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Substituted Sulfaquinoxalines. III. Extension of the Glyoxalate Synthesis of 2-Aminoquinoxaline[1]

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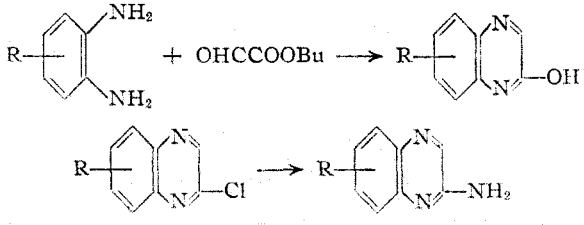
The preparation of 2-aminoquinoxaline by the glyoxalate synthesis[3] offered a convenient method for procuring substituted 2-aminoquinoxalines and the corresponding sulfonamido derivatives, of which a series was desired for antimalarial testing.[4] In this paper sixteen 2-sulfanilamidoquinoxaline derivatives bearing substituents in the benzenoid ring are reported. As shown in the accompanying



equations, the requisite 2-aminoquinoxalines were prepared by condensing butyl glyoxalate with the corresponding *o*-phenylenediamine (R = alkyl, alkoxy, halogen, nitro, carboxy or sulfonic acid group) to give a 2-hydroxyquinoxaline, which was then chlorinated and aminated.

The necessary diamines were obtained by reduction of the corresponding nitroanilines or dinitro compounds. In some cases these diamines were converted without isolation into the hydroxyquinoxalines by addition of butyl glyoxalate to the reaction mixture resulting from the reduction. Generally, however, the diamines were isolated and purified as the neutral sulfates. The reaction with butyl glyoxalate performed in water or water–ethanol gave the 2-hydroxyquinoxalines in good yields. These compounds are high-melting solids, insoluble in most organic solvents, but soluble in dilute ammonium or sodium hydroxide.

Chlorination of the hydroxy compounds was achieved by treatment with phosphorus chlorides (usually phosphorus pentachloride in phosphorus oxychloride). The products were purified to white to yellow solids by recrystallization from ligroin or benzene. At this stage the isomers resulting from condensation of the unsymmetrical diamines with butyl glyoxalate in the two possible ways were separated by fractional crystallization. The pure chloroquinoxalines were aminated with liquid ammonia, usually in methanol solution, at temperatures and reaction times that varied widely for optimum yields with the differently substituted chloroquinoxalines. The amines are weakly basic, pale yellow compounds, soluble in warm dilute hydrochloric acid and conveniently crystallized from benzene or benzene–ethanol solutions.

The reactivity of the amino group in the differently substituted compounds (as indicated by the ease of reaction with *p*-acetylaminobenzenesulfonyl chloride) varied considerably, and in the cases of substitution of the benzene nucleus with strongly meta-directing groups (nitro, carboxy and sulfonic acid) the condensation failed under the usual conditions. Sulfonamides of the nitro compounds were obtained from the reaction of the chloro derivatives with *p*-acetylaminobenzenesulfonamide, while the carboxy derivatives were converted into the esters, and these reacted with *p*-acetylaminobenzenesulfonyl chloride. No sulfonamides were obtained from the sulfonic acid derivatives.

As noted above the isomeric pairs that resulted when the diamines were unsymmetrically substituted were separated as the 2-chloroquinoxalines. Attempts to separate the isomeric 2-hydroxy or 2-amino compounds were unsuccessful. Furthermore, since the sulfonamides were used for pharmacological screening, no attempt was made to identify the isomers. Two isomers were observed in every case with the exception of the 6(or 7)-carboxylic acid. However, of three vicinally substituted diamines, two gave only one of the isomeric quinoxalines in appreciable quantity.

The compounds prepared are listed in the following tables. The higher melting isomeric chloro derivative has been arbitrarily labelled a, and the subsequent derivatives are related to the chloro isomers. A paper by Platt (*J. Chem. Soc.*, 1310 (1948)) which appeared after this contribution was in press describes the preparation by an ambiguous method of both 2-hydroxy-6-methylquinoxaline and 2-hydroxy-7-methylquinoxaline and their respective chloro and amino derivatives. A comparison of melting points indicates that our 2-chloro-6-(or 7)-methylquinoxaline a is in fact 2-chloro-6-methylquinoxaline.

Experimental

Substituted *o*-Nitroanilines

The compounds used were either purchased or obtained by standard preparation according to procedures in the literature. However, a new method of synthesis of 2-nitro-6-chloroaniline was developed using the method described in the literature for the preparation of 2-nitro-6-bromoaniline.[5]

(1) For the previous paper in this series see Wolf, Beutel and Stevens, THIS JOURNAL, **70**, 4264 (1948).

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(3) Gowenlock, Newbold and Spring, *J. Chem. Soc.*, 622 (1945).

(4) For the results of the testing, see F. Y. Wiselogle, Ed., "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946.

(5) Holleman, *Rec. trav. chim.*, **27**, 153 (1908).

TABLE I

2-HYDROXYQUINOXALINES[a]

Substituent	Yield, %	Analyses, %[6] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
6-CH_3[b,c]	72	67.48	67.78	5.03	4.92
6-Cl[b]	85	53.20	53.63	2.79	3.08
6-Br[b]	81	42.69	41.91	2.24	2.53
6-NO_2[b]	76	50.27	51.13	2.64	2.14
6-OCH_3[b,d]	82	61.35	61.02	4.38	4.40
5-CH_3[e]	65	67.48	67.64	5.03	5.34
5-Cl[e]	79	53.20	52.96	2.79	2.94
5-OCH_3[b]	93	61.35	61.64	4.58	4.63
5-CH_3-6-Cl-8-$CH(CH_3)_2$[b]	68	60.88	61.05	5.54	5.72
5,7-Cl_2[b]	..	44.68	44.81	1.87	2.17
6-SO_3H[b,f]	83				
6-COOH[f,g]	88				
6-CN[f,g]	85				

[a] Mixtures of isomers were not separated, although purification may have resulted in enrichment of one isomer. [b] These products consist of a mixture of both possible substituted 2-hydroxyquinoxalines. [c] *Anal.* Calcd.: N, 17.50. Found: N, 17.45. [d] *Anal.* Calcd.: N, 15.99. Found: N, 15.63. [e] These products consist of 5- or 8-substituted 2-hydroxyquinoxalines. [f] These derivatives were not analyzed, but were converted directly into the corresponding chloro derivatives (Table II). [g] These products consist of 6- or 7-substituted 2-hydroxyquinoxalines.

2-Nitro-6-chloroaniline.—A solution of 100 g. of *o*-nitroaniline in 100 ml. of concentrated sulfuric acid and 275 ml. of 20% oleum was warmed at 160° for five minutes. The mixture was poured into 2 kg. of ice and water, and a solution of 50 g. of chlorine in 700 ml. of glacial acetic acid was added at 0–5° while the mixture was mechanically stirred. The mixture was allowed to stand twenty-four hours at room temperature and then filtered. The insoluble material (2–8 g.) was discarded and the filtrate transferred to 5-liter round-bottom flask equipped with a thermometer immersed in the liquid, a steam inlet, a condenser for downward distillation and an electric heating mantle. The mixture was gradually heated to 135°. At this temperature most of the acetic acid has distilled, and the product begins to steam distil. Dry steam was introduced and the product steam distilled. The temperature of the contents of the flask gradually rises to 150° during the distillation. Toward the end of the distillation the mixture foams badly, and the introduction of an anti-foam agent is helpful. The distillate (approximately 5 l.) was filtered and the product recrystallized from Skellysolve B. The product, 36.3 g. (29% yield), melts at 72–73°.

Substituted *o*-Phenylenediamines

Most of the diamines used have been previously prepared by various methods. The two methods used in the experiments were reduction with iron and hydrochloric acid and catalytic reduction. The product was generally isolated as the neutral sulfate by adding sulfuric acid to the alcohol solutions obtained from the reduction until no more precipitate was obtained. The sulfate salts were found to be non-hygroscopic, stable derivatives and could be purified by recrystallization from water or ethanol–water. The preparation of 3-chloro-1,2-diaminobenzene has not been previously described.

3-Chloro-1,2-diaminobenzene Sulfate.—A mixture of 37 g. of crude 2,3-dinitrochlorobenzene, 840 ml. of ethanol, 56 ml. of water and 72 g. of iron powder was warmed to 50°, and 11.5 ml. of concentrated hydrochloric acid was added at a rate sufficient to maintain gentle refluxing.

(6) Microanalyses were kindly performed by R. N. Boos, W. H. Humphrey, E. Thornton, L. Rosalsky and E. Miess of these Laboratories.

TABLE II

2-CHLOROQUINOXALINES[a]

Substituent	Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
6-CH_3, a	98	102–104	60.51	61.15[b]	3.95	3.95
6-CH_3, b		56–57	60.51	60.50[c]	3.95	3.93
6-Cl, a		156–157	48.51	48.80	2.03	2.18
6-Cl, b		120–122	48.51	48.54	2.03	2.33
6-Br, a	91	152–153.5	39.46	39.67	1.65	1.71
6-Br, b		118–120	39.46	39.65	1.65	1.64
6-NO_2, a	96.5	184–186	45.84	45.85	1.92	1.81
6-NO_2, b		161–163	45.84	46.17	1.92	2.29
6-SO_2Cl, a	74.5	127–128	36.52	36.63	1.53	1.71
6-SO_2Cl, b		98–98.5	36.52	36.74	1.53	1.56
6-SO_2NH_2, a	81.5	251–253	39.44	39.63	2.48	2.45
6-SO_2NH_2, b	41	238–240	39.44	39.82	2.48	2.43
6-OCH_3, a		102–104	55.55	55.42	3.62	3.78
6-OCH_3, b		70–71	55.55	55.73	3.62	3.82
6-COOH	72	210–212	51.81	51.50[d]	2.41	2.31
6-$COOC_2H_5$	75	93–95	55.82	55.86[e]	3.83	3.98
6-CN	90	178	57.01	57.23[f]	2.13	2.08
6-$CONH_2$	94	229.5	52.07	52.07	2.91	3.03
5-CH_3	90	92–93	60.51	60.70	3.95	4.00
5-Cl	70	138–139	48.51	48.23	2.03	2.07
5-OCH_3[g]	87.5	85–87	55.55	55.84	3.62	3.71
5-CH_3-6-Cl-8-$CH(CH_3)_2$[h]	92.5	.....	56.50	56.63	4.74	4.86
5,7-Cl_2, a		.....	41.15	41.39	1.30	1.35
5,7-Cl_2, b		.....	41.15	41.08	1.30	1.47

[a] The isomers are designated a, for the higher melting and b, for the lower melting. Therefore, compounds labeled 6- are either 6- or 7- substituted 2-chloroquinoxalines, those labeled 5- are either 5- or 8- substituted 2-chloroquinoxalines, etc. The subsequent products are labeled a or b referring to the chloro compound from which they were derived. [b] *Anal.* Calcd.: N, 15.68. Found: N, 15.08. [c] *Anal.* Calcd.: N, 15.68. Found: N, 15.59. [d] *Anal.* Calcd.: N, 13.42. Found: N, 13.97. [e] *Anal.* Calcd.: N, 11.48. Found: N, 11.8. [f] *Anal.* Calcd.: N, 22.17. Found: N, 21.70. [g] The mixture which was obtained melted at 85–87° and was not analyzed. Separation of isomers was very difficult, but a small amount of material, m. p. 115–117°, was isolated and had the analysis listed. [h] This product is a mixture of both possible isomers.

After the addition was complete, the mixture was refluxed one hour, neutralized with sodium hydroxide and filtered through Supercel. The filtrate was treated dropwise with 50% sulfuric acid until a permanent pink tinge developed. The precipitated diamine sulfate was filtered, washed with alcohol and ether and dried. The product, shiny platelets which turn purplish on the edges on drying, weighed 33.0 g. (94% yield). The product was obtained in similar yield when the 2-nitro-6-chloroaniline was thus reduced.

Substituted 2-Hydroxyquinoxalines

The general procedure is illustrated below.

2-Hydroxy-5(or 8)-chloroquinoxaline.—A suspension of 33.0 g. of 2,3-diaminochlorobenzene sulfate in 350 ml. of water and 140 ml. of 95% ethanol was neutralized by the cautious addition of sodium bicarbonate. Butyl glyoxalate, 18.3 g., was added and the mixture refluxed two hours. The solution was cooled and filtered, yielding crude product (29.3 g.). The crude product was purified by dissolving in 2.5 *N* sodium hydroxide, treating with decolorizing charcoal, and precipitating by acidification with acetic acid (24.4 g., 79% yield), m. p. 310°.

Substituted 2-Chloroquinoxalines

The chloro compounds were prepared by chlorination of the hydroxy compounds with phosphorus chlorides. The isomers obtained were separated by fractional crystallization.

2-Chloro-6(and 7)-bromoquinoxaline.—A mixture of 89.5 g. of 2-hydroxy-6(and 7)-bromoquinoxaline, 63 g. of

TABLE III

SUBSTITUTED 2-AMINOQUINOXALINES

Substituent	Yield, %	Reaction time, hr.	Reaction temp., °C.	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
6 (or 7)-methyl, a		8	175	178–180	67.89	67.97	5.70	5.40	26.39	26.23
6 (or 7)-methyl, b		8	175	171–173	67.89	67.87	5.70	5.82	26.39	26.21
6 (or 7)-chloro, a			100	215–217	53.20	53.17	2.66	2.61	23.27	23.18
6 (or 7)-chloro, b			100	194–195	53.20	53.50	2.66	2.86	23.27	23.35
6 (or 7)-bromo, a	58	10	120	190–192	42.68	42.95	2.69	2.93	18.67	18.52
6 (or 7)-bromo, b	74	10	120	187–189	42.68	43.03	2.69	2.78	18.67	18.60
6 (or 7)-nitro, a	61	16	105	303–306	50.27	50.09	3.16	3.35	29.31	29.02
6 (or 7)-nitro, b		2.5	65	277–280	50.27		3.16		29.31	29.17
6 (or 7)-sulfonamide, a	64	16	140	269–271	42.74	43.21	3.58	3.20	24.86	24.53
6 (or 7)-sulfonamide, b		16	140	266–268	42.74	43.50	3.58	3.78	24.86	24.64
6 (or 7)-sulfonic acid, a	35	16	115	Over 300	41.83	42.01	3.51	3.61	18.29	18.43
6 (or 7)-methoxy, a	66	8	150	192–193[a]	61.71	61.56	5.18	5.12	23.99	
6 (or 7)-methoxy, b	54	8	175	193–195[a]	61.71	61.93	5.18	5.30	23.99	24.02
6 (or 7)-carboxy		7	110	288 dec.	57.17	56.87	3.73	3.73		
6 (or 7)-carbomethoxy	70[b]			248.5	59.10	59.30	4.47	4.66	20.68	21.06
6 (or 7)-cyano	64	15	120	265	63.51	63.70	3.53	3.67	31.93	32.52
5 (and 8)-methoxy	37	5	105	233–235					23.99	23.78
5 (or 8)-methyl	67	14	140	202–203	67.89	67.72	5.70	5.67	26.39	26.53
5 (or 8)-chloro	68	3	120	219–220	53.20	53.74	2.66	3.67	23.27	23.58
5-Methyl-6-chloro-8-isopropyl (and isomer)	72	18	100	250[c]	52.91	53.11	5.55	5.53		
5,7-dichloro (or isomer)					45.72	45.01	2.34	2.50	19.55	19.32

[a] Mixed melting point 173–177°. [b] By esterification of acid. [c] Hydrochloride salt.

TABLE IV

SUBSTITUTED 2-N⁴-ACETYLSULFANILAMIDOQUINOXALINES

Substituent	Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
6 (or 7)-methyl, a	80	246–247	57.25	57.29	4.52	4.67	15.69	15.67
6 (or 7)-methyl, b		205–209	57.25	57.19	4.52	4.38	15.69	15.50
6 (or 7)-chloro, a		241–242	50.78	50.20	3.48	3.63	14.86	14.62
6 (or 7)-chloro, b		266–268	50.78	51.04	3.48	3.51		
6 (or 7)-bromo, a	73	266–267	45.35	45.64	3.12	3.29	13.32	13.04
6 (or 7)-bromo, b	91	248–250	45.35	45.10	3.12	3.40	13.32	13.26
6 (or 7)-nitro, a	56[a]	272–273					18.26	18.40
6 (or 7)-nitro, b	50[a]	246–249	50.10	49.05	3.15	3.53	18.26	18.05
6 (or 7)-amino, b	20[b]	255–265					19.65	19.45
6 (or 7)-methoxy, a	90	230–231	54.85	54.57	4.33	4.51	15.10	14.70
6 (or 7)-methoxy, b	90	183	54.85	54.25	4.33	4.32	15.10	14.68
6 (or 7)-carbomethoxy		202	54.00	54.31	4.03	4.68	14.00	13.98
6 (or 7)-carbamido		277[a]	52.98	52.96	3.92	4.40	18.18	17.51
5 (or 8)-methyl	91	228–229	57.25	57.08	4.52	4.10	15.69	15.73
5 (or 8)-chloro	62	252–255	50.78	51.15	4.48	3.80	14.86	15.14
5-Methyl-6-chloro-8-isopropyl (and isomer)	88	215–235	55.64	55.72	4.67	4.92		

[a] From the reaction of the corresponding chloro compound with acetylsulfanilamide in the presence of potassium carbonate and copper powder. [b] From the reduction of the corresponding nitro compound.

phosphorus pentachloride and 200 ml. of phosphorus oxychloride was heated on the steam-bath and stirred for one hour. The dark brown solution was slowly poured onto 1.5 kg. of ice and filtered. The wet precipitate was taken up in 2 l. of hot ethanol, treated with decolorizing charcoal, concentrated to 600 ml., cooled and filtered. The crude mixture of isomers, 80 g., was dissolved in 1.5 l. of hot Skellysolve B. On cooling, substantially pure isomer, a, m. p. 148–150 (26 g. 27% yield) was obtained. The mother liquor was concentrated to 1 l., cooled and filtered, yielding a mixture, m. p. 110–135° (12 g., 13.2% yield). The filtrate concentrated to 100 ml. yielded on cooling material melting at 117–119° (30 g. 31% yield, total yield 71%). Recrystallization of the first fraction yielded a product, m. p. 152–153.5°, and the last fraction yielded a product, m. p. 118–120°.

2-Chloroquinoxaline-6(and 7)-Sulfonyl Chloride.—A mixture of 2-hydroxyquinoxaline-6(and 7)-sulfonic acid (143.7 g.), phosphorus pentachloride (396 g.) and phosphorus oxychloride (443 ml.) was refluxed for one and one-half hours. The nearly clear solution was cooled and poured on ice while the mixture was stirred vigorously. When all the phosphorus halides were decomposed the crude product was filtered, washed with water and

TABLE V

SUBSTITUTED 2-SULFANILAMIDOQUINOXALINES

Substituent	Yield, %	Method[a]	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
6 (or 7)-methyl, a	80	II	215–216	57.31	57.32	4.49	4.38	17.82	17.67
6 (or 7)-methyl, b		II	255–256	57.31	57.35	4.49	4.38	17.82	18.15
6 (or 7)-chloro, a		I	248–249	50.23	50.20	3.32	3.53	16.74	16.40
6 (or 7)-chloro, b		I	238–239	50.23	50.32	3.32	3.45	16.74	16.58
6 (or 7)-bromo, a	91	II	244–246	44.35	44.34	2.92	2.92	14.78	14.62
6 (or 7)-bromo, b	62	II	239–240	44.35	44.32	2.92	3.05	14.78	14.97
6 (or 7)-nitro, a	80	I	220–221	48.71	48.75	3.21	3.56		
6 (or 7)-nitro, b		II	224–226	48.71	49.02	3.21	3.81		
6 (or 7)-amino, a	67		275–276	53.33	52.95	4.15	4.45		
6 (or 7)-methoxy, a	90	II	239–240	54.53	54.26	4.27	4.25	17.27	16.99
6 (or 7)-methoxy, b	90	II	235–237	54.53	54.31	4.27	4.29	17.27	17.10
6 (or 7)-carboxy	55	II	223	52.32	52.25	3.52	3.58	16.27	15.97
5 (or 8)-methyl	97	II	205–206	57.31	57.68	4.49	4.72	17.80	17.60
5 (or 8)-methyl	88	I	192–194	57.31	57.29	4.49	4.46	17.80	17.23
5 (and 8)-methoxy		II	105	54.53	54.12	4.27	4.09	17.27	17.30
5 (or 8)-chloro	97	II	213–215	50.23	50.12	3.32	3.58	16.74	16.70
5-Methyl-6-chloro-8-isopropyl (and isomer)	86	II	92–115	55.30	55.25	4.90	4.72	14.33	14.54

[a] I. Deacetylation carried out with ethanolic hydrogen chloride. II. Deacetylation carried out with aqueous sodium hydroxide.

dried, yielding crude product, m. p. 92–120° (124.3 g., 74.8%).

This mixture was separated with rather poor recovery by crystallization from benzene–ligroin mixtures to give equal amounts of the two isomers.

Isomer a crystallized as large colorless prisms from ligroin, m. p. 127–128°; isomer b was obtained as dendritic clusters of tiny colorless needles from ligroin, m. p. 98–98.5°.

2-Chloroquinoxaline-6(or 7)-sulfonamide, b.—Fifteen grams of 2-chloroquinoxaline-6(or 7) sulfonylchloride b was added to 250 ml. of concd. ammonia and the mixture heated on the steam-bath for five minutes. After standing overnight, the slurry was filtered and washed with water. The residue was purified by dissolving in 5% sodium hydroxide, treating with charcoal and precipitating with dilute acetic acid, yielding product, m. p. 225–235° (5.7 g., 41%). Crystallization of this material from glacial acetic acid gave prisms of m. p. 238–240° dec.

2-Chloroquinoxaline-6(or 7)-sulfonamide, a.—Fifteen grams of 2-chloroquinoxaline-6(or 7)-sulfonyl chloride, a, was converted into the sulfonamide as described above. After crystallization from glacial acetic acid, the product weighed 11.3 g. (81.5%), m. p. 251–253 with dec.

2-Chloroquinoxaline-6(or 7)-carboxamide.—A mixture of 30 g. of 2-chloroquinoxaline-6(or 7)-carboxylic acid, 66 g. of phosphorus pentachloride and 60 ml. of phosphorus oxychloride was heated two hours at 120°. The clear solution was concentrated to dryness *in vacuo* and the residue dissolved in 400 ml. of toluene. After treatment with decolorizing charcoal, the solution was concentrated *in vacuo* to about one-quarter of the initial volume. Five grams of the crude chloro acid chloride that separated was added in portions to 50 ml. of concentrated aqueous ammonia at room temperature. After allowing to stand one hour, the mixture was filtered yielding 2-chloro-6(or 7)-carbamidoquinoxaline (4.28 g.). Crystallization from methanol yielded material, m. p. 229.5°.

2-Chloroquinoxaline-6(or 7)-carboxylic Acid.—The mixture obtained by chlorinating 92 g. of 2-chloro-6(or 7)-carboxyquinoxaline, was poured into water and the resultant suspension stirred overnight. The crude product was dissolved in dilute sodium hydroxide and precipitated by acidification with dilute hydrochloric acid. Recrystallization of the crude, air-dried product from 500 ml. of isopropyl alcohol yielded material, m. p. 210–212° (75 g., 72% yield).

Substituted 2-Aminoquinoxalines

In general, anhydrous ammonia was added to a solution or suspension of the chloro compound in methanol or ethanol and the mixture heated in a bomb under the conditions specified in Table III.

2-Amino-5(or 8)-chloroquinoxaline.—A mixture of 21 g. of 2, 5(or 8)-dichloroquinoxaline, 300 ml. of ethanol and 50 ml. of liquid ammonia was heated at 120° for three hours. The mixture was concentrated to dryness *in vacuo* and the residue dissolved in 250 ml. of hot 2.5 *N* hydrochloric acid and filtered from insoluble material, 0.3 g. The hot acid solution was treated with Darco G-60 (5 g.) and the product precipitated by adding a slight excess of 2.5 *N* sodium hydroxide. The flocculent precipitate was collected, air-dried and recrystallized from ethanol yielding light yellow granules, m. p. 218–220°, 10 g. Concentration of the mother liquor yielded a solid, (4.5 g., total yield 68%). A sample recrystallized from benzene was obtained as bright yellow platelets, m. p. 219–220°.

2-Aminoquinoxaline-6(or 7)-sulfonic Acid, a.—Hydrolysis of 2-chloroquinoxaline-6(or 7)-sulfonyl chloride a (19.5 g.) was accomplished by warming the compound on the steam-bath with a slight excess of 1 *N* sodium hydroxide. The nearly clear solution that resulted after fifteen minutes was filtered, made acid to litmus with hydrochloric acid and concentrated to dryness *in vacuo*.

The mixture of 2-chloroquinoxaline-6(or 7)-sulfonic acid a and salt thus obtained was suspended in 300 ml. of methanol and 60 cc. liquid ammonia and heated under pressure at 115° for fifteen hours. After the amination, the mixture was concentrated to dryness, and the residue was dissolved in the minimum quantity of water, treated with charcoal, filtered and made strongly acid with concd. hydrochloric acid. The white precipitate of 2-aminoquinoxaline-6(or 7)-sulfonic acid hydrochloride was collected, washed with 10% hydrochloric acid and dried, weight 6.0 g. (35.3% from the dichloro compound). Crystallization of this material from water yielded product with m. p. over 300°.

2-Amino-6(or 7)-carbomethoxyquinoxaline.—A solution of 10 g. of 2-amino-6(or 7)-carboxyquinoxaline (obtained by the usual aminating procedure) in 100 ml. of methanol containing 6 g. of anhydrous hydrogen chloride was heated at reflux two and one-half hours. The mixture was concentrated to dryness *in vacuo*. The residue was dissolved in warm water and the crude product precipitated by the addition of dilute ammonia water. The crude product, 8

g., m. p. 190–213°, was recrystallized three times from dioxane yielding a product that melts at 248.5°.

Substituted 2-N⁴-Acetylsulfanilamidoquinoxalines

The amines were dissolved or suspended in pyridine and *p*-acetylaminobenzenesulfonyl chloride added while the mixture was stirred.

2-N⁴-Acetylsulfanilamido-5(or 8)-chloroquinoxaline.—To a mixture of 11.7 g. of the amine in 60 ml. of dry pyridine was added 16.7 g. of *p*-acetylaminobenzene sulfonyl chloride in four portions at ten-minute intervals, During the addition, the mixture warmed up to 35°. After being stirred for one hour, the resultant clear yellow solution was heated on a water-bath at 65° for one-half hour. The mixture was then poured into 800 ml. of hot water and the product, which crystallized when the mixture was stirred, was filtered and air dried. The crude product, 20.0 g., was dissolved in 250 ml. of 1.3 *N* sodium hydroxide and filtered; 4.45 g. of insoluble material, m. p. 208–210°, was obtained. The filtrate was acidified with glacial acetic acid yielding light yellow amorphous material, m. p. 245–252° (14.7 g., 62% yield). The analytical sample was crystallized from glacial acetic acid, m. p. 252–255°.

2-N⁴-Acetylsulfanilamido-6(or 7)-carboxamidoquinoxaline.—A mixture of 1.08 g. of 2-chloro-6(or 7)-carbamidoquinoxaline, 1.07 g. of acetylsulfanilamide, 0.65 g. of potassium carbonate and 50 mg. of copper powder in a Pyrex test-tube was stirred and heated at 180–190° in an oil-bath for fifteen minutes. The dark mixture was extracted with 10 cc. of 10% sodium hydroxide, filtered from the chloro compound that had not reacted and precipitated by acidification with dilute acetic acid. The oil that separated solidified on trituration with isopropyl alcohol. Recrystallization from glacial acetic acid yielded product, m. p. 277° about 500 mg.

Sulfonamides

The acetyl derivatives were hydrolyzed by boiling with aqueous sodium hydroxide or ethanolic hydrogen chloride.

2-Sulfanilamido-5(or 8)-chloroquinoxaline.—A solution of 11.95 g. of the acetyl compound in 75 ml. of 2.5 *N* sodium hydroxide was heated for one-half hour on a steam-bath. The crude product, 10.25 g., 97% yield, was precipitated by neutralization with acetic acid. The crude product, m. p. 210–213°, was purified in 87% recovery by dissolving in hot 5 *N* ammonium hydroxide, treating with charcoal and precipitating with acetic acid, m. p. 213–215°.

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Summary

The preparation of sixteen substituted derivatives of 2-sulfanilamidoquinoxaline is described, as well as the preparation of seventy-four other new quinoxaline compounds.

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2-Acyloxyacetylthiophenes

BY FRANK KIPNIS,* HAROLD SOLOWAY AND JOHN ORNFELT

During synthetic work on substances containing the thiophene ring, it became desirable to prepare 2-hydroxyacetylthiophene (I) and a series of

I, R = OH III, R = Br
II, R = OCOR′

esters (II) derived therefrom. The intermediate which seemed to offer most promise was bromoacetylthiophene (III) which had been prepared by Brunswig[1] by the addition of bromine to a solution of 2-acetylthiophene in carbon disulfide stirred with a stream of carbon dioxide. In the present work, it was found more convenient to prepare this compound by treatment of the ketone in carbon tetrachloride with bromine in the presence of iron filings as catalyst.

By hydrolysis of the bromine compound with sodium formate in methanol,[2] 2-hydroxyacetylthiophene was prepared in fair yield. The esters, which are related to the phenacyl compounds, were prepared by several methods which gave acceptable yields. In view of the ready availability of 2-acetylthiophene[3] and 2-bromoacetylthiophene, it may be indicated that the esters would probably serve as suitable derivatives for carboxylic acids, supplementing those derived from the phenacyl halides.

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(1) Brunswig, *Ber.*, **19**, 2891 (1886).

(2) Levene and Walti, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 5.

(3) Supplied by the Socony-Vacuum Oil Co., Paulsboro, N. J.

Experimental

2-Bromoacetylthiophene (III).—To a 1000-ml. interjoint flask fitted with a sealed stirrer, reflux condenser with drying tube, dropping funnel and thermometer, was added 42 g. (0.33 mole) of 2-acetylthiophene, 300 ml. of dry carbon tetrachloride and a few iron filings. The mixture was stirred and heated on the water-bath to 60° (internal) and then the bath was removed. A solution of 53.5 g. (0.67 atom) of bromine in 100 ml. of carbon tetrachloride was then added at such a rate that gentle refluxing occurred (about twenty minutes). The solution was refluxed for an additional thirty minutes, at the end of which time evolution of hydrogen bromide had ceased and the bromine coloration was absent. The volatiles were removed by distillation under slightly reduced pressure, and the residue was fractionated through a 30-cm. Vigreux column at 95–98° (1.5 mm.) to give 55 g. (80% yield) of a slightly yellow, extremely lachrymatory oil (n^{20}D 1.6258) which solidified below room temperature. The product was rather unstable at room temperature, but could be stored without decomposition at −10°. In agreement with Brunswig,[1] bromoacetylthiophene on treatment with alcoholic ammonia gave a carmine coloration, followed by a deep red-blue color on standing.

2-Hydroxyacetylthiophene (I).—In a 500-ml. 3-neck flask fitted with a sealed stirrer, reflux condenser and drying tube was placed 20.5 g. (0.1 mole) of 2-bromoacetylthiophene, 13.6 g. (0.2 mole) of anhydrous sodium formate and 180 ml. of absolute methanol. The stirrer was started and the solution was refluxed for ten hours. The volatiles were distilled at slightly reduced pressure, acetone