methylamine[5] (20 ml.). The flask was heated until the temperature of the contents reached about 210°. The residue (viscous brown oil) was cooled, dissolved in hot 95% ethanol, decolorized with Norit A, and filtered. On cooling, 5.5 g. (56%) of white woolly crystals, m.p. 147–150°, was obtained. Two recrystallizations from the same solvent raised the melting point to 154–155° (short woolly needles).

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.10; N, 5.01. Found: C, 60.32; H, 6.30; N, 5.21.

N-Methyl-2-(3,5-dimethoxy-4-hydroxyphenyl)succinimide (IV).—The reaction was carried out as for III. From I (10 g., 0.037 mole), IV (6.4 g., 66%) was obtained as yellowish white crystals, m.p. 183–186°. Two recrystallizations, using Norit A once for decolorization, raised the melting point to 186–187°, white crystals.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66; N, 5.28. Found: C, 58.67; H, 5.76; N, 5.15.

(5) C. A. Miller and L. M. Long, *J. Am. Chem. Soc.*, **73**, 4895 (1951).

Synthesis of Some Hydroxylamine Derivatives of Pyrimidines and Purines[1]

PAULINE K. CHANG

Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut

Received July 27, 1965

Because of interest in orotic acid analogs in this laboratory,[2] 6-N-hydroxylaminouracil (I) and uracil-6-hydroxamic acid (II) have been synthesized. 6-N-Hydroxylaminopurine ribonucleoside (III) was regarded as an analog of adenosine, because 6-N-hydroxylaminopurine[3] is active as an analog of both adenine and hypoxanthine.[4]

2,4-Dimethoxy-6-chloropyrimidine[5,6] failed to react with hydroxylamine; however, the demethylated derivative, 6-chlorouracil,[7] reacted smoothly with hydroxylamine to give I. Compound II was prepared from methyl orotate,[8] whereas III was prepared from 6-chloropurine ribonucleoside[9] and hydroxylamine.

Experimental Section[10]

6-N-Hydroxylaminouracil (I).—A solution of KOH (11.2 g., 0.2 mole) in ethanol (40 ml.) was added to a solution of hydroxylamine hydrochloride (12 g., 0.17 mole) in boiling ethanol (200 ml.). The precipitated KCl was filtered. 6-Chlorouracil[7] (1 g., 0.007 mole) was added to the solution of hydroxylamine. The mixture was refluxed for 1 hr. and allowed to cool to room temperature with stirring (1 hr.). The product, which separated as a solid, was washed with water and ethanol to give analytically pure I (0.73 g., 74%), m.p. 280° dec., λ_{max}^{pH2} 264 mμ (ε 6250).

Anal. Calcd. for $C_4H_5N_3O_3$: C, 33.57; H, 3.52; N, 29.36. Found: C, 33.56; H, 3.77; N, 29.25.

Uracil-6-hydroxamic Acid (II).—A mixture of methyl orotate[8] (1.25 g., 0.0074 mole), $NH_2OH \cdot HCl$ (1.4 g., 0.02 mole), and water (10 ml.) was cooled to 0°. With stirring, NaOH (12.5 *N*, 3.6 ml.) was added to the mixture dropwise at 3°. The now clear solution was adjusted to pH 5 with concentrated HCl. Crude II, which separated out as a yellow solid, was recrystallized from water to yield the monohydrate (1.2 g., 86%), m.p. 250° dec., λ_{max}^{pH2} 274 mμ (ε 7420). It was recrystallized twice from water to give the analytical sample.

Anal. Calcd. for $C_5H_5N_3O_4 \cdot H_2O$ [sample dried at 60° (0.1 mm.)]: C, 31.75; H, 3.73; N, 22.22. Found: C, 31.72; H, 3.99; N, 22.29. Calcd. for $C_5H_5N_3O_4$ [sample dried at 120° (0.1 mm.)]: C, 35.10; H, 2.95; N, 24.56. Found: C, 35.22; H, 3.15; N, 24.37.

6-N-Hydroxylamino-9-β-D-ribofuranosylpurine (III).—To a solution of hydroxylamine hydrochloride (0.7 g., 0.01 mole) in boiling ethanol (10 ml.) was added a solution of KOH (0.56 g., 0.01 mole) in ethanol (3 ml.). The precipitated KCl was filtered. 6-Chloro-9-β-D-ribofuranosylpurine[9,11] (0.286 g., 0.002 mole), dissolved in ethanol (20 ml.), was added to the solution of NH_2OH. The mixture was refluxed for 1 hr. and then concentrated *in vacuo* at 40°. The residue (412 mg.) was recrystallized from hot ethanol to yield the pure product (200 mg., 70%), m.p. 195° dec., λ_{max}^{pH2} 262.5 mμ (ε 16,700). The analytical sample was recrystallized once more from ethanol.

Anal. Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.72. Found: C, 42.42; H, 4.77; N, 24.94.

(11) Purchased from Cyclo Chemical Corp., Los Angeles, Calif.

(1) This work was supported by a grant (CA-02817) from the National Cancer Institute, U. S. Public Health Service.

(2) R. E. Handschumacher, *Cancer Res.*, **23**, 643 (1963).

(3) A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.*, **80**, 3932 (1958).

(4) A. C. Sartorelli, A. L. Bieber, P. K. Chang, and G. A. Fischer, *Biochem. Pharmacol.*, **13**, 507 (1964).

(5) H. J. Fisher and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 727 (1932).

(6) S. B. Greenbaum and W. L. Holmes, *ibid.*, **76**, 2899 (1954).

(7) J. P. Horwitz and A. J. Tomson, *J. Org. Chem.*, **26**, 3392 (1962).

(8) J. J. Fox, N. Yung, and I. Wempen, *Biochem. Biophys. Acta*, **23**, 295 (1957).

(9) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(10) Melting points were determined in a capillary tube in a copper block and are corrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and by Midwest Microlab, Inc., Indianapolis, Ind.

Quinoxaline Sulfonamides

S. H. DANDEGAONKER AND C. K. MESTA

Department of Chemistry, Karnatak University, Dharwar, India

Received June 16, 1965

The development of the field of chemotherapy has more recently led to a renewed interest in the quinoxalines in connection with their potential values as pharmaceuticals.[1-5] We have synthesized some halogenated quinoxaline sulfonamides in view of the reported effect of chlorine atoms on the activity of quinoxalines.[6]

Sulfonamides on condensation with 2,3-dichloroquinoxaline using the procedure of Wolf, *et al.*,[7] gave disulfonamide derivatives when 2 moles of sulfonamide was used, and a mixture of predominantly mono- and small amounts of disulfonamides when 1 mole of sulfonamide was employed. The reaction of sulfanilamide and 2,3-dichloroquinoxaline confirmed the findings of Wolf and co-workers[7] and Platt and Sharp[8] that the free amino group does not take part in condensation.

2,3-Dichloroquinoxaline on reaction with benzamide in different ratios gave only 2,3-dibenzamidoquinoxaline under similar conditions. Acetamide, on heating with dichloroquinoxaline at 130° or refluxing in ethanol, afforded a mixture of products, with or without chlorine. Interaction of sodamide with dichloroquinoxaline in boiling toluene either in a stoichiometric ratio or with an excess gave a mixture of unidentifiable products.

Experimental Section

2,3-Dihydroxyquinoxaline[9] (91%), white needles, m.p. 320°; 2,3-dichloroquinoxaline[10] (75%), colorless shining long needles,

(1) R. M. Acheson, *J. Chem. Soc.*, 4731 (1956).

(2) O. Gawron, and F. E. Spoerri, *J. Am. Chem. Soc.*, **67**, 514 (1945).

(3) R. H. Mizzoni and P. E. Spoerri, *ibid.*, **67**, 1652 (1945).

(4) K. Pfister, III, A. P. Sullivan, J. Weijlard, and M. Tisbler, *ibid.*, **73**, 4955 (1951).

(5) J. Weijlard and M. Tisbler, U. S. Patent 2,404,199 (July 16, 1946); *Chem. Abstr.*, **40**, 6100 (1946).

(6) A. F. Crowther, F. H. S. Curd, D. G. Davey, and G. S. Stacey, *J. Chem. Soc.*, 1260 (1949).

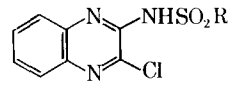
(7) F. J. Wolf, K. Pfister, III, R. H. Beutal, R. M. Wilson, C. A. Robinson, and J. R. Stevens, *J. Am. Chem. Soc.*, **71**, 6 (1949).

(8) B. C. Platt and T. M. Sharp, *J. Chem. Soc.*, 2129 (1948).

(9) M. A. Phillips, *ibid.*, 1143 (1931); 2393 (1928).

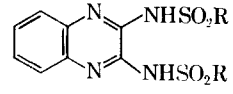
(10) O. Hinsberg and J. Pollak, *Ber.*, **29**, 784 (1896).

TABLE I: 2-R-3-CHLOROQUINOXALINES



No.	R	Procedure	Yield, %	M.p., °C.	Properties	Crystn. solvent	Formula	—Nitrogen, %— Calcd.	Found
1	2-(*o*-Methylbenzenesulfonamido)-	A	65.5	251–253	Yellow shining stout needles	AcOH	$C_{15}H_{12}ClN_3O_2S$	12.60	12.66
2	2-(*p*-Methylbenzenesulfonamido)-	A	62.6	250–251	Pale yellow shining needles	EtOH	$C_{15}H_{12}ClN_3O_2S$	12.60	12.86
3	2-(*p*-Acetamidobenzenesulfonamido)-	A	43.2	264–266	Dark brown microscopic needles	AcOH	$C_{16}H_{13}ClN_4O_3S$	14.87	14.56
4	2-(*p*-Bromobenzenesulfonamido)-	A	50.0	242–243	Yellow shining microscopic needles	AcOH	$C_{14}H_9BrCl\ N_3O_2S$	10.54	10.70
5	2-(*p*-Aminobenzenesulfonamido)-	A	58.0	216–217 dec.	Brown amorphous pwd.	Dioxane	$C_{14}H_{11}ClN_4O_2S$	16.74	16.56
6	5,7-Dichloro-2-(*o*-methylbenzenesulfonamido)-	B	67.7	232–234	Green shining crystals	EtOH	$C_{15}H_{10}Cl_3N_3O_2S$	10.43	10.79
7	5,7-Dichloro-2-(*p*-methylbenzenesulfonamido)-	B	68.4	285–287	Colorless shining tiny globules	EtOH	$C_{15}H_{10}Cl_3N_3O_2S$	10.43	10.70
8	5,7-Dichloro-2-(*p*-acetamidobenzenesulfonamido)-	B	35.7	242–243	Yellow shining needles	EtOH	$C_{16}H_{11}Cl_3N_4O_3S$	12.57	12.45
9	5,7-Dichloro-2-(*p*-bromobenzenesulfonamido)-	B	67.0	252–254	Yellow shining plates	Ethylene dichloride	$C_{14}H_7BrCl_3N_3O_2S$	8.98	9.10

TABLE II: 2,3-DI-R-QUINOXALINE



No.	R	Procedure	Yield, %	M.p., °C.	Properties	Crystn. solvent	Formula	—Nitrogen, %— Calcd.	Found
1	-(*o*-methylbenzenesulfonamido)-	B	63.7	246–248	Yellow shining needles	AcOH	$C_{22}H_{20}N_4O_4S_2$	11.97	11.79
2	-(*p*-methylbenzenesulfonamido)-	B	64.2	255–256	Pale yellow shining microscopic needl s	C_6H_6	$C_{22}H_{20}N_4O_4S_2$	11.97	12.08
3	-(*p*-acetamidobenzenesulfonamido)-	B	66.8	290–291 dec.	Greenish yellow needles	AcOH	$C_{24}H_{22}N_6O_6S_2$	15.17	14.95
4	-(*p*-bromobenzenesulfonamido)-	B	64.0	269–270	Brown shining plates	EtOH	$C_{20}H_{11}Br_2N_2O_4S_2$	9.36	9.08
5	-(*p*-aminobenzenesulfonamido)-	B	67.5	280–281 dec.	Greenish amorphous pwd.	Dioxane	$C_{20}H_{18}N_6O_4S_2$	17.87	17.56
6	-(*o*-methylbenzenesulfonamido)-5,7-dichloro-	B	34.7	247–148	Pale yellow amorphous pwd.	Aq. Me_2CO	$C_{22}H_{18}Cl_2N_4O_4S_2$	10.42	10.77
7	-(*p*-methylbenzenesulfonamido)-5,7-dichloro-	B	28.7	270–272	Pale yellow needles	AcOH	$C_{22}H_{18}Cl_2N_4O_4S_2$	10.42	10.52
8	-(*p*-methylbenzenesulfonamido)-5,7-dichloro-	B	29.7	211–212 dec.	Greenish yellow leaflets	Aq. Me_2CO	$C_{24}H_{20}Cl_2N_6O_6S_2$	13.48	13.69
9	-(*p*-bromobenzenesulfonamido)-5,7-dichloro-	B	41.3	265–67 dec.	Yellow tiny needles	C_6H_6	$C_{20}H_{12}Br_2Cl_2N_4O_4S_2$	8.40	8.72
10	-(*p*-aminobenzenesulfonamido)-5,7-dichloro-	B	28.5	285–287 dec.	Pale yellow crystals	AcOH	$C_{20}H_{16}Cl_2N_6O_4S_2$	15.59	15.46
11	-benzamido-		52.5	320	Colorless amorphous pwd.	Insol. in org. solvents	$C_{20}H_{16}N_4O_2$	15.22	14.97

m.p. 149–50°; 4,6-dichloro-2-nitroaniline[11] (65%), brown long needles, m.p. 110–111°; 4,6-dichloro-*o*-phenylenediamine[12] ($SnCl_2$–HCl reduction, 36%; NaOH–Zn dust reduction in alcohol, 30%), colorless shining long needles from water, m.p. 59–60°; and *o*-toluene,[13a] *p*-toluene-, *p*-acetanidophenyl,[13a] *p*-aminophenyl,[13b] and *p*-bromophenylsulfonamides[14] were obtained by known procedures.

2,3-Dihydroxy-5,7-dichloroquinoxaline was obtained in excellent yield (86%) from the corresponding 4,6-dichloro-*o*-phenylenediamine and oxalic acid by the procedure of Shriner and Upson[15] as buff-colored shining leaflets; recrystallized from ethanol, m.p. 320°.

Anal. Calcd. for $C_8H_4Cl_2N_2O_2$: N, 12.13. Found: N, 12.17.

2,3,5,7-Tetrachloroquinoxaline.—2,3-Dihydroxy-5,7-dichloroquinoxaline, on heating with PCl_5 at 160° for 2 hr., was obtained by a procedure similar to that used by Stevens, *et al.*[16] It was converted in 52% yield to 2,3,5,7-tetrachloroquinoxaline, a pale brown solid; recrystallization from ethanol yielded colorless shining long needles, m.p. 114–115°.

Anal. Calcd. for $C_8H_2Cl_4N_2$: N, 10.45. Found: N, 10.20.

Example for Condensations. A. 2,3-Dichloroquinoxaline and Sulfonamide.—An intimate mixture of dichloroquinoxaline (2.0 g., 0.01 mole), *o*-toluenesulfonamide (1.77 g., 0.01 mole), K_2CO_3 (1.5 g.), KI (0.2 g.), and copper powder (0.1 g.) was heated slowly on an oil bath at 140–145°. The temperature of the bath was then raised to 180–185° and heating was continued for 7 hr. A white crystalline sublimate was noticed on the sides of the flask. The product was extracted with NaOH solution (10%, 50 ml.). The alkaline filtrate was acidified with dilute acetic acid. The precipitate thus obtained was filtered off, washed, and crystallized from acetic acid (Norit) to give 2-(*o*-methylbenzenesulfonamido)-3-chloroquinoxaline (3.02 g., 65.5%) as orange-yellow shining stout needles, m.p. 251–253°.

B. 2,3,5,7-Tetrachloroquinoxaline and Sulfonamide.—Tetrachloroquinoxaline (1.0 g., 0.0027 mole), *o*-toluenesulfonamide (0.638 g., 0.0027 mole), KI (0.5 g.), and copper powder (0.1 g.) were heated initially at 100–105° and then at 145–150° for 7 hr. A yellowish white sublimate was observed on the sides of flask. The product was cooled and extracted with water. The clear filtrate was acidified with glacial acetic acid. The precipitate was collected and crystallized from ethanol as green shining crystals.

(11) R. S. Datta and H. K. Mitter, *J. Am. Chem. Soc.*, **41**, 2036 (1919).
(12) S. H. Dandegaonker and G. B. Desai; *Indian J. Chem.*, **1**, 298 (1963).
(13) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1951: (a) pp. 780–782; (b) p. 871.
(14) E. R. Huntress and F. H. Carten, *J. Am. Chem. Soc.*, **62**, 511 (1940).
(15) R. L. Shriner and R. W. Upson, *ibid.*, **63**, 2277 (1941).
(16) J. R. Stevens, K. Pfister, III, and F. J. Wolf, *ibid.*, **68**, 1635 (1946).

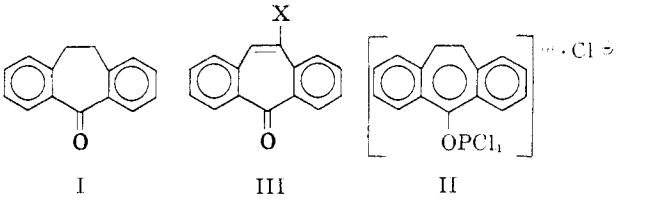
Transformation Products of 5H-Dibenzo[*a*,*d*]-10,11-dihydrocycloheptene-5-one

H. L. SLATES AND N. L. WENDLER

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey

Received June 7, 1965

An efficient and novel conversion of 5H-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene-5-one (I) to its 10,11-dehydro derivative III can be effected by PCl_5 in refluxing benzene. A red crystalline dibenzotropylium ion species formulated as II is formed as an intermediate.[1] The latter on decomposition with water yields III (X = H), whereas thermal decomposition affords the chloro derivative III (X = Cl).



I III II

(1) For another example of dibenzotropylium ion see G. Berti, *J. Org. Chem.*, **22**, 230 (1957).

Experimental Section[2]

Reaction of 5H-Dibenzo[*a*,*d*]-10,11-dihydrocycloheptene-5-one with Phosphorus Chlorides.—To a solution of 25.0 g. of dibenzo[*a*,*d*]cycloheptadien-5-one (I) in 2.5 ml. of $POCl_3$ and 50 ml. of dry benzene was added 75 g. of PCl_5 (3 equiv.) and the mixture was stirred under reflux for 2.5 hr. with protection from moisture. After *ca.* 15 min. a clear red solution resulted and a crystalline complex slowly separated accompanied by evolution of HCl. At the end of the reflux period (3 hr.), the reaction mixture was chilled to 10° and the dark red complex was isolated by filtration and washed twice with 25 ml. of dry benzene. The red complex (hygroscopic) was decomposed by portionwise addition (highly exothermic reaction) to a vigorously stirred solution of 300 ml. of 5:1 methanol–water. The complex was added at such a rate as to maintain gentle ebullition. The aqueous methanol solution of the product was allowed to cool slowly with stirring and was finally chilled to 10°. The crystalline product was isolated by filtration, sucked dry on the filter, washed with 50 ml. of water, and air dried; yield, 20.2 g. of dibenzo[*a*,*d*]cycloheptatrien-5-one (III, X = H); colorless needles, m.p. 84–86° (micro hot stage). From the mother liquors there was obtained, after recrystallization from methanol, an additional 1.0 g. of III (X = H), nearly colorless needles, m.p. 82–85° (micro hot stage), total yield 21.2 g. (85%). This material was found to be identical with authentic III (X = H).[3]

10-Chloro-5H-Dibenzo[*a*,*d*]cycloheptene-5-one (III, X = Cl).—A 0.5-g. sample of the crystalline red complex obtained from the reaction of I with PCl_5 was heated for 1 hr. at 100° *in vacuo* (~30-mm. water pump). The cooled reaction residue on trituration with acetic acid deposited III (X = Cl) which melted after recrystallization from methanol at 125–126.5°, λ_{max} (isooctane) 252 mμ (ε 1358) and 303 mμ (ε 540). The n.m.r. spectrum is in agreement with structure III (X = Cl).

Anal. Calcd. for $C_{15}H_9ClO$: C, 74.85; H, 3.77; Cl, 14.73. Found: C, 74.84; H, 3.79; Cl, 14.83.

(2) Melting points were taken on a micro hot stage and are corrected. Ultraviolet spectra were measured on a Cary recording spectrophotometer.
(3) W. Treibs and H. J. Klinkhammer, *Chem. Ber.*, **84**, 671 (1951).

The Synthesis of Aryloxyureas

VICTOR J. BAUER AND HARRY P. DALALIAN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York

Received June 23, 1965

Sulfonylureas have won wide acceptance in the treatment of maturity-onset diabetes.[1] Recently a sulfenylurea has been reported[2] to produce hypoglycemia in rabbits. In this communication, we describe the synthesis of nine aryloxyureas, a class of compounds which may be considered to be analogs of sulfonylureas.

The aryloxyureas were prepared by the reaction of an aryloxyamine hydrochloride and potassium cyanate or an organic isocyanate and are crystalline solids which are readily soluble in dilute aqueous sodium carbonate (see Table I).

(1) W. C. Cutting, "Handbook of Pharmacology," Appleton-Century-Crofts, New York, N. Y., 1964, p. 374.
(2) Y. Nitta, N. Ando, Y. Ikeda, M. Koiyumi, and A. Shioga, *J. Pharm. Soc. Japan*, **82**, 191 (1962).