Summary

The equilibrium and dissociation rate constants are reported for the acid-catalyzed reversible dissociation of seven *t*-butyl esters into the respective carboxylic acids and *i*-butene, in dioxane solution at 25°. The reverse esterification rate constant, determined experimentally in one case, matches the value calculated from the preceding data.

The relationship between these results and the known parent acid ionization constants, viewed in terms of the general problem of structure and reactivity, indicates faster yet less complete esterification for the weaker carboxylic acids. The dissociation rate constants yield to quantitative treatment, and the Hammett reaction constant is calculated graphically for the aromatic esters.

Additional clues for more intimate analysis of the reaction mechanism are interpreted.

Physical constants for three new *t*-butyl esters are presented.

BRONXVILLE 8, N. Y. RECEIVED FEBRUARY 24, 1948

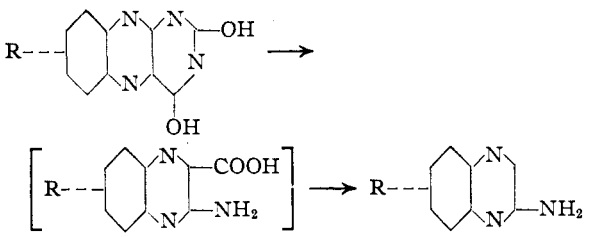
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

Substituted Sulfaquinoxalines. II. Some Derivatives and Isomers of 2-Sulfanilamidoquinoxaline[1]

BY F. J. WOLF, R. H. BEUTEL AND J. R. STEVENS[2]

In view of the promising chemotherapeutic action of sulfaquinoxaline[3,4] as well as its unique pharmacological properties,[5] the preparation of isomers and derivatives was undertaken.

The preparation of 6,7-dimethyl-2-aminoquinoxaline, 6(or 7)-chloro-2-aminoquinoxaline and a mixture of 2(and 3)-amino-5,6-benzoquinoxaline was carried out by degradative cleavage of the corresponding alloxazine under essentially the same conditions as those described in the literature for the cleavage of alloxazine[3] and substituted alloxazines.[6]



Only one of the two possible isomers was obtained when 7(or 8)-chloroalloxazine was cleaved; whereas, cleavage of benzalloxazine yielded 2- and 3-amino-5,6-benzoquinoxaline.

As the above method is not applicable to the preparation of 2-amino-3-alkylquinoxaline compounds, 2-amino-3-methylquinoxaline was prepared from 2-hydroxy-3-methylquinoxaline[7] by chlorination and amination of the resulting chloro compound.

Attempts to convert 2-hydroxy-3-methylquinoxaline into the amine by modifications of the Bucherer reaction were unsuccessful. However, when more rigorous conditions were applied to 2-hydroxyquinoxaline[8] the desired 2-aminoquinoxaline was obtained[9] in low yield.

In addition, the isomeric 5-aminoquinoxaline and 6-aminoquinoxaline[10] were prepared. The former was obtained from the reaction of 2,3-diaminoacetanilide with sodium glyoxal bisulfite followed by hydrolysis of the resulting 5-acetaminoquinoxaline to the desired product.

The amines were converted into the desired sulfonamides by the usual procedures and in addition the *p*-aminobenzoate of 2-aminoquinoxaline was prepared.

Acknowledgment.—The authors are indebted to Dr. R. T. Major and Dr. M. Tishler for their kind encouragement and advice.

Experimental

Alloxazines.—The preparation of 7(or 8)-chloroalloxazine is typical of the method.

7(or 8)-Chloroalloxazine.—A mixture of 60 g. of 4-chloro-2-nitroaniline and 200 g. of iron powder in 300 ml. of ethanol was stirred and refluxed and 12 ml. of 6 *N* hydrochloric acid was added dropwise during the first three hours. After eighteen hours the reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in 135 ml. of 2.5 *N* hydrochloric acid and 400 ml. of water, heated to 85° and added to a solution of 50 g. of alloxan monohydrate in 400 ml. of water at 85°. The mixture was stirred for one hour at 85–90° (a yellow precipitate appeared almost instantly) and filtered. The precipitate, after washing with water and ethanol and drying, weighed 75.4 g. (88% yield based on the nitro compound). The product was sufficiently pure for degradation purposes and did not melt when heated at 360°.

2-Amino-6,7-dimethylquinoxaline.—7,8-Dimethylalloxazine[11] (lumichrome) is not attacked by prolonged boiling with 30% sodium hydroxide. It was cleaved to 2-amino-3-carboxy-6,7-dimethylquinoxaline by heating at 170–175° with concentrated aqueous ammonia.

(1) For the previous paper in this series see Stevens, Pfister and Wolf, THIS JOURNAL, **68**, 1035 (1946).

(2) Present address, J. T. Baker Co., Phillipsburg, N. J.

(3) Weijlard, Tishler and Erickson, THIS JOURNAL, **66**, 1957 (1944).

(4) Smith and Robinson, *Proc. Exptl. Biol. Med.*, **57**, 292 (1944).

(5) Seeler, Mushett, Graessle and Silber, *J. Pharm.*, **82**, 357 (1944).

(6) Weijlard and Tishler, THIS JOURNAL, **67**, 1231 (1945).

(7) Hinsberg, *Ann.*, **292**, 249 (1896).

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

(9) This work was carried out by Mr. Weijlard in this Laboratory.

(10) Hinsberg, *Ann.*, **237**, 345 (1887).

(11) Kuhn and Rudy, *Ber.*, **67**, 1826 (1934).

TABLE I

SULFANILAMIDOQUINOXALINES

Compound	Yield, %	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-[N⁴-Acetylsulfanilamido]-6,7-dimethylquinoxaline	65	239–240	58.36	4.90		57.98	4.90	
2-[N⁴-Acetylsulfanilamido]-6-(or 7)-chloroquinoxaline	65	266–268	50.99	3.48		51.04	3.51	
2-(and 3-)[N⁴-Acetylsulfanilamido]-5,6-benzoquinoxaline	95	155–205	61.21	4.11		61.35	4.33	
2-[N⁴-Acetylsulfanilamido]-3-methylquinoxaline	65	244–245	57.30	4.53		57.39	4.97	
5-[N⁴-Acetylsulfanilamido]-quinoxaline	94	234	56.13	4.12		56.13	4.22	
6-[N⁴-Acetylsulfanilamido]-quinoxaline	...	279	56.13	4.12	16.36	56.08	4.31	16.1
2-Sulfanilamido-6,7-dimethylquinoxaline	85	246–247	58.52	4.91	17.05	58.44	5.15	16.81
2-Sulfanilamido-6-(or 7)-chloroquinoxaline	45	241–242	50.27	3.32	16.75	50.20	3.63	16.62
2-(and 3-)-Sulfanilamido-5,6-benzoquinoxaline	78	205–208			15.98			16.11
2-Sulfanilamido-3-methylquinoxaline	54	211–212	57.31	4.47	17.82	57.62	4.63	17.98
5-Sulfanilamidoquinoxaline	92	169–170	55.98	4.03	18.66	56.36	4.15	18.2
6-Sulfanilamidoquinoxaline	93.5[a]	230–231	55.98	4.03	18.66	56.10	3.99	18.8

[a] Based on 6-aminoquinoxaline.

A suspension of 28 g. of lumichrome in 150 ml. of 28% ammonia water was heated in bomb tubes at 170–175° for thirteen hours. The mixture was diluted with 10 volumes of water, heated to 90° and filtered. The amorphous orange precipitate was extracted with 300 ml. of hot 2 *N* ammonium hydroxide; the combined filtrates were acidified with acetic acid and the flocculent orange precipitate was filtered and dried. The product, 14.4 g. (60% yield), decomposed with evolution of gas at 215–220°.[12]

A mixture of 5.0 g. of crude 2-amino-3-carboxy-6,7-dimethylquinoxaline and 50 ml. of nitrobenzene was slowly heated to boiling. The elimination of carbon dioxide was rapid at first and was almost complete by the time the mixture had reached boiling temperature. The solution was refluxed for ten minutes, and the dark solution was allowed to stand for eighteen hours. The reaction mixture was filtered and the precipitate washed well with benzene. The combined filtrates were extracted three times with 25-ml. portions of 2.5 *N* hydrochloric acid. The aqueous extracts were combined, washed twice with benzene and made alkaline with sodium hydroxide. The crude product was filtered, taken up in 100 ml. of warm 2.5 *N* hydrochloric acid, treated with Darco G-60 and precipitated by the addition of 2.5 *N* sodium hydroxide. The yellow amorphous product, 2.97 g. (93% yield) melted at 270–273°. It was suitable for conversion into the sulfonamide compound. An analytical sample prepared by recrystallization from ethyl acetate melts at 275–278°.

Anal. Calcd. for $C_{12}H_{11}N_3$[13]: C, 69.35; H, 6.40. Found: C, 69.12; H, 6.67.

2(and 3)-Amino-5,6-benzoquinoxaline.—"Benzalloxazine,"[14] 60 g., was heated with 450 ml. of 28% aqueous ammonia at 175° for twelve hours. The reaction mixture was diluted with 2 l. of water, heated to 90°, treated with Norit and filtered. The filtrate was cooled and acidified with acetic acid, and the orange gelatinous precipitate was filtered and dried. The crude product, 15.5 g. (28.6% yield), melting with evolution of gas at 212–215°, was used in the next step.

The crude amino acid, 15.5 g., was decarboxylated as described for the 6,7-dimethyl derivative. The crude product, 8.0 g. (63.5% yield), was dissolved in 250 ml. of hot benzene. On cooling 5.4 g. of bright yellow material, m. p. 190–195°, was obtained. The mother liquor on concentration yielded solids 2.0 g., m. p. 140–180°. By fractional crystallization of the first crop, it was possible to obtain a low yield of analytically pure material, melting at 215–217°.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.89; H, 4.65; N, 21.52. Found: C, 73.79; H, 5.07; N, 21.64.

When the residue, obtained by evaporating the mother liquor from recrystallization of the second crop from benzene, was again recrystallized, evaporation of the mother liquor yielded a bright yellow analytically pure material, m. p. 150–152°.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.89; H, 4.65. Found: C, 73.91; H, 4.52.

The intermediate fractions contained most of the product and melted over wide ranges. Since preparation of either isomer in a pure state involved a large loss of material, the mixture was converted to the sulfonamides.

2-Amino-6(or 7)-chloroquinoxaline.—A mixture of 7.0 g. of 7(or 8)-chloroalloxazine and 30 ml. of 28% ammonia water was heated in a bomb at 165° for ten hours. The mixture was diluted with 10 volumes of water, heated to 90° and filtered. The filtrate was acidified with hydrochloric acid, and the gelatinous precipitate was filtered and dried. The crude product, 5.1 g. (81.5% yield), was difficult to purify and was used without purification in the next step. The compound melted with evolution of gas at 188–190°.

The amine was obtained when 4 g. of the crude amino acid was refluxed with 40 ml. of nitrobenzene for fifteen minutes. The product was extracted with dilute hydrochloric acid and precipitated with sodium hydroxide. The crude amine, 1.2 g. (37% yield) melted at 192–196° (skeleton unmelted at 225°). When 0.5 g. of the product was heated with 20 ml. of ethanol, 0.15 g. of insoluble material that did not melt at 400° was obtained. The ethanol filtrate when concentrated to 5 ml. and cooled yielded material, m. p. 193–195° (0.2 g.). An analytical sample, m. p. 197–200°, was obtained by sublimation at 150° in high vacuum.

Anal. Calcd. for $C_8H_6N_3Cl$: C, 53.50; H, 3.37; N, 23.39. Found: C, 53.36; H, 3.70; N, 23.19.

The amine was obtained more readily by cleaving 7(or 8)-chloroalloxazine with approximately 75% sulfuric acid. 7(or 8)-Chloroalloxazine was added to the solution obtained by mixing 50 ml. of water and 200 ml. of concentrated sulfuric acid. The mixture was heated to 200° as rapidly as foaming would allow and held at this temperature for twenty minutes and then poured on ice, and the solution was made strongly alkaline with sodium hydroxide. The precipitate, 7.0 g. (23% yield), was purified by dissolving in hot 1.3 *N* hydrochloric acid, treating with Darco G-60, and precipitating with sodium hydroxide. The product, 5.0 g. (16% over-all yield) melting at 198–199°, was used without further purification for the preparation of the sulfonamide derivative.

2-Chloro-3-methylquinoxaline.—200 ml. of phosphorus oxychloride was added to a refluxing mixture of 57.5 g. of 2-hydroxy 3-methylquinoxaline[7] and 300 ml. of benzene. After refluxing for two hours, most of the material had dissolved to give a dark purplish solution. The re-

(12) All melting points are uncorrected.

(13) Microanalyses were kindly performed by R. N. Boos, W. K. Humphry, E. H. Thornton and E. Meiss.

(14) Kuhn and Cook, *Ber.*, **70**, 761 (1937).

action mixture was added to a stirred mixture of 2 kg. of ice and water. The benzene layer was separated, and the water layer was extracted with six 250-ml. portions of benzene. The benzene extracts were combined, heated with 10 g. of Norit, and concentrated to dryness *in vacuo*. Recrystallization of the residue from ethanol gave the product (37.5 g.) in 52% yield, m. p. 84–86°.

Anal. Calcd. for $C_9H_7N_2Cl$: C, 60.50; H, 3.95. Found: C, 60.97; H, 4.61.

2-Amino-3-methylquinoxaline.—A mixture of 40 g. of 2-chloro-3-methylquinoxaline, 30 ml. of liquid ammonia and 250 ml. of absolute ethanol was heated for eight hours at 120°. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was extracted with 200 ml. of warm 1.2 *N* hydrochloric acid. The insoluble non-reacted chloro compound weighed 8.0 g. The acid solution was filtered, heated with Norit for five minutes, filtered again and the crude amine precipitated with sodium hydroxide. The crude product was purified by recrystallization from 200 ml. of benzene, and the mother liquor was used for two extractions of the insoluble material, total yield 20.4 g. (70% of theoretical based on the chloro compound used), m. p. 163–165°.

Anal. Calcd. for $C_9H_9N_3$: C, 67.89; H, 5.70. Found: C, 68.20; H, 5.95.

5-Acetylaminoquinoxaline.—A solution of 6.0 g. of 2,3-dinitroacetanilide[15] in 150 ml. of methanol was shaken with hydrogen in the presence of Raney nickel catalyst until the reduction was complete. The reaction mixture was quickly filtered from the catalyst into a solution of 8.0 g. of sodium glyoxal bisulfite in 150 ml. of water. After removing the methanol and heating at 100° for one hour, the reaction mixture was cooled and made alkaline with 25 ml. of 2.5 *N* hydroxide. After cooling to 5° the product, 2.76 g. (55% yield), m. p. 131°, was obtained by filtration. Without further purification the product was converted into the amine.

5-Aminoquinoxaline.—A mixture of 2.5 g. of 5-acetylaminoquinoxaline and 25 ml. of 2 *N* sulfuric acid was heated one hour on the steam-bath, cooled and neutralized with sodium bicarbonate. After cooling to 5° the product was filtered and washed with ice-water, yielding 1.9 g. (87.5% yield) of bright yellow crystals, m. p. 92°.

Anal. Calcd. for $C_8H_7N_3$: C, 66.17; H, 4.86; N, 28.94. Found: C, 66.24; H, 4.78; N, 28.4.

2-*p*-Aminobenzamidoquinoxaline.—A mixture of 11.0 g. of *p*-nitrobenzoyl chloride and 8.5 g. of 2-aminoquinoxaline in 15 ml. of pyridine was heated on the steam-bath for one hour and poured into 170 ml. of water. The crude product, 13.6 g., was recrystallized from ethyl acetate. The purified material, m. p. 211°, weighed 7.8 g.

A suspension of 10 g. of the *p*-nitrobenzoate in 300 ml. of methanol was shaken with hydrogen in the presence of 2 g. of Raney nickel catalyst. The hydrogenation was stopped when 3.1 moles of hydrogen had been absorbed. After adding an equal volume of acetone the solution was filtered from the catalyst and concentrated to dryness *in vacuo*. The residue was dissolved in 50 ml. of 2.5 *N* hydrochloric acid, filtered from a small amount of insoluble material and precipitated by adding 1 *N* sodium hydroxide. The crude product, 7.9 g., was recrystallized from a mixture of equal parts of ethanol and ethyl acetate. The pure material, 5.5 g. (62% yield), melts at 229–230°

Anal. Calcd. for $C_{15}H_{13}ON_4$: C, 67.90; H, 4.58; N, 21.19. Found: C, 68.07; H, 4.73; N, 21.6.

Sulfonamides.—The amines were treated with *p*-acetylaminobenzenesulfonyl chloride in pyridine solution. The acetyl compounds were obtained in yields of 70–95%. The preparation of 2(and 3)-sulfanilamido-5,6-benzoquinoxaline is typical.

2(and 3)-[N⁴-Acetylsulfanilamido]-5,6-benzoquinoxaline).—At room temperature 5.6 g. of *p*-acetylaminobenzenesulfonyl chloride was added to a solution of 4.5 g. of 2(and 3)-amino-5,6-benzoquinoxaline in 25 ml. of pyridine. The mixture was stirred for one and one-half hours and then poured into 500 ml. of water. Heating and stirring the mixture made the gum that first separated solidify. The precipitate was filtered and dissolved in 200 ml. of 2 *N* sodium hydroxide and filtered from the insoluble material (0.2 g.). After being stirred for ten minutes with 1 g. of Norit, the solution was filtered and made acidic. The dried yellow product weighed 8.6 g. (95% yield). The acetyl derivatives were hydrolyzed with ethanolic hydrogen chloride.

2(and 3)-Sulfanilamido-5,6-benzoquinoxaline.—A mixture of 8.6 g. of the acetyl compound, 50 ml. of absolute ethanol and 25 ml. of concentrated hydrochloric acid was stirred and refluxed one and one-half hours. The solution darkened, and a reddish precipitate appeared. The mixture was poured into 300 ml. of water and 30% sodium hydroxide added until the solution was alkaline. After 2 g. of Norit was added the solution was heated to boiling, filtered, and the product precipitated by acidification with acetic acid. The light yellow powder weighed 6.0 g. (78% yield).

Summary

Isomers and nuclear substituted derivatives of 2-sulfanilamidoquinoxaline were prepared. The degradation of 7,8-dimethylalloxazine, 7(or 8)-chloroalloxazine and "benzalloxazine" to the corresponding 2-aminoquinoxaline has been carried out. The preparation of 2-amino-3-methylquinoxaline by another method has been described.

RAHWAY, N. J. RECEIVED FEBRUARY 28, 1948

(15) Kaufmann and Hussy, *Ber.*, **41**, 1740 (1908).