into 1500 ml. of stirred denatured ethanol (2B) at room temperature. The polymer was obtained as a white precipitate and the mixture was boiled to complete the coagulation. On cooling, the clear supernatant alcohol solution was carefully decanted. Final purification was effected by similar treatment with two fresh 1500-cc. portions of denatured ethanol. After drying in an evaporating dish at 60° for forty-eight hours in a circulating air oven, the copolymer was analyzed in duplicate for nitrogen by the Kjeldahl method.

Emulsion Polymerization.—Potassium persulfate used was the product of the General Chemical Co. Santomerse D used was the product of Monsanto Chemical Co. (an alkyl aryl sodium sulfonate). A master batch of emulsifier solution was prepared by dissolving 200 g. of Santomerse D in 4800 ml. of distilled water. All emulsion polymerizations utilized 300 g. of this emulsifier solution and 150 g. of total comonomers. Emulsifier solution was added to a stirred 1-liter, three-necked flask and appropriate weights (Table I) of styrene, acrylonitrile and catalyst (benzoyl peroxide or potassium persulfate) were added. Catalyst concentrations are based on total monomers. The reaction mixture was stirred for one and one-half hours at room temperature and then, in the case of the benzoyl peroxide catalyzed experiments, raised to 60 ± 1° during twenty minutes by means of a Glas-Col mantle. The potassium persulfate catalyzed experiments were heated to 75 ± 2° over a thirty-minute period. Polymerization at these temperatures was continued until a low conversion had been obtained. Conversions during the reaction were approximated by estimating turbidity when 5 ml. of emulsion was added to 200 ml. of ethanol. Polymerization times at 60° and at 75° for the compositions employed are summarized in Table I. The entire reaction mixture was then poured into 3000 ml. of stirred ethanol and this mixture was boiled to coagulate the product. The polymer, which usually was obtained as a fine white powder, was filtered on a Buchner funnel, boiled with 1500 ml. of fresh ethanol and refiltered. This operation was then repeated. In some cases there was a tendency for polymer particles to stick together after the first boiling operation. Such products were re-comminuted by mixing in a Waring blender with fresh alcohol prior to filtration. The resulting fine powder was then purified by the above procedure. All products were dried in an evaporating dish at 60° in a circulating air oven for forty-eight hours. Conversions corrected for residue in the polymerization flask and for samples withdrawn during polymerization, were determined gravimetrically. These data and the nitrogen content of the products are given in Table I.

Solubility Determination.—Into four stoppered 50-ml. Erlenmeyer flasks were weighed two 25.000-g. portions of water and two 25.000-g. portions of 4% Santomerse D solution. The flasks were placed in a water-bath regulated to 60.3 ± 0.02°. Styrene and acrylonitrile were added dropwise to the water samples by means of a calibrated micro-pipet and the flasks agitated after each addition. Acrylonitrile was added two drops at a time and styrene was added a drop at a time. The saturation point was taken at the first appearance of turbidity and the amount of styrene and of acrylonitrile added was calculated from the number of drops added. A similar procedure was followed for the Santomerse D solutions and the turbidity was matched visually with that of the water solutions. Estimation of turbidity was more difficult in the case of the Santomerse solutions and, as shown above, the experimental error was larger.

Acknowledgments.—The authors are indebted to Miss M. Magin for the nitrogen determinations.

Summary

Proximity of the monomer–polymer composition curves for the system styrene–acrylonitrile determined for mass and emulsion methods of polymerization, is interpreted as giving support to an oil phase mechanism for emulsion polymerization.

Data are reported to show that an oil phase mechanism is operative in emulsion copolymerization for both oil soluble and water soluble catalysts.

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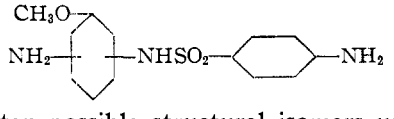
[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Aminosulfanilanisides[1]

BY FRANK H. BERGEIM, KATHYRN LOSEE AND W. A. LOTT

In our investigation of relatively simple carbocyclic compounds as possible antimalarials, we prepared several isomeric aminosulfanilanisides of the following general structure



Of the ten possible structural isomers using the three groupings shown above we have prepared the seven which are listed as the first seven compounds in Table I. In addition there are listed in Table I some related sulfanilamide end-products together with methods for their preparation and other pertinent data.

(1) Presented before the Division of Medicinal Chemistry at the 109th Meeting of the American Chemical Society, Atlantic City, N. J., April 10, 1946

The penultimate intermediates required for the preparation of the end-products listed in Table I are listed in Table II. There is also included in this table an outline of the procedures used for the preparation of these intermediates. The outlined procedures are similar in many instances and are based on representative general procedures, A, B, C, D, E and F, illustrated by specific examples in the experimental part.

Many of the end-products in Table I were prepared by the acid hydrolysis of the corresponding acetylated intermediates of Table II. Other end-products of Table I were obtained by reducing the penultimate nitro intermediates of Table II with iron and hydrochloric acid, iron and acetic acid, or catalytically. The succinoyl and acetaldehyde bisulfite end-products required specific procedures which are described in the experimental part.

TABLE I

AMINOSULFANILANISIDES AND RELATED END-PRODUCTS

Compound no.	Name	Empirical formula	M. p., °C.	Method of prepn.	Yield, %	Analyses, % Calcd. N	Calcd. S	Found N	Found S
1	3-Amino-4-sulfanilamidoanisole	$C_{13}H_{15}N_3O_3S$	194–195	*a*	40	14.33	10.93	14.06	10.95
2	4-Amino-3-sulfanilamidoanisole	$C_{13}H_{15}N_3O_3S$	178–179	*b*	47	14.33	10.93	14.33	10.77
3	3-Amino-5-sulfanilamidoanisole	$C_{13}H_{15}N_3O_3S$	132.5–133	*c*	70	14.33	10.93	14.31	10.26
4	5-Amino-2-sulfanilamidoanisole	$C_{13}H_{15}N_3O_3S$	186–188	*d*	42	14.33	10.93		10.93
5	2-Amino-4-sulfanilamidoanisole	$C_{13}H_{15}N_3O_3S$	172–173	*e*	56	14.33	10.93	13.91	10.43
6	4-Amino-2-sulfanilamidoanisole	$C_{13}H_{15}N_3O_3S$	231–232	*f*	62	14.33	10.93	14.46	11.50
7	2-Amino-5-sulfanilamidoanisole	$C_{13}H_{15}N_3O_3S$	151–152	*g*	50	14.33	10.93	13.84	10.80
8	3-Dimethylamino-4-sulfanilamidoanisole	$C_{15}H_{19}N_3O_3S$	163–164	*h*	85	13.08	9.96	13.27	9.69
9	4-Dimethylamino-3-sulfanilamidoanisole	$C_{15}H_{19}N_3O_3S$	128.5–129.5	*i*	90	13.08	9.96	13.16	9.92
10	3-Amino-4-sulfanilamidophenetole	$C_{14}H_{17}N_3O_3S$	244–245	*j*	58	13.68	10.42	13.58	10.62
11	5-Diethylamino-2 or 4-sulfanilamidophenetole	$C_{18}H_{25}N_3O_3S$	183–184	*k*	77	11.57		11.53	
12	3-Amino-4-sulfanilamidotoluene	$C_{13}H_{15}N_3O_2S$	216–217	*l*	50	15.17	11.55	15.83	11.21
13	3,4-Disulfanilamidoanisole	$C_{19}H_{20}N_4O_5S_2$	110.5–111.5	*m*	27	12.50		12.93	
14	3-Ethylsulfonamido-4-sulfanilamidoanisole	$C_{15}H_{19}N_3O_5S_2$	161–162	*n*	32	10.91	16.62	10.65	16.40
15	3-Succinoylamino-4-(N^4-succinoylsulfanilamido)-anisole	$C_{21}H_{23}N_3O_9S$	151–155 (dec.)	*o*	20	8.52		8.49	
16	Disodium 3-amino-4-sulfanilamidoanisole bis-acetaldehyde bisulfite	$C_{17}H_{21}N_3O_9S_2Na_2\cdot 4H_2O$		*p*	58	6.72	15.37	6.60	15.66
17	4-Sulfanilamidoanisole	$C_{13}H_{14}N_2O_3S$	188–189	*q*	21	10.07	11.51	10.28	11.78
18	3-Amino-4-(3-amino-4-methoxyphenylsulfonamido)-anisole	$C_{14}H_{17}N_3O_4S$	119–121	*r*	35	13.00	9.90	12.80	10.04

[a] This compound was made by reducing 3-nitro-4-sulfanilamidoanisole with iron and acetic acid (Procedure D) or iron and hydrochloric acid (Procedure E). It was also made by the hydrolysis of 4-(N^4-acetylsulfanilamido)-3-aminoanisole (Procedure B). C. Marchant, C. C. Lucas, L. McClelland and P. H. Greey, *Can. J. Research*, **20B**, 5–16 (1942), also made this compound by the reduction of 3-nitro-4-sulfanilamidoanisole and found a m. p. of 195°. [b] Hydrolysis by Procedure B using 4-acetamido-3-sulfanilamidoanisole. [c] Reduction of 3-nitro-5-sulfanilamidoanisole by Procedure D. [d] Reduction of 5-nitro-2-sulfanilamidoanisole by Procedure D. [e] Procedure B for the hydrolysis of 2-acetamido-4-(N^4-acetylsulfanilamido)-anisole. [f] By the reduction of 4-nitro-2-sulfanilamidoanisole according to Procedure D. Reported by Marchant, *et al.*, ref. [a], to have a m. p. of 231–232°. [g] Hydrolysis of 2-acetamido-4-(N^4-acetylsulfanilamido)-anisole by Procedure B. [h] From 4-(N^4-acetylsulfanilamido)-3-dimethylaminoanisole by Procedure B. [i] From 3-(N^4-acetylsulfanilamido)-4-dimethylaminoanisole by alkaline hydrolysis (Procedure C). [j] Made by the reduction of 3-nitro-4-sulfanilamidophenetole using Procedure D. [k] Hydrolysis of 2 or 4-(N^4-acetylsulfanilamido)-5-diethylaminophenetole by Procedure B. [l] Prepared by the reduction of 3-nitro-4-sulfanilamidotoluene according to Procedure E. [m] Made by reducing 4-(N^4-acetylsulfanilamido)-3-nitroanisole (32) by Procedure E to 4-(N^4-acetylsulfanilamido)-3-aminoanisole (35), treating with acetylsulfanilyl chloride as in Procedure A to form 3,4-bis-(N^4-acetylsulfanilamido)-anisole and, without isolating the latter in a pure state, hydrolyzing according to Procedure B to compound (13). [n] By treating 4-(N^4-acetylsulfanilamido)-3-aminoanisole (35) with ethylsulfonyl chloride as in Procedure A and hydrolyzing the resultant product according to Procedure B. [o] Prepared by treating 3-amino-4-sulfanilamidoanisole with succinic anhydride. See experimental part. [p] By treating 3-amino-4-sulfanilamidoanisole with sodium acetaldehyde bisulfite. See experimental part. [q] By the hydrolysis of 4-(N^4-acetylsulfanilamido)-anisole as in Procedure B. Also made by Marchant, *et al.*, ref. [a], who found a m. p. of 194° (cor.). [r] By the reduction of 4-(4-methoxy-3-nitrophenylsulfonamido)-3-nitroanisole as in Procedure D.

The isomeric aminosulfanilanisides (1) and (6) reported by Marchant, *et al.*,[2] were prepared independently by us prior to the above publication. The publication of our results has been withheld due to a Government secrecy order. The Canadian authors did not report any antimalarial tests.

Of the seven isomeric aminosulfanilanisides tested for antimalarial activity[3] only compound (1) showed definite activity and that activity was weak. The acetyl derivative of (1) and the sodium acetaldehyde bisulfite derivative of (1) also showed definite but weak activity. There was a trace of activity in compounds (3), (4), (8) and (18). All of the other compounds which were tested, (2), (5), (6), (7), (10), (12), (19), (20), (14), (36), (42), (11) and (17), were inactive.

(2) Ref. *a*, Table I.

(3) The compounds were assayed for their antimalarial activity against *Plasmodium lophurae* and *Plasmodium cathemerium* infections in the duck by Dr. H. B. van Dyke (present address: Department of Pharmacology College of Physicians and Surgeons Columbia University, New York, N. Y.) and Dr. H. A. Walker of the Division of Pharmacology of the Squibb Institute for Medical Research.

Experimental[4]

The general procedure used for condensing an acylaminophenylsulfonyl chloride with an aminocarbocycle is illustrated by the following example.

4-(N^4-Acetylsulfanilamido)-3-nitroanisole (32), Procedure A.—One hundred sixty-eight grams (1 mole) of 4-amino-3-nitroanisole was dissolved in 336 cc. of pyridine. There was then added portionwise with good stirring 233.5 g. (1 mole) of acetylsulfanilyl chloride, not allowing the temperature to rise above 50°. After standing for a few hours at room temperature the solution was diluted with water, made acid to congo red with dilute hydrochloric

(4) All melting points are uncorrected.

TABLE II

PENULTIMATE INTERMEDIATES FOR AMINOSULFANILANISIDES AND RELATED COMPOUNDS

Intermediate no.	Used for cpd. no. ( ) in Table I	Name	Empirical formula	M. p., °C.	Method of prepn.	Yield, %	Analyses, % N Calcd.	Found
19	1	3-Nitro-4-sulfanilamidoanisole	$C_{13}H_{13}N_3O_5S$	118–119	*a*	97	*b*	
20	2	4-Acetamido-3-sulfanilamidoanisole	$C_{15}H_{17}N_3O_4S$	137–139	*c*	73	12.52*d*	12.22
21	3	3-Nitro-5-sulfanilamidoanisole	$C_{13}H_{13}N_3O_5S$	205–206	*e*	51	13.00	12.60
22	4	5-Nitro-2-sulfanilamidoanisole	$C_{13}H_{13}N_3O_5S$	173–174	*f*	41	13.00	12.95
23	5	2-Acetamido-4-(N^4-acetylsulfanilamido)-anisole	$C_{17}H_{19}N_3O_5S$	242–244	*g*	72	11.12	11.15
24	6	4-Nitro-2-sulfanilamidoanisole	$C_{13}H_{13}N_3O_5S$	187–188	*h*	17	13.00	13.17
25	7	2-Acetamido-5-(N^4-acetylsulfanilamido)-anisole	$C_{17}H_{19}N_3O_5S$	207–209	*i*	66	11.12	10.71
26	8	4-(N^4-Acetylsulfanilamido)-3-dimethylaminoanisole	$C_{17}H_{21}N_3O_4S$	B. p. 175.5 at 3.5 mm.	*j*	52	11.55	11.57
27	9	3-(N^4-Acetylsulfanilamido)-4-dimethylaminoanisole	$C_{17}H_{21}N_3O_4S$	157	*k*	70	11.55	11.71
28	10	3-Nitro-4-sulfanilamidophenetole	$C_{14}H_{15}N_3O_5S$	114–116	*l*	20	12.46	12.71
29	11	2 or 4-(N^4-Acetylsulfanilamido)-5-diethylaminophenetole	$C_{20}H_{27}N_3O_4S$	179.5–181	*m*	54	10.37	10.23
30	12	3-Nitro-4-sulfanilamidotoluene	$C_{13}H_{13}N_3O_4S$	170–171	*n*	62	13.68	13.93
1 in Table I	15	3-Amino-4-sulfanilamidoanisole			*o*			
1 in Table I	16	3-Amino-4-sulfanilamidoanisole			*o*			
31	18	4-(4-Methoxy-3-nitrophenylsulfonamido)-3-nitroanisole	$C_{14}H_{13}N_3O_8S$	150–152	*p*	66	10.96	10.43

[a] See ref. [a] Table I, m. p. 117° (cor.). [b] Calcd.: S, 9.93. Found: S, 10.15. [c] Made by treating 4-acetamido-3-aminoanisole with *p*-nitrobenzenesulfonyl chloride as in Procedure A, and reducing the resultant nitro compound as in Procedure F. [d] Calcd.: S, 9.55. Found: S, 9.53. [e] From 3-nitro-5-aminoanisole and acetylsulfanilyl chloride as in Procedure A followed by hydrolysis as in Procedure B. [f] From 2-amino-5-nitroanisole and acetylsulfanilyl chloride by Procedure A, followed by hydrolysis by Procedure B. [g] Made by reducing 2-acetamido-4-nitroanisole catalytically (Procedure F), and subsequent treatment with acetylsulfanilyl chloride (Procedure A). [h] See ref. [a] Table I in which the m. p. is reported as 188° (cor.). [i] From 2-acetamido-5-aminoanisole and acetylsulfanilyl chloride (Procedure A). [j] Made by treating 4-acetamido-3-aminoanisole with dimethyl sulfate, hydrolyzing as in Procedure B to 4-amino-3-dimethylaminoanisole and treating the latter product with acetylsulfanilyl chloride (Procedure A). [k] 4-Dimethylamino-3-nitroanisole was reduced catalytically using palladium-charcoal to 4-dimethylamino-3-aminoanisole (See experimental part). This product was converted to compound (27) by treating with acetylsulfanilyl chloride (Procedure A). [l] Prepared from 4-amino-3-nitrophenetole by treating with acetylsulfanilyl chloride (Procedure A) and subsequent hydrolysis according to Procedure B. [m] Made by treating *m*-diethylaminophenetole with diazotized sulfanilamide, reducing the azo compound to 2 or 4-amino-5-diethylaminophenetole, and finally treating with acetylsulfanilyl chloride (Procedure A) to give compound (29). [n] From 4-amino-3-nitrotoluene and acetylsulfanilyl chloride (Procedure A) followed by hydrolysis by Procedure B. [o] See footnote [a] Table I. [p] Made by treating 4-amino-3-nitroanisole with 4-methoxy-3-nitrobenzenesulfonyl chloride according to Procedure A.

acid and the precipitated product filtered and washed with water. Recrystallization from 50% ethanol gave a 75% yield of product of m. p. 173–174°. Occasionally, as for example in the preparation of compound (31), when the reactants were rather insoluble in pyridine they were first mixed in a mortar as powders, pyridine was added and the mixture was heated one-half hour on the steam-bath after which the product was worked up in the usual way. This procedure was used in the preparation of 3,4-disulfanilamidoanisole (13). In one instance, compound (27), the working up of the reaction mixture was varied by distilling off the pyridine under reduced pressure prior to treating with water. For the preparation of 4-nitro-3-(*p*-toluenesulfonamido)-anisole (41), the time of heating had to be increased to three and one-half hours at 60–80° to obtain a substantial yield.

The hydrolysis of the various mono and diacetyl sulfanilamides was usually carried out by heating with a solution of equal volumes of 10% hydrochloric acid and 95% ethanol. This acid hydrolysis procedure is illustrated by the following example.

3-Nitro-4-sulfanilamidoanisole (19), Procedure B.—One hundred and seventy-five grams (0.54 mole) of 4-(N^4-acetylsulfanilamido)-3-nitroanisole was refluxed for one hour with 3500 cc. of a 1:1 solution of 10% hydrochloric acid and 95% ethanol. The resultant clear solution was cooled and adjusted to *p*H 5–6 by the addition of 40% sodium hydroxide. The granular product which precipitated was filtered, washed with water and crystallized from 95% ethanol. The yield was 97% of a product of m. p. 118–119°.

Occasionally hydrolysis of the acetyl compounds was carried out in alkaline media (10% sodium hydroxide). The following example illustrates this general procedure.

4-Dimethylamino-3-sulfanilamidoanisole (9), Procedure C.—Twenty grams (0.06 mole) of 3-(N^4-acetylsulfanilamido)-4-dimethylaminoanisole was refluxed with 100 cc. of 10% sodium hydroxide until hydrolysis was complete (two hours). The solution was cooled and neutralized with glacial acetic acid. The precipitate which formed was filtered off and crystallized twice from 95% ethanol; yield 90%; m. p. 128.5–129.5°.

When the preparation of a product involved the reduction of a nitro compound to an amino compound usually one of three general procedures was used; iron and acetic acid (Procedure D), iron and hydrochloric acid (Procedure E), and catalytic reduction (Procedure F). Each of these procedures is illustrated by the following examples.

3-Amino-4-sulfanilamidoanisole (1), Procedure D.—One hundred grams (0.3 mole) of 3-nitro-4-sulfanilamidoanisole was dissolved in 700 cc. of glacial acetic acid by heating to boiling. To this boiling solution there was

TABLE III

MISCELLANEOUS INTERMEDIATES

Cpd. no.	Name	Empirical formula	M. p., °C.	Method of prepn.	Yield, %	Analyses, Calcd.	% N Found
32	4-(N^4-Acetylsulfanilamido)-3-nitroanisole	$C_{15}H_{15}N_3O_6S$	173–174	*a*	75	[b]	
33	4-(N^4-Acetylsulfanilamido)-3-nitrophenetole	$C_{16}H_{17}N_3O_6S$	154–155	*c*	50	11.08	11.84
34	4-(N^4-Acetylsulfanilamido)-3-nitrotoluene	$C_{15}H_{15}N_3O_5S$	173–175	*d*	86	12.03	11.97
35	4-(N^4-Acetylsulfanilamido)-3-aminoanisole	$C_{15}H_{17}N_3O_4S$	172–173	*e*	85	12.52*f*	12.48
36	3-Acetamido-4-(N^4-acetylsulfanilamido)-anisole	$C_{17}H_{19}N_3O_5S$	202–204	*g*	90	11.13	11.05
37	4-Acetamido-3-(*p*-nitrophenylsulfonamido)-anisole	$C_{15}H_{15}N_3O_6S$	183–185	*h*	68	11.50*i*	11.64
38	3-Amino-4-dimethylaminoanisole hydrochloride	$C_9H_{14}N_2O\cdot HCl$	131–132	*j*	93	13.86	13.45
39	2-Acetamido-4-aminoanisole	$C_9H_{12}N_2O_2$	107–108	*k*	63	15.55	15.63
40	4-Ethylsulfonamido-3-nitroanisole	$C_9H_{12}N_2O_5S$	92–93	*l*	21	10.76	10.49
41	4-Nitro-3-(*p*-toluenesulfonamido)-anisole	$C_{14}H_{14}N_2O_5S$	134–135	*m*	79	8.69	8.69

[a] Made by treating 3-nitro-4-aminoanisole with acetylsulfanilyl chloride as in Procedure A. See also ref. *a*, Table I, in which the m. p. is given as 175° (cor.). [b] Calcd.: S, 8.78. Found: S, 8.43. [c] Prepared by Procedure A using 3-nitro-4-aminophenetole and acetylsulfanilyl chloride. [d] Procedure A using 3-nitro-4-aminotoluene and acetylsulfanilyl chloride. [e] Made by the reduction of 4-(N^4-acetylsulfanilamido)-3-nitroanisole as in Procedure E. [f] Calcd.: S, 9.55. Found: S, 10.08. [g] By the treatment of 4-(N^4-acetylsulfanilamido)-3-aminoanisole with acetic anhydride. See experimental part. [h] From 4-acetamido-3-aminoanisole and *p*-nitrobenzenesulfonyl chloride as in Procedure A. [i] Calcd.: S, 8.78. Found: S, 9.11. [j] Prepared by the catalytic reduction of 4-dimethylamino-3-nitroanisole hydrochloride using palladium-charcoal catalyst. Calcd.: Cl, 17.32. Found: Cl, 17.10. [k] By the catalytic reduction of 2-acetamido-4-nitroanisole according to Procedure F. [l] By reaction of ethylsulfonyl chloride with 4-(N^4-acetylsulfanilamido)-3-aminoanisole as in Procedure A. F. Reverdin, *Helv. Chim. Acta*, **12**, 1053 (1929), prepared this compound by a different method and obtained a m. p. of 95°. [m] By Procedure A using 3-amino-4-nitroanisole and *p*-toluenesulfonyl chloride.

added during one-half hour 100 g. (1.8 moles) of iron powder. After refluxing for an additional half hour the iron was filtered from the hot solution, washed with hot acetic acid, and the filtrate diluted with 4–5 volumes of water. An almost white crystalline product separated out. The crude yield was 65%. Recrystallization from 95% ethanol gave a 40% yield of product of m. p. 194–195°.

4-(N^4-Acetylsulfanilamido)-3-aminoanisole (35), Procedure E.—Two hundred grams (0.6 mole) of 4-(N^4-acetylsulfanilamido)-3-nitroanisole (32), 200 g. (3.6 moles) of powdered iron, and one liter of 95% ethanol were heated to reflux temperature. There was added gradually while refluxing, 40 cc. of 18% hydrochloric acid, after which refluxing was continued one and one-quarter hours. The mixture was then filtered hot and the filtrate diluted with two volumes of water. The crystalline product which precipitated was recrystallized from 30% ethanol; yield 84.8%; m. p. 172–173°. When the iron–acetic acid reduction method was used for the preparation of this compound the yield was considerably lower (48%).

4-Acetamido-3-sulfanilamidoanisole (20), Procedure F.—Twelve and five-tenths grams (0.03 mole) of 4-acetamido-3-(*p*-nitrophenylsulfonamido)-anisole was dissolved in 250 cc. of 95% ethanol and hydrogenated at atmospheric pressure using platinum oxide catalyst. When the theoretical hydrogen had been absorbed, the catalyst was filtered off and the filtrate concentrated under reduced pressure until crystallization began. The crude product was recrystallized from 95% ethanol; yield 73%; m. p. 137–139°.

3-Succinoylamino-4-(N^4-succinoylsulfanilamido)-anisole (15).—To a solution of 58.6 g. (0.2 mole) of 3-amino-4-sulfanilamidoanisole in one liter of dioxane there was added with stirring on a steam-bath a solution of 40 g. (0.4 mole) of succinic anhydride in 500 cc. of dioxane. After the addition of the anhydride was complete the mixture was refluxed for five hours. The dioxane was then removed under reduced pressure until a sirupy residue of 200 cc. remained. This residue was dissolved in 500 cc. of 2.5% sodium hydroxide, treated with charcoal, filtered and acidified to congo red with 10% hydrochloric acid. An oil precipitated which crystallized after triturating with water and drying *in vacuo*. The crude product was purified by washing with 10% hydrochloric acid, water and finally drying *in vacuo*; m. p. 151–155° (dec.).

Disodium 3-Amino-4-sulfanilamidoanisole bis-Acetaldehyde Bisulfite (16).[5]—One hundred grams (0.34 mole) of 3-amino-4-sulfanilamidoanisole, 119 g. (0.68 mole) of 85% sodium acetaldehyde bisulfite and 80 cc. of water were heated on a steam-bath for two hours. The mixture was then concentrated by heating at 40–50° under a pressure of 2–3 mm., 300 cc. of 95% ethanol was added and the mixture shaken vigorously. On standing two layers formed. The lower aqueous layer was concentrated under reduced pressure to dryness yielding 123 g. of product; yield 58%.

3,4-Diaminoanisole (42).—This diamine has not previously been described in the literature although Meldola and Eyre[6] claim that it can be made by reducing 4-amino-3-nitroanisole. We prepared the base in pure form by reducing 4-amino-3-nitroanisole with stannous chloride and hydrochloric acid. It is a white crystalline product; m. p. 47.5–48° and b. p. 167–170° (11 mm.). In one experiment 100 g. (0.72 mole) of 4-amino-3-nitroanisole was added at room temperature to 2250 cc. of hydrochloric acid (sp. gr. 1.14) containing 400 g. (1.77 moles) of $SnCl_2\cdot 2H_2O$. The temperature rose spontaneously to 52°. After standing several hours at room temperature the solution was partly neutralized to give a normal hydrochloric acid concentration and the tin was precipitated with hydrogen sulfide. The tin sulfide formed was removed by filtration, the filtrate concentrated to small volume, strongly alkalinized and extracted with ether. Evaporation of the ether gave a dark colored crystalline base which was converted to a dihydrochloride by dissolving in ethanol and adding ethereal hydrogen chloride; yield of crude dihydrochloride 53.4 g. (42%). It had an indefinite decomposition point of about 188° and was somewhat deficient in chlorine. *Anal.* Calcd. for $C_7H_{12}Cl_2N_2O$: Cl, 33.64. Found: Cl, 32.08. When the free base was liberated from the hydrochloride with alkali and distilled under reduced pressure a pure product was obtained. *Anal.* Calcd. for $C_7H_{10}N_2O$: N, 20.27. Found: N, 20.40.

3-Amino-4-dimethylaminoanisole Hydrochloride (38).[7]—Twenty-five grams (0.11 mole) of 4-dimethylamino-3-nitroanisole hydrochloride was suspended in 100 cc. of water and reduced at room temperature in the presence of 5% palladium-on-charcoal at 50 pounds initial pressure. After one and one-half hours the reduction was complete. The catalyst was removed and the filtrate concentrated to dryness *in vacuo*. The residue was dissolved in absolute ethanol, treated with charcoal, filtered, and the filtrate

(5) This compound was made by Miss Barbara Stearns of this Division.

(6) R. Meldola and J. V. Eyre, *J. Chem. Soc.*, 991 (1902).

(7) This compound and the two compounds derived from it, numbers (27) and (9) were made by Dr. John T. Sheehan of this Division.

concentrated to small volume. On cooling the monohydrochloride separated out. It was recrystallized from absolute ethanol; yield 20 g. (92%). The dihydrochloride melted at 192–193°. A sample of the monohydrochloride converted to the free base distilled at 124–130° (3–4 mm.).

3-Acetamido-4-(N^4-acetylsulfanilamido)-anisole (36).—Fifteen grams (0.05 mole) of 4-(N^4-acetylsulfanilamido)-3-aminoanisole and 45 cc. (0.5 mole) of acetic anhydride were heated on a steam-bath for about fifteen minutes. The product which crystallized out on cooling was filtered off, washed with water and recrystallized from a 70–30 acetone–alcohol mixture; yield 90%.

Acknowledgment.—The authors wish to thank Mr. J. F. Alicino of this Institute for the microanalyses reported.

Summary

Seven isomeric aminosulfanilanisides together with some of their derivatives have been described.

3-Amino-4-sulfanilamidoanisole (or using the aniside nomenclature 2′-aminosulfanil-*p*-aniside[8]), its N^4-acetyl derivative, and its sodium acetaldehyde bisulfite derivative, have been found to have definite antimalarial activity.

(8) This compound is identified as SN 374 in the forthcoming monograph, "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor.

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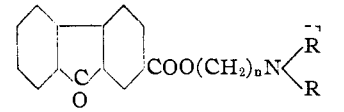
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Alkylamine Derivatives of Fluorene

BY FRANCIS EARL RAY AND IAN R. MACGREGOR[1]

Derivatives substituting both the aliphatic 9-carbon[2,3] and the aromatic carbons[4,5] of fluorene have been found to have therapeutic properties.



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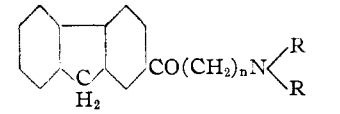

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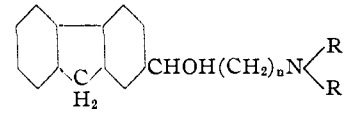
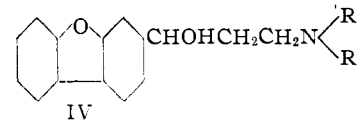
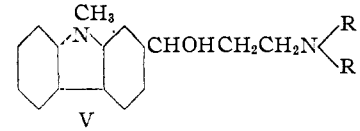


III



IV



V

Ray and Rieveschl[4] found that esters of fluorenone-2-carboxylic acid of the type I possessed considerable topical anesthetic power and antispasmodic action. As is well known,[6] the ester linkage is not essential for activity. We therefore decided to replace the ester linkage with the keto, as in II, or hydroxy, as in III, group. Fluorene was selected instead of fluorenone because of its greater solubility. Previous experience suggested that the activity might be expected to reach a maximum when $n = 2$. Hydroxy compounds of type III would be analogous to the derivatives of dibenzofuran, of the type IV, and 9-methylcarbazole, of the type V, which showed analgesic activity in cats.[7]

Ketones, of the type II, in which $n = 1$ were prepared by the side chain bromination of 2-acetylfluorene and its subsequent reaction with a mono- or dialkylamine. Those ketones in which $n = 2$ were obtained by means of the Mannich[8] reaction from 2-acetylfluorene, paraformaldehyde and a primary or secondary amine hydrochloride. When ammonium chloride was substituted for the amine hydrochloride, a tertiary amine, VI, resulted, while methylamine hydrochloride yielded a small amount of the tertiary amine VII in addition to the desired product.

$(C_{13}H_9COCH_2CH_2)_3N\cdot HCl$ (VI) $(C_{13}H_9COCH_2CH_2)_2NCH_3\cdot HCl$ (VII)

No cyclization of the kind reported by Mannich and Ball[9] was observed.

Secondary amines reacted well with the exception of diethylamine. This agrees with the observations of Kermack and Muir[10] who found that diethylamine was so inert that it failed to react with ethyl methyl ketone and formaldehyde,

(1) Abstracted from a thesis submitted to the Graduate School, University of Cincinnati, by I. R. MacGregor in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Lehmann and Knoefel, *J. Pharmacol.*, **74**, 217, 274 (1942); **76**, 194 (1942).

(3) Burtner and Cusie, THIS JOURNAL, **65**, 262, 1582 (1943).

(4) Ray and Rieveschl, *ibid.*, **65**, 836 (1943).

(5) Bielschosky and Green, *Nature*, **149**, 526 (1942).

(6) Goodman and Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., N. Y., 1941, pp. 185–225.

(7) Nelson, *J. Pharmacol.*, **65**, 424 (1939); Eddy, *ibid.*, **68**, 159 (1936).

(8) "Organic Reactions," **1**, 327 (1942).

(9) Mannich and Ball, *Arch. Pharm.*, **264**, 65 (1926).

(10) Kermack and Muir, *J. Chem. Soc.*, 3089 (1931).