	2	A	52	140.5–141	50.13	50.52	5.00	5.08
2′,6′-Dibromo-	7268	P	60–70	4	B	9	204 – 205	35.47	35.74	2.46	2.75
4′-*t*-Amyl-2′,6′-dibromo-	8507	P	60–70	3	B	10	237 – 239	42.88	42.80	4.23	3.86
4′-*t*-Butyl-2′,6′-dibromo-	8683	P	60	4	B	11	227 – 228	41.56	41.61	3.92	3.92
Other types											
α-Trifluorosulfanilo-*m*-toluide	6934	P	60		A	19	116.5–117.5	49.36	49.29	3.51	3.53
α-Trifluorosulfanilo-*p*-toluide	7600	P	60	2	A	49	172 – 172.5	49.36	49.30	3.51	3.58
α^3,α^5-bis-(Trifluoro)-sulfanilo-3,5-xylide	7722	P	60	1	A	51	168.5–169	43.6	43.7	2.86	2.82

[a] The couplings were run either in pyridine (P) or in ether in the presence of sodium carbonate (C). [b] The acetyl compound was hydrolyzed either with boiling dilute acid (A) or base (B). [c] Melting points are corrected. [d] Known compound; not analyzed. [e] The hydrochloride was analyzed for ionic halogen: calcd.: Cl, 8.58%; found: Cl, 8.58%. [f] Hydrochloride analyzed: calcd.: Cl, 8.58%; found, Cl, 8.53%. [g] The acetyl derivative of this compound was not made by a coupling, but by a Meerwein–Ponndorf reduction of the acetyl derivative of SN-8304.

of hot ethanol and allowed to crystallize very slowly.[21] A crop of crystals weighing 33 g. and melting at 156.5–157.5° was obtained. From the mother liquor by slow crystallization another crop of 8 g. of crystals was obtained, m. p. 156.2–157.2°. It was assumed that this material was 1-acetamino-3,5-di-(trifluoromethyl)-benzene.

The 41 g. of 1-acetamino-3,5-di-(trifluoromethyl)-benzene (0.15 mole) was refluxed with 25 ml. of concd. hydrochloric acid, 25 ml. of water, and 100 ml. of ethanol for three hours. The alcohol was distilled and 50 ml. of water was added. The 3,5-di-(trifluoromethyl)-aniline hydrochloride which precipitated was filtered and dried. It weighed 33 g. (83% based on the amount of acetyl derivative taken). *Anal.* Calcd. for $C_8H_6NF_6Cl$: Cl, 13.39. Found: Cl, 13.46. A small sample of the hydrochloride was converted to the free amine, m. p. 168.2–169.2°.

2,6-Dichloro-*p*-phenylenediamine.[22]—A solution of 20.7 g. of 2,6-dichloro-4-nitroaniline (Eastman) (0.10 mole) in 150 ml. of ethanol was reduced in a low pressure Parr hydrogenator in the presence of Raney nickel. After the mixture had been filtered, water was added to the alcoholic solution of the amine. Fine needles of the product separated, m. p. 124–125°; wt. 15 g. (85%).

2-Chloro-4-nitro-N,N-dimethylaniline.[23]—Eighty-one grams of 4-nitro-N,N-dimethylaniline[24] (0.5 mole) dissolved in 125 ml. of glacial acetic acid and 250 ml. of concentrated hydrochloric acid was placed in a flask equipped with a stirrer, a gas inlet tube and a gas outlet tube leading to a trap. Chlorine gas was introduced over the surface of the vigorously stirred mixture until the theoretical amount of chlorine for the monochloro derivative had been absorbed. The reaction mixture was poured over cracked ice and neutralized with sodium hydroxide solution, keeping the temperature below 10°. The resulting solid was washed with water and recrystallized from ethanol to a constant melting point of 76–77°. Eighty grams (82%) was obtained.

2-Chloro-N¹,N¹-dimethyl-*p*-phenylenediamine.[25]—Fifteen grams of 2-chloro-4-nitro-N,N-dimethylaniline (0.075 mole) was dissolved in the minimum amount of

(21) Slow crystallization from alcohol allows the separation of the desired meta isomer, which should be less soluble in view of physical considerations. It is also very likely that most of the decomposition during the nitration is at the expense of the para isomer.

(22) This amine was prepared previously by Witt, *Ber.*, **8**, 145 (1875), by reduction of the corresponding nitro compound with zinc and hydrochloric acid, and by Morgan, *J. Chem. Soc.*, **113**, 594 (1918), by reduction of the nitro compound with zinc dust and ammonium chloride.

(23) This compound was prepared by Weber, *Ber.*, **10**, 761 (1877), and by Ayling, Garvin and Hinkel, *J. Chem. Soc.*, 755 (1942), by chlorination of 4-nitro-N,N-dimethylaniline in chloroform solution at room temperature.

(24) This compound is available commercially, but was prepared by the reaction between 4-chloronitrobenzene and anhydrous dimethylamine at 170° for two hours in a steel bomb (see ref. 26).

(25) This compound was prepared previously by van Duin, *Rec. trav. chim.*, **51**, 878 (1932); *C. A.*, **26**, 5550 (1932), and by Ayling (see ref. 23) by reduction of the corresponding nitro compound with stannous chloride.

diethyl ether and reduced in a low pressure Parr hydrogenator in the presence of Raney nickel. The amine was not isolated since all attempts to do so resulted in decomposition. Instead the ether solution of the amine, after removal of the catalyst, was coupled directly with N-acetylsulfanilyl chloride.

2,6-Dichloro-4-nitro-N,N-dimethylaniline.—The method of Mills[26] was adapted to the preparation of this compound. Ninety-five grams of 3,5-dichloro-4-bromonitrobenzene[27] (0.35 mole) was dissolved in 500 ml. of ethanol and placed in a steel bomb with 38 g. of anhydrous dimethylamine (0.84 mole). The mixture was heated at 200° with shaking for two hours. After cooling, the product was removed from the bomb and recrystallized from ethanol to give 58 g. (70%) of 2,6-dichloro-4-nitro-N,N-dimethylaniline, m. p. 104–105°.

2,6-Dichloro-N^1,N^1-dimethyl-*p*-phenylenediamine.[28]—A solution of 15 g. of 2,6-dichloro-4-nitro-N,N-dimethylaniline (0.065 mole) in 150 ml. of ethanol was reduced in a low pressure Parr hydrogenator in the presence of Raney nickel. After reduction was complete, the solution was filtered into ice water. The precipitate was recrystallized from ethanol to give 8.7 g. (67%), of 2,6-dichloro-N^1,N^1-dimethyl-*p*-phenylenediamine, m. p. 87–88°.

2-Amino-5-chloro-4,6-dimethylpyrimidine.—Ten grams of 2-amino-4,6-dimethylpyrimidine.[29] (0.0814 mole) was dissolved in hot water (a few ml. of ethanol was added to cause solution), and the solution was cooled to 0–10°. To this was added dropwise a solution of 18 g. of chlorine (0.245 mole) in ice water. A white precipitate began to form after about one-fourth of the aqueous chlorine had been added. The precipitate, believed to be a perchloride, was filtered, washed and suspended in 1500 ml. of water. Sulfur dioxide was passed through the suspension until the precipitate dissolved. The solution was concentrated by evaporation at reduced pressure to about 80 ml., and the free amine was precipitated by carefully neutralizing the solution at 0–10° with ammonium hydroxide. The yield of 2-amino-5-chloro-4,6-dimethylpyrimidine, m. p. 182–184°, was 10.9 g. (85%). *Anal.* Calcd. for $C_6H_8N_3Cl$: C, 45.72; H, 5.12. Found: C, 45.76; H, 4.98.

5-Bromo-1-naphthylamine.[30]—A solution of 25.4 g. of 5-bromo-1-nitronaphthalene[31,32] (0.114 mole) in 120 ml. of hot benzene was reduced in a low-pressure Parr hydrogenator in the presence of Raney nickel. After the reduction was complete the catalyst was removed, the solution was placed in a flask, and a slow stream of hydrogen bromide was blown over the surface of the liquid with vigorous stirring until an excess of hydrogen bromide was present. The precipitated hydrobromide was filtered and washed with anhydrous ether. There was obtained 25.7 g. (84%) of 5-bromo-1-naphthylamine hydrobromide.

5-Aminoquinoline.[33]—A solution of 20 g. of 5-nitroquinoline[34,35,36] (0.115 mole) in sufficient methanol to effect solution was refluxed for twenty minutes with 1 cc. of Raney nickel.[37] The catalyst was removed by filtration and the solution was reduced in the presence of fresh Raney nickel in a low pressure Parr hydrogenator. After the reduction was complete, the catalyst was removed and a rapid stream of hydrogen chloride was passed over the surface of the solution with cooling and stirring. The precipitated rust-colored hydrochloride was filtered and washed with anhydrous ether. The yield of 5-aminoquinoline dihydrochloride was 20 g. (80%), m. p. 230–240°.

Preparation of Sulfanilamide Derivatives.—The preparation of 3′-bromo-4′-*t*-butylsulfanilanilide (SN-6933) and N^1-(5-chloro-4,6-dimethyl-2-pyrimidyl)-sulfanilamide (SN-6887) are illustrative of the method of formation of other sulfanilamide derivatives described in this paper. The preparation of these two substances and of 3′-chloro-4′-dimethylaminosulfanilanilide (SN-5069) and N^1-(2-hydroxy-3-camphanyl)-sulfanilamide (SN-8350) are described in detail. As can be seen from the data in Table I, the general method of synthesis of these compounds was to condense N-acetyl-sulfanilyl chloride with the appropriate amine or amine salt in pyridine, a procedure widely reported in the literature[38,39,40,41,42] and to hydrolyze the resulting N^4-acetylsulfanilamide derivative with acid or base, the choice being determined by the nature of the compound.

Nineteen of the twenty-two sulfanilamide derivatives covered by this paper are new compounds; they are listed in Table I. Sulfanilanilide[43,44,45] (SN-276), α^3,α^5-*bis*-(trifluoro)-sulfanilo-3,5-xylide[46] (SN-7722), and N^1-(5-quinolyl)-sulfanilamide (SN-8412)[35,47] have all been prepared previously.

3′-Bromo-4′-*t*-butylsulfanilanilide (SN-6933).—A solution of 15 g. of 3-bromo-4-*t*-butylaniline hydrochloride[48] (0.057 mole) and 14 g. of N-acetyl-sulfanilyl chloride (0.060 mole) (commercial grade, recrystallized from chloroform), in 60 ml. of dry pyridine (analytical reagent grade, refluxed over barium oxide) was warmed at 70–80° for two hours with stirring. The solution was cooled and poured in a thin stream, with stirring, into 200 ml. of ice and water containing 60 ml. of concentrated hydrochloric acid. The precipitate which formed was filtered off and added to 200 ml. of water containing sufficient sodium hydroxide to cause solution of the solid. A few grams of Norit was added, and the solution was stirred and filtered. The 2-bromo-4-acetylsulfanilamido-*t*-butylbenzene was reprecipitated by adding the filtrate dropwise with stirring to 100 ml. of ice and water containing 20 ml. of concentrated hydrochloric acid. The precipitate was filtered and placed in a flask with 200 ml. of ethanol and 100 ml. of concentrated hydrochloric acid. The solution was refluxed for two hours, after which 150 ml. of ethanol was removed by distillation. The residue was diluted to 500

(26) Mills (to Dow Chemical Co.), U. S. Patent 1,935,515 (Nov. 14, 1933); *C. A.*, **28**, P 485 (1934).

(27) Flurscheim and Simon, *J. Chem. Soc.*, **93**, 1481 (1908).

(28) This compound was prepared previously by Ayling (see ref. 23) by chlorination of 2-chloro-4-acetamino-N,N-dimethylaniline in chloroform at room temperature.

(29) Combes and Combes, *Bull. soc. chim.*, (3) **7**, 791 (1892).

(30) This amine was prepared previously by Ullmann, *Ber.*, **35**, 2804 (1902), by reduction of the corresponding nitro compound with stannous chloride (see refs. 31 and 32).

(31) Scheufelin, *Ann.*, **231**, 185 (1885).

(32) McLeish and Campbell, *J. Chem. Soc.*, 1103 (1937).

(33) This amine was prepared previously by Dufton, *ibid.*, **61**, 785 (1892), and also by Dikshoorn (see ref. 34) by reduction of the corresponding nitro compound with stannous chloride, and by Kaufmann, *Ber.*, **50**, 1627 (1917), by reduction of the nitro compound with iron and acetic acid. Fieser (see ref. 36) reduced the nitro compound with hydrogen and Adams platinum, and Winterbottom (see ref. 35) reduced the nitro compound with hydrogen and Raney nickel.

(34) Dikshoorn, *Rec. trav. chim.*, **48**, 147 (1929); *C. A.*, **23**, 1903 (1929).

(35) Winterbottom, THIS JOURNAL, **62**, 160 (1940).

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ml. with water, made basic, warmed with a few grams of Norit and filtered. The filtrate was made neutral, and the resulting precipitate was recrystallized three times from 50% ethanol. There was obtained 11.5 g. (52%) of 3'-bromo-4'-*t*-butylsulfanilanilide, m. p. 140.5–141°. *Anal.* Calcd. for $C_{16}H_{19}N_2O_2SBr$: C, 50.13; H, 5.00. Found: C, 50.52; H, 5.08.

N¹-(5-Chloro-4,6-dimethyl-2-pyrimidyl)-sulfanilamide (SN-6887).—A solution of 14.7 g. of 2-amino-5-chloro-4,6-dimethylpyrimidine (0.093 mole) and 23.0 g. of N-acetylsulfanilyl chloride (0.099 mole) in 40 ml. of dry pyridine was warmed at 60–70° for two hours with stirring. The coupling product, 2-acetylsulfanilamido-5-chloro-4,6-dimethylpyrimidine, was precipitated by pouring the reaction mixture slowly, with stirring, into 200 ml. of ice and water containing 40 ml. of concentrated hydrochloric acid. The precipitate was dissolved in 200 ml. of water containing 4.5 g. of sodium hydroxide, decolorized with Norit, filtered and the acetyl derivative reprecipitated by adding to the filtrate 9 ml. of concentrated hydrochloric acid. The precipitate was filtered, and refluxed for three hours with 10 g. of sodium hydroxide in 180 ml. of water.[49] The hydrolysis mixture was treated with Norit, filtered, and the product precipitated by acidifying the filtrate to *p*H 6. The product was recrystallized from ethanol. There was obtained 16.6 g. (47%) of N¹-(5-chloro-4,6-dimethyl-2-pyrimidyl)-sulfanilamide, m. p. 226–228°. *Anal.* Calcd. for $C_{12}H_{13}N_4O_2SCl$: C, 46.08; H, 4.19; Cl, 11.33. Found: C, 46.29; H, 4.38; Cl, 11.53.

3'-Chloro-4'-dimethylaminosulfanilanilide (SN-5069).—The reduction mixture from 15 g. of 2-chloro-4-nitro-N,N-dimethylaniline (0.075 mole) in ether (see section on preparation of 2-chloro-N¹,N¹-dimethyl-*p*-phenylenediamine) was added to 18 g. of N-acetylsulfanilyl chloride (0.077 mole) and 4 g. of sodium carbonate, in a flask equipped with a stirrer and an efficient reflux condenser. This mixture was stirred and refluxed for one and one-half hours. The reaction mixture was poured over cracked ice; the ether layer was separated and concentrated. The acetylsulfanilamido-3-chloro-4-dimethylaminobenzene which precipitated was recrystallized from ethanol. There was obtained 15 g. of the acetyl compound. The acetyl compound was refluxed for twenty minutes with 300 ml. of 10% hydrochloric acid. The hydrolysis mixture was cooled during neutralization with 10% sodium hydroxide solution. The crude 3'-chloro-4'-dimethylaminosulfanilanilide which separated was filtered, dissolved in ethanol, and treated with Norit. The decolorized solution was cooled rapidly in an ice-bath and the supernatant liquid was decanted from the oil which separated first. Further cooling of the supernatant liquid gave 6.9 g. (24%) of product, m. p. 101–103.5°. *Anal.* Calcd. for $C_{14}H_{16}N_3O_2SCl$: C, 51.61; H, 4.95; Cl, 10.88; N, 12.90. Found: C, 51.51; H, 5.18; Cl, 10.93; N, 12.93.

N¹-(2-Hydroxy-3-camphanyl)-sulfanilamide (SN-8350).—In a two-necked flask were placed 500 ml. of dry isopropyl alcohol, 19.3 g. of α-(N-acetylsulfanilamido)-camphor (0.053 mole) and 70 g. of aluminum isopropoxide (0.343 mole). The flask was attached to an efficient two-foot fractionating column packed with glass helices and fitted with a stillhead with a controlled takeoff. The flask was placed in an electrically heated oil-bath, the temperature of which was kept at 120°. The acetone was removed by distilling slowly at a high reflux ratio. Distillation was continued until the distillate no longer gave a test for acetone with 2,4-dinitrophenylhydrazine reagent. About 100 ml. of distillate was collected; the distillation required eight hours. When another 100 ml. of isopropyl alcohol had been removed by distillation, the reaction mixture in the flask was poured with stirring into ice and water containing 125 ml. of concentrated hydrochloric acid. The white precipitate of α-(N-acetylsulfanilamido)-borneol was filtered and washed with very dilute hydrochloric acid. The yield of acetyl compound was 18 g. (93%) m. p. 201.5–203.5°.

The 18 g. of acetyl compound was dissolved in 120 ml. of hot ethanol, and then 60 ml. of 1:1 hydrochloric acid was added to the solution. The acid solution was refluxed for twenty minutes, and then 120 ml. of distillate was removed during another twenty-minute period. A few grams of Darco was added, and the mixture was stirred and filtered. The cooled filtrate yielded some of the product as the hydrochloride. This was filtered off, the filtrate was neutralized to *p*H 7 with sodium hydroxide solution, and the product obtained in this manner was combined with that obtained by the solution of the hydrochloride in ethanol followed by neutralization to *p*H 7. The crude N¹-(2-hydroxy-3-camphanyl)-sulfanilamide was dissolved in 100 ml. of ethanol, treated twice with Darco, and diluted with 100 ml. of water. Upon cooling there was obtained 12.2 g. of product, m. p. 158–159° (71% based upon amount of α-(N-acetylsulfanilamido)-camphor taken). *Anal.* Calcd. for $C_{16}H_{24}N_2O_3S$: C, 59.25; H, 7.46. Found: C, 59.30; H, 7.49.

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Summary

1. Three new amines were prepared, 2,6-dibromo-4-*t*-butylaniline, 2,6-dibromo-4-*t*-amylaniline and 2-amino-5-chloro-4,6-dimethylpyrimidine, for use as intermediates in the preparation of sulfanilamide derivatives.

2. Fifteen other amines were prepared for use as intermediates in the preparation of sulfanilamide derivatives, either by methods reported in the literature or by modifications of the reported methods.

3. Twenty-two sulfanilamide derivatives were prepared for testing as possible antimalarials. Nineteen of these are new compounds.

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(49) Hydrolysis with dilute acid resulted in cleavage of the sulfonamide linkage.