m. p. of 116–118°. Andreocci reported 116° after one recrystallization from ether and gasoline.

Bromination of *l*-β-Desmotropo-santonous Acid.—*l*-β-desmotropo-santonous acid was brominated as above. The bromo-*l*-β-desmotropo-santonous acid was obtained as rectangular plates, m. p. 122–123°. Since Andreocci reported the m. p. of this acid as 92°, his procedure was repeated. The methyl ester of *l*-β-desmotropo-santonous acid was brominated as usual. The crude bromo-ester was saponified by 10% aqueous potassium hydroxide solution without further purification. The alkaline solution was then filtered and acidified. The solid separated was collected and dissolved in ether. The ethereal solution was extracted with sodium bicarbonate solution. The bicarbonate extract was then acidified and the collected precipitate crystallized from a mixture of ether and gasoline. After four recrystallizations from ether and gasoline, the bromo-*l*-β-desmotropo-santonous acid gave the m. p. of 120–122°; mixed m. p. with the above product 120–121°.

Coupling of Bromo-*d*-α-desmotropo-santonous Acid with *p*-Nitrobenzenediazonium Chloride.—Twenty-five hundredths gram of bromo-*d*-α-desmotropo-santonous acid was dissolved in 5 ml. of 10% potassium hydroxide solution. The solution was cooled to 0° and a cold solution of *p*-nitrobenzenediazonium chloride (one-tenth of the solution obtained by diazotizing 1 g. of *p*-nitroaniline in 2.5 ml. of concentrated hydrochloric acid with 0.55 g. of sodium nitrite in a few ml. of water) was added. The coupling took place immediately and the solution showed a deep red color. The solution was then acidified and the precipitate collected. The dried product was recrystallized two times from alcohol as red needles, m. p. 214–215°. A qualitative test for halogen gave a negative result.

Coupling of *d*-α-Desmotropo-santonous Acid with *p*-Nitrobenzenediazonium Chloride.—Thirty-seven hundredths gram of *d*-α-desmotropo-santonous acid was coupled with one-fifth of the above diazotized solution as above. The dyestuff was recrystallized two times from alcohol and obtained as red soft needles, m. p. 214–215°, not depressed with the dyestuff obtained above.

Coupling of Bromo-*d*-β-desmotropo-santonin (X) with Benzenediazonium Chloride.—The procedure of Wedekind and Schmidt[9] was followed using bromo-*d*-β-desmotropo-santonin instead of *d*-β-desmotropo-santonin. An immediate coupling occurred and the solution showed a deep red color. The solution was then acidified and the precipitate collected. It was treated with boiling alcohol and the alcohol insoluble substance was crystallized from benzene as yellow fine needles, m. p. 259–260° with decomposition. It gave no depression of m. p. by admixture with an authentic sample of benzeneazo-*d*-β-desmotropo-santonin (XI) (m. p. 261–262°) obtained by coupling *d*-β-desmotropo-santonin (XII) with diazotized aniline (Wedekind and Schmidt[9]).

Summary

1. Bromo-*l*-α-desmotropo-santonin acetate was obtained by the enol acetylation of monobromo-santonin.

2. The desmotropo-santonins could be directly brominated to the corresponding bromo-desmotropo-santonins. The racemic bromo-desmotropo-santonins could be obtained by either brominating the racemic desmotropo-santonins or racemizing the bromo-*d*- and bromo-*l*-desmotropo-santonins.

3. The bromo-*d*-β- and bromo-*l*-β-desmotropo-santonins could be converted into the bromo-*d*-α- and bromo-*l*-α-desmotropo-santonins, respectively, by fusing with alkali.

4. The bromo-*d*-β and bromo-*l*-α-desmotropo-santonous acids were prepared by the direct bromination of the corresponding desmotropo-santonous acids.

5. The position of the bromine atom in the bromo-desmotropo-santonins and the bromo-desmotropo-santonous acids has been established.

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

Sulfaquinoxaline and Some Related Compounds

BY JOHN WEIJLARD, MAX TISHLER AND A. E. ERICKSON

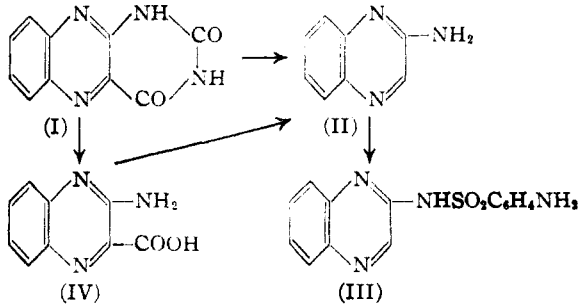
Of the large number of the known N[1] heterocyclic derivatives of sulfanilamide, only a few have proved acceptable as chemotherapeutic agents. These drugs, including sulfapyridine, sulfathiazole, sulfadiazine and sulfapyrazine have the common structural unit N=C—NH of which the N=C group is part of an aromatic, heterocyclic system. With the exception of certain of the methyl derivatives such as sulfamethyldiazine, nearly all other ring substituted derivatives of this class have been found to be less effective than the parent compounds. This generalization also extends to the benzoheterocyclic sulfa drugs, such as 2-sulfanilamidoquinoline, 2-sulfanilamidobenzothiazole, and 2-sulfanilamidoimidazole.[1]

In connection with the synthesis of new sulfonamides, we prepared 2-sulfanilamidoquinoxaline (III) which, in contrast to the known benzoheterocyclic sulfa compounds, is of interest as a chemotherapeutic agent. The pharmacology and the chemotherapeutic activity of sulfaquinoxaline and of some of its derivatives mentioned in this report are being extensively studied by the Merck Institute for Therapeutic Research, and detailed reports of these investigations will be published elsewhere. Bacterial efficacy experiments with sulfaquinoxaline indicate that this drug is as effective as sulfadiazine or sulfapyrazine in experimental pneumococcal infections in mice when fed every six hours over a five day period, and much more effective when fed once daily over a five day period. Sulfaquinoxaline was found to be remarkable in that following a single dose, the drug remains in the blood for a long time and, consequently, chemotherapeutically effective blood concentrations can be maintained by ad-

(1) For general literature reviews, see E. H. Northey, *Ind. Eng. Chem.*, **35** 829 (1943).

ministering the drug at comparatively infrequent intervals.[2]

2-Aminoquinoxaline, II, required for the preparation of sulfaquinoxaline, was synthesized from alloxazine, I, by two different procedures. In one method, alloxazine was cleaved to 2-aminoquinoxaline by heating with concd. sulfuric acid at 240–250° for ten minutes. The second method consists of hydrolyzing alloxazine to 2-aminoquinoxaline-3-carboxylic acid[3] by heating with concd. ammonia water at 170–175° for five hours and decarboxylating the amino acid. In connection with the hydrolysis of alloxazine it is interesting to note that the use of sodium hydroxide in place of ammonium hydroxide does not lead to the amino acid but rather to 2-hydroxyquinoxaline-3-carboxylic acid.[4] In this connection, our observation that 2-aminoquinoxaline-3-carboxylic acid on treatment with alkali at elevated temperatures yields the hydroxy acid is of interest.



Sulfaquinoxaline was prepared by treating 2-aminoquinoxaline with acetylsulfanilyl chloride in the presence of pyridine and hydrolyzing the resulting acetyl derivative. In addition, several N^4 derivatives of sulfaquinoxaline have been prepared (caproyl-, benzoyl-, succinyl-), as well as 2-sulfanilamidoquinoxaline-3-carboxylic acid. The latter was synthesized by condensing 2-amino-3-carboethoxyquinoxaline with acetylsulfanilyl chloride and hydrolyzing the resulting compound. Condensation of the free 2-aminoquinoxaline-3-carboxylic acid with the sulfonyl chloride failed.

Experimental

2-Aminoquinoxaline-3-carboxylic Acid.—Ten grams of crude alloxazine was mixed with 50 cc. of concentrated ammonia and heated in a steel bomb at 170–175° for five hours. The reaction mixture was diluted with 150 cc. of water, and the greater part of the ammonia removed by boiling the solution for a short while. The hot solution was treated with *norite*, filtered and acidulated with hydrochloric acid to *p*H 2.5 and chilled to 2°. The light yellow crystals were collected on a filter, washed with water and dried at 80°; yield 6.3 g., 71.3%; m. p. 204°.

Anal. Calcd. for $C_9H_7O_2N_3$: C, 57.12; H, 3.73; N, 22.22. Found: C, 56.71; H, 3.77; N, 22.12.

2-Aminoquinoxaline.—(a) Two grams of alloxazine was mixed with 10 cc. of 95% sulfuric acid and heated at 240–245° for ten minutes. The reaction mixture was diluted with water, made alkaline with sodium hydroxide and extracted to completion with ether; yield 0.76 g. of pale yellow needles (56%); m. p. 155–156°.

Anal. Calcd. for $C_8H_7N_3$: C, 66.16; H, 4.86; N, 28.96. Found: C, 66.08; H, 5.04; N, 28.78.

(b) Two grams of 2-aminoquinoxaline-3-carboxylic acid was dissolved in 8 cc. of hot nitrobenzene, and the solution was boiled under reflux for ten minutes, then cooled and diluted with 40 cc. of petroleum ether. The crystals were collected and washed with liberal amounts of petroleum ether; yield 1.53 g., m. p. 150–151°. Purification was effected by dissolving in 10% alkali and extracting with ether to completion. After distilling off the ether, the residue weighed 1.41 g. (92%) yield, m. p. 155–156°.

Anal. Found: C, 66.05; H, 5.17; N, 28.78.

2-Acetylaminoquinoxaline.—On acetylating 2-aminoquinoxaline with acetic anhydride, yellow crystals were obtained, m. p. 192.5–193.5°.

Anal. Calcd. for $C_{10}H_9ON_3$: C, 64.14; H, 4.85; N, 22.46. Found: C, 64.17; H, 5.14; N, 22.70.

2-Amino-3-carbethoxyquinoxaline.—A mixture of 10 g. of 2-aminoquinoxaline-3-carboxylic acid, 250 cc. of absolute alcohol and 100 cc. of saturated alcoholic hydrochloric acid was boiled under reflux for three hours. The resulting solution was concentrated to 200 cc., chilled to 0° and the crystalline product filtered; yield 10.1 g. of the ester hydrochloride, m. p. 173–175°. The ester hydrochloride was suspended in water and treated cautiously with 5 g. of sodium bicarbonate. The product was filtered, washed well with water and dried; yield 8.5 g., m. p. 165–166°. For analysis, a sample was recrystallized from ethanol (m. p. unchanged).

Anal. Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.80; H, 5.10; N, 19.36. Found: C, 60.63; H, 5.05; N, 19.66.

2-Sulfanilamidoquinoxaline.—To 200 cc. of dry, reagent pyridine at −5° was added with stirring 0.69 g. of powdered aminoquinoxaline followed in about two minutes by 1.23 g. of acetylsulfanilyl chloride. The reactants dissolved readily. After five minutes the same amount of amine and chloride were added in the same manner maintaining the internal temperature around 0°. Portionwise additions of the reactants were made in five-minute intervals until 20.7 g. of amine and 36.9 g. of the chloride had been added. The mixture was stirred at 0° for one hour and then for four hours, at room temperature. The reaction mixture was concentrated to dryness under reduced pressure and the residue was granulated by adding water and stirring at 0°. The filtered, crude 2-N^4-acetylsulfanilamidoquinoxaline weighed 44.5 (91.2%). For analysis a sample of 0.10 g. was purified by dissolving in 5 cc. of hot acetic acid containing 1 cc. of acetic anhydride, cooling and diluting with 20 cc. of water. The pure product melts at 243–244°.

Anal. Calcd. for $C_{16}H_{14}O_3N_4S$: C, 56.10; H, 4.12; N, 16.37. Found: C, 56.37; H, 4.15; N, 16.38.

The deacetylation of the crude acetyl compound was carried out in alcoholic hydrochloric acid. A mixture of 6 g. of the above crude acetyl compound, 25 cc. of concd. hydrochloric acid and 50 cc. of ethanol was refluxed one hour. Water (125 cc.) was added to the mixture followed by ammonia water until the mixture was slightly acid. The mixture was chilled, filtered and the product washed with water. The product was purified by dissolving in 50 cc. of 3% sodium hydroxide, treating with norite, filtering and adding acetic acid to the filtrate to weak acidity. The filtered product was washed well with water and dried; yield 3.85 g., m. p. 247–248°.

Anal. Calcd. for $C_{14}H_{12}O_3N_4S$: C, 55.96; H, 4.03; N, 18.66. Found: C, 56.07; H, 4.27; N, 18.54.

(2) The study of the pharmacology and chemotherapeutic activity of sulfaquinoxaline and some of its derivatives is being carried out by Dr. A. O. Seeler and by Dr. H. Robinson of the Merck Institute for Therapeutic Research.

(3) 2-Aminoquinoxaline-3-carboxylic acid was prepared previously by Philips, *Ber.*, **28**, 1655 (1895), from quinoxaline-2,3-dicarboxylic acid in three steps involving a Hofmann degradation.

(4) Kühling, *ibid.*, **24**, 2364 (1891); Hinsberg, *Ann.*, **292**, 245 (1896); Kühn and Bär, *Ber.*, **67**, 898 (1934).

TABLE I

Compound[a]	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-N⁴-Benzoyl-S-quinoxaline[b]	259–260	$C_{21}H_{16}O_3N_4S$	62.34	3.99	13.86	62.18	4.04	13.72
2-N⁴-Caproyl-S-quinoxaline[c]	199–200	$C_{20}H_{22}O_3N_4S$	60.28	5.56	14.07	59.98	5.60	13.81
2-N⁴-Succinyl-S-quinoxaline[d]	234–235	$C_{18}H_{16}O_5N_6S$	53.97	4.07	14.00	53.96	4.05	14.30
2-N⁴-Acetyl-S-3-carboethoxyquinoxaline[e]	236–237	$C_{19}H_{18}O_5N_4S$	55.04	4.38	13.53	54.85	4.78	13.55
2-S-3-Carboxyquinoxaline[e]	238–239	$C_{15}H_{12}O_4N_4S$	52.30	3.51	16.28	52.58	3.91	16.46

[a] S = Sulfanilamido. [b] This compound was obtained by the action of benzoyl chloride on the sulfa drug in pyridine, and purified by crystallizing in a mixture of acetone, isopropanol and water. [c] Prepared from caproyl chloride on the sulfa drug in pyridine, and purified in alcohol–water. This compound shows a tendency to melt or soften at 150–152°, but it solidifies at once, then melts at 199–200°. [d] Prepared with succinyl anhydride and the sulfa drug in pyridine at 90° for two hours. The reaction mixture was diluted with water and the product obtained after adding excess of acetic acid. This compound has a free acid group, and dissolves in sodium bicarbonate solutions. [e] Prepared in the manner described for sulfaquinoxaline.

Acknowledgment.—The authors wish to thank Dr. R. T. Major and Dr. J. R. Stevens for their interest and suggestions.

Summary

1. The synthesis of 2-aminoquinoxaline as well as its conversion to 2-sulfanilamidoquinoxaline has been described.

2. Preliminary chemotherapeutic studies indicate that 2-sulfanilamidoquinoxaline is very effective in bacterial infections and that it has the unusual property of being eliminated by animals very slowly so that effective concentrations can be maintained by administering it at comparatively infrequent intervals.

RAHWAY, N. J. RECEIVED JULY 19, 1944

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

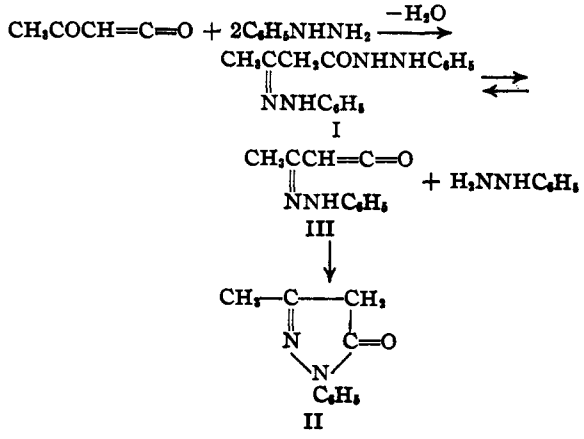
The Reactions of Arylhydrazines with Diketene and the Preparation of 1-Aryl-5-methyl-3-pyrazolones

BY H. Z. LECHER, R. P. PARKER AND R. C. CONN

While investigating some potential uses of diketene, we studied its reaction with arylhydrazines under various conditions. It was known to prepare 1-aryl-3-methyl-5-pyrazolones from these starting materials. We found that the isomeric 1-aryl-5-methyl-3-pyrazolones too may be easily prepared from them. In contrast to the 5-pyrazolones these 3-pyrazolones have not been as extensively investigated. This is probably due to the fact that their preparation has been cumbersome.

In their investigation of diketene Chick and Wilsmore[1] treated it with phenylhydrazine and obtained the phenylhydrazone of acetoacetic phenylhydrazide (I). More recently Johnson[2] treated phenylhydrazine with diketene in different proportions and under different conditions and obtained 1-phenyl-3-methyl-5-pyrazolone (II). He used equal molecular quantities in an inert solvent and worked at temperatures higher than 40°. He stated that an intermediate compound is formed during his process, but did not specify the nature of this compound.

By adding two molecular proportions of phenylhydrazine to one of diketene in benzene solution we obtained I in good yield, if the temperature was not allowed to rise. Above room temperature some II was formed, the quantity increasing as the temperature was raised. Addition of one molecular proportion of diketene to I resulted in the formation of II in a 79% yield.



From this it seemed probable that I undergoes a slight thermal dissociation into phenylhydrazine and the phenylhydrazone of diketene (III). This dissociation also seemed to be reversible because I was recovered unchanged after being heated alone in boiling benzene.

Some substantiation of this hypothesis was afforded by the behavior of I on heating above its melting point. Melting was followed by decomposition with liberation of ammonia and forma-

(1) Chick and Wilsmore, *J. Chem. Soc.*, **93**, 948 (1908).
(2) F. Johnson, U. S. Patent 2,017,815.