TABLE II

ALKOXYTRIAZINES AND SALTS

I, R	Compound HA	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3[a]		119–120	$C_{12}H_{15}N_5O$	58.76	58.70	6.16	6.24
CH_3	Acetic[b]	97–99 d.	$C_{14}H_{19}N_5O_3$	55.07	54.91	6.27	6.08
CH_3	Picric[d]	205–206 d.	$C_{18}H_{18}N_8O_8$[e]				
CH_3	Trichloroacetic	137–138 d.	$C_{14}H_{16}N_5Cl_3O_3$	41.12	40.90	3.95	3.89
CH_3	Heptafluorobutyric	128–130 d.	$C_{15}H_{16}F_7N_5O_3$	40.27	40.38	3.61	3.83
CH_3	Hydrochloric[c]	143–144 d.	$C_{12}H_{16}ClN_5O$	51.15	51.42	5.73	5.88
C_2H_5[a]		120–121	$C_{13}H_{17}N_5O$	60.21	60.16	6.61	6.41[f]
C_2H_5	Acetic[b]	95–100 d.	$C_{15}H_{21}N_5O_3$	56.41	56.55	6.63	6.34
C_2H_5	Picric[d]	197–198 d.	$C_{19}H_{20}N_8O_8$	46.74	46.65	4.13	4.12
n-C_3H_7[a]		117–118	$C_{14}H_{19}N_5O$	61.52	61.79	7.01	6.93
n-C_3H_7	Picric[d]	191–193 d.	$C_{20}H_{22}N_8O_8$	47.81	47.68	4.41	4.63
n-C_3H_7	Trichloroacetic	128–129 d.	$C_{16}H_{20}Cl_3N_5O_3$	44.00	43.60	4.62	4.52

[a] Recrystallized from MeOH–H_2O. [b] Recrystallized from 10% acetic acid. [c] Recrystallized from CH_3CN. [d] Recrystallized from H_2O. [e] Calcd.: N, 23.6. Found: N, 24.2. [f] Calcd. N, 27.0. Found: N, 27.0.

solution of the base and the product recrystallized from acetonitrile (Table II).

Acetylation of I, X = CH_2-CH_2OCH_3.—Two grams (0.0065 mole) of I, X = CH_2-CH_2OCH_3, as the acetic acid salt was treated with 40 ml. of acetic anhydride, 2 drops of pyridine was added and the solution refluxed for 2 hours. The solvent was removed and the residual oil dissolved in ether and treated with Norite. From the ether solution was obtained 2.09 g. of product which on recrystallization from acetonitrile and water gave the monoacetate, m.p. 158–159°.

Anal. Calcd. for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.4. Found: C, 58.49; H, 5.66; N, 24.6.

2-Amino-4-anilino-6-(β-hydroxyethyl)-*s*-triazine. A. From β-Propiolactone.—Phenylbiguanide, 17.7 g. (0.1 mole), was dissolved in 100 ml. of hot acetonitrile and cooled to 38°. β-Propiolactone, 8.0 g. (0.11 mole), diluted to 25 ml. with acetonitrile was added slowly with stirring. Within 15 minutes a heavy yellow oil separated and the supernatant liquid was decanted from the oil and placed in the ice-box at 10°. The oil was triturated with ethanol to give 3.24 g. of white powder (VII), m.p. 195–197°, recrystallized from methanol, 2.7 g. (9.7%), m.p. 205–206°.

Anal. Calcd. for $C_{11}H_{15}N_5O_2$ (VII): C, 53.00; H, 6.07; N, 28.1. Found: C, 53.21; H, 6.26; N, 28.2.

The supernatant liquid after several weeks at ice-box temperature gave 6.0 g. of white crystals, m.p. 145–150°. Recrystallization from a methanol–water solution gave 4.2 g. (18.2%), m.p. 159–160° of I, X = CH_2-CH_2OH.

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.3. Found: C, 57.12; H, 5.46; N, 30.2.

The picrate was prepared in water and recrystallized from water, m.p. 224–225°.

Anal. Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.37; H, 3.50; N, 24.3. Found: C, 44.17; H, 3.76; N, 23.9.

B. From I, X = CH_2-CH_2OCH_3.—Five grams (0.0164 mole) of I, X = CH_2-CH_2OCH_3, as the acetic acid salt was dissolved in 15 ml. of dioxane and the solution heated to reflux. To this was added 250 ml. of aqueous 10% trichloroacetic acid so that reflux was maintained. An oily product separated and the solution turned milky. Reflux was continued for two hours and the reaction mixture was decanted from the oily polymeric product, concentrated to 60 ml. and any solid removed by filtration. The filtrate was diluted with 30 ml. of methanol and treated with Norite. On standing, the solution gave small white pellets of I, X = CH_2-CH_2OH, 500 mg. (18.9%), m.p. 156–158°, mixed m.p. 156–159°.

Acknowledgment.—We are grateful to Dr. Louis H. Freedman of the U. S. Vitamin Corporation for his generosity in allowing one of us to use the facilities of their laboratories. We are also grateful to the American Cyanamid Company for a generous supply of phenylbiguanide.

BROOKLYN, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

Monomer Synthesis. Methylation of 2-Aminopyrimidine[1]

BY C. G. OVERBERGER AND IRVING C. KOGON[2]

RECEIVED SEPTEMBER 2, 1953

Useful procedures for the methylation of 2-aminopyrimidine and 2-N-methylaminopyrimidine on the amine nitrogen have been developed and structures of methylated products determined by unequivocal synthesis. 2-N-Dimethylamino-4-hydroxypyrimidine and the 4-chloro derivative have been prepared and characterized. Reduction of the 4-chloro derivative gave the 2-N-dimethylaminopyrimidine. Reaction of *n*-butyllithium with 2-N-dimethylaminopyrimidine gave 2-N-dimethylamino-4-butylpyrimidine. With an excess of butyllithium the dibutyl product was obtained.

In connection with the synthesis of vinyl pyrimidines, it was necessary to investigate several model syntheses. This paper describes the synthesis of derivatives of 2-aminopyrimidine. In particular it was desirable to develop methods to methylate 2-aminopyrimidine on the amino nitrogen and not the ring nitrogen. Although one of the ultimate reasons for the synthesis of vinyl pyrimidines was for the purpose of studying internal cell induced polymerization and its effect on abnormal cell mitosis, some of these intermediates described here were also screened by the Sloan-Kettering group and found to be inactive.

N-Methylaminopyrimidine was prepared from 2-

(1) This is the ninth in a series of articles concerned with the synthesis of monomers and their polymerization; for the eighth, see C. G. Overberger and Seymour L. Shapiro, THIS JOURNAL, **76**, 1061 (1954).

(2) Public Health Research Fellow 1951–1953. This paper comprises a portion of a thesis presented by Mr. Irving C. Kogon in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

aminopyrimidine and methyl iodide with potassium carbonate and without base, the latter procedure giving an 82.5% yield of product, identical with a sample prepared in 84% yield from 2-chloropyrimidine and methylamine. This latter procedure has also been reported recently by Brown and Short.[3] The picrates prepared from the products obtained were identical. This clearly demonstrates that alkylation occurred on the amino nitrogen.

The structure of the 2-dimethylaminopyrimidine was further confirmed by its synthesis from 2-dimethylamino-4-chloropyrimidine by reduction, the 2-dimethylamino-4-chloropyrimidine being prepared by an unequivocal synthesis (see below). A search of the literature revealed that in general, in order to alkylate a 2-aminopyridine or 2-N-methylaminopyridine on the amino nitrogen, it is first necessary to prepare the sodium salt. Reaction of the sodium salt of 2-aminopyridine with dimethyl sulfate gives the 2-methylaminopyridine.[4] Reaction of methyl iodide directly with 2-aminopyridine has been reported to give largely the 1-methyl-2-pyridoneamide, the nitrogen in the ring being alkylated.[5] Attempted preparation of the monoethyl derivative from the 2-amino compound with lithium amide failed and gave largely starting material.

2-N-Dimethylaminopyrimidine was prepared from the 2-N-monomethylamino derivative with lithium amide and the product shown to be identical with a sample prepared from 2-chloropyrimidine and dimethylamine again demonstrating that alkylation occurred as indicated. Brown and Short[3] have recently reported this compound prepared by the latter procedure. Brown and Short have demonstrated that the ultraviolet absorption spectra for their 2-amino-, 2-N-monomethylamino- and 2-N-dimethylaminopyrimidines are all similar except for small changes in wave length. This is a good indication that the structures of the methylated compounds are those formulated since the synthesis of the 2-amino compound is essentially unequivocal. We have checked their absorption spectra data at a *p*H of 7 and find complete agreement. These data are consistent for aminopyrimidines. The attempted preparation of 2-dimethylaminopyrimidine with formic acid and formaldehyde failed; a product was obtained which could not be characterized. Reaction of the 2-amino compound with dimethyl sulfate according to the procedure of Williams also gave only starting material.[6]

2-N-Dimethylamino-4-hydroxypyrimidine was prepared from dimethylguanidine sulfate, malic acid and fuming sulfuric acid in 72% yield. The 4-chloro derivative was prepared in 78% yield by reaction of the 4-hydroxy compound with phosphorus oxychloride. Attempted preparation of the 2-dimethylamino-4-chloro compound from the 2-amino-4-chloropyrimidine with formic acid and formaldehyde gave unidentifiable products. Reduction of the 4-chloro compound with hydrogen over 10% palladium on charcoal with magnesium oxide added gave 2-N-dimethylaminopyrimidine, identical in its properties with the previously prepared samples.

Reaction of *n*-butyllithium with 2-N-dimethylaminopyrimidine gave a 17% yield of 2-N-dimethylamino-4-butylpyrimidine. Reaction with three equivalents of *n*-butyllithium gave 2-N-dimethylamino-4,6-di-butylpyrimidine and several unidentifiable products. A similar reaction has been reported with 4-methylpyrimidine and phenyllithium to give 4-methyl-2-phenylpyrimidine[7] and 4-methyl-6-phenylpyrimidine and with 2-aminopyrimidine to give 2-amino-4-phenylpyrimidine.[8]

The 2-N-methylaminopyrimidine and the 2-N-dimethylamino pyrimidine were inactive when tested with sarcoma 180.

Experimental[9]

2-N-Methylaminopyrimidine from 2-Chloropyrimidine.—2-Chloropyrimidine was prepared according to the method of Howard[10] but the yields and the analysis are not reported and the details therefore are included here.

A solution of 309 g. of concentrated hydrochloric acid (4.66 moles) was placed in a flask and cooled to 0° followed by 47.5 g. (0.5 mole) of 2-aminopyrimidine which was added portionwise with stirring to give a homogeneous solution. The solution was then cooled to −15° and a cold solution of 63 g. of sodium nitrite in 100 ml. of water was added dropwise over a period of 55 minutes. Vigorous evolution of gas occurred immediately, the solution was stirred an additional 60 minutes and the temperature allowed to rise slowly to −10°. The mixture was then neutralized with methyl red indicator with a 30% solution of sodium hydroxide, the reaction temperature not being allowed to rise above 0°. The cold solution was immediately filtered, washed thoroughly with ether and extracted with 300 ml. of ether. Removal of the solvent after drying and crystallization of the residue from Skellysolve A (b.p. 35°) yielded a white product, 18.4 g. (33%), m.p. 64–65°. Recrystallization from Skellysolve A gave rectangular crystals, m.p. 64.5–65.5° (63.5–64.5°).[10] Young and Amstutz[11] also reported m.p. 65–67°, b.p. 78–80° (21 mm.), and it was stated that the procedure would be published in the future.

Anal.[12] Calcd. for $C_4H_3ClN_2$: Cl, 30.70. Found: Cl, 30.85.

A solution of 22.4 g. (0.2 mole) of 2-chloropyrimidine and 75 ml. of absolute ethanol was heated to reflux and anhydrous monomethylamine bubbled into the solution for 4.5 hours. The solution was cooled, and 100 ml. of ether was added. After the removal of monomethylamine hydrochloride and solvent, the residue was crystallized from 400 ml. of Skellysolve A to give a white crystalline product.[13] 18 g. (83.6%), m.p. 58–59° (49%, b.p. 91–92° (14 mm.), m.p. 59–61° uncor.).[3]

Anal. Calcd. for $C_5H_7N_3$: C, 55.04; H, 6.41; N, 38.5. Found: C, 54.81; H, 6.45; N, 38.6.

The picrate was prepared by adding excess ethereal picric acid to an ethereal solution of the base; yellow powder, m.p. 194–195°. On recrystallization from ethanol, the product melted at 195–196°.

(3) D. L. Brown and G. N. Short, *J. Chem. Soc.*, 331 (1953).

(4) A. E. Tschitschibabin and I. L. Knunjanz, *Ber.*, **61**, 2215 (1928).

(5) A. E. Tschitschibabin and O. A. Zeide, *J. Russ. Phys. Chem.*, **46**, 1216 (1914) (*J. Chem. Soc. Abstr.*, **1**, 590 (1915)); A. E. Tschitschibabin, R. A. Konowalowa and A. A. Konowalowa, *Ber.*, **54B**, 814 (1921). No attempt is made here to include all references concerning alkylation of 2-amino- or 2-methylamino nitrogen heterocyclic derivatives. It should be emphasized however that structures of such alkylated products cannot be assumed.

(6) R. Williams, *J. Chem. Soc.*, 1129 (1939).

(7) T. O. Heyes and J. C. Roberts, *ibid.*, 328 (1951).

(8) U. K. Detweiler and E. O. Amstutz, THIS JOURNAL, **73**, 5451 (1951).

(9) All melting points are corrected.

(10) K. L. Howard, U. S. Patent 2,447,409 (1949); *C. A.*, **43**, 8105 (1949).

(11) T. E. Young and E. D. Amstutz, THIS JOURNAL, **73**, 4773 (1951).

(12) Analysis by Drs. Weiler and Strauss, Oxford, England; Dr. K. Ritter, Basel, Switzerland; Dr. F. Schwarzkopf, New York, N. Y.

(13) J. W. Copenhaver and R. F. Kleinschmidt, Brit. Patent 663,303; *C. A.*, **46**, 1021 (1952). These authors do not report any physical constants or yields.

Anal. Calcd. for $C_{11}H_{11}N_6O_7$: N, 24.8. Found: N, 24.5.

The methylamino compound fluoresces with a blue color under ultraviolet light.

2-N-Monomethylaminopyrimidine from Methyl Iodide and 2-Aminopyrimidine.—A solution of 18.8 g. (0.2 mole) of 2-aminopyrimidine, 225 ml. of absolute alcohol and 56.8 g. (0.4 mole) of methyl iodide was refluxed for 24 hours and then chilled in an ice-bath. The light tan precipitate was removed by filtration and air-dried for 30 minutes, 42.5 g. (90.5%), m.p. 238–239°. Recrystallization from ethanol gave a white product, 42.0 g. (90%), m.p. 241–242°.

Anal. Calcd. for $C_5H_7IN_3$: N, 17.8; I, 53.7. Found: N, 17.7; I, 53.7.

To one-half of the hydriodic acid salt was added 100 ml. of ethanol and the reaction warmed on a steam-bath until a homogeneous solution was obtained. A saturated solution of sodium hydroxide in ethanol was added until the solution was alkaline to litmus. Ethanol was removed by distillation, the solution chilled in an ice-bath and the solid sodium iodide removed by filtration and washed on the filter with ether. After removal of the solvent, this product was distilled to give a white solid 9.5 g. (87% based on 2-aminopyrimidine), b.p. 102–103° (28 mm.). The product was recrystallized from Skellysolve A, 9.0 g. (82.5%), m.p. 58–59.5°. A mixed melting point with 2-N-methylaminopyrimidine prepared by reaction of 2-chloropyrimidine and monomethylamine gave no depression, m.p. 57.5–58.5°, mixed m.p. 57–58.5°.

The picrate was prepared in the usual manner, m.p. 194–195°, recrystallized from ethanol to give a m.p. 195–196°, mixed m.p. 194–195°.

When the reaction was carried out with potassium carbonate added, a lower yield was obtained. From 18.8 g. (0.2 mole) of 2-aminopyrimidine, 56.8 g. (0.4 mole) of methyl iodide, 225 ml. of absolute alcohol and 27.4 g. (0.4 mole) of potassium carbonate, there was obtained on refluxing for 24 hours, 5.0 g. (49.5% based on recovered 2-aminopyrimidine), m.p. 58–59° of purified product. The product was purified by two distillations followed by recrystallization from Skellysolve A. A mixed melting point with a sample of 2-N-methylaminopyrimidine prepared from 2-chloropyrimidine and monomethylamine, m.p. 57.5–58.5 showed no depression, mixed m.p. 57–58.5°.

The picrate was prepared in the usual manner, m.p. 189–192° and was recrystallized from ethanol to give a m.p. 193–195°. A mixed melting point was not depressed.

2-Dimethylaminopyrimidine from 2-Chloropyrimidine.—A solution of 45.6 g. (0.4 mole) of 2-chloropyrimidine and 150 ml. of absolute alcohol was heated to reflux and anhydrous dimethylamine bubbled into the solution for 6 hours. One hundred milliliters of ethanol was then removed through a Vigreux column, the residue then cooled in an ice-bath for one hour and 75 ml. of ether added. After the removal of the white precipitate of dimethylamine hydrochloride and the solvent, the residue was distilled through a Claisen flask to give a colorless liquid, 42.5 g. (88.2%), b.p. 86° (28 mm.), $n^{25}D$ 1.5420, d^{25}_4 1.0489 (46%, b.p. 78–81° (17 mm.), $n^{22}D$ 1.5438).[3]

Anal. Calcd. for $C_6H_9N_3$: C, 58.45; H, 7.36; N, 34.12. Found: C, 58.57; H, 7.51; N, 34.07.

The compound fluoresces with a blue color under ultraviolet light. The picrate was prepared by adding excess ethereal picric acid to an ethereal solution of the free base, m.p. 169–171°, and was recrystallized from ethanol, rectangular crystals, m.p. 170.5–171.5°.

Anal. Calcd. for $C_{12}H_{10}N_6O_7$: N, 23.86. Found: N, 23.84.

2-Dimethylaminopyrimidine from 2-N-Methylaminopyrimidine.—A solution of 10.9 g. (0.1 mole) of 2-N-monomethylaminopyrimidine, 50 ml. of dry benzene and 2.8 g. (0.12 mole) of lithium amide was refluxed for 1.5 hours until no more ammonia was detected coming from the reaction mixture. After the mixture was allowed to cool, there was added 14.2 g. (0.1 mole) of methyl iodide followed by reflux for an additional 15 hours. The hot solution was then filtered and the precipitate washed thoroughly with hot benzene. After the removal of the solvent, the residue was distilled to give a light yellow liquid, 3.8 g. (30.8%), b.p. 105–110° (40 mm.), $n^{25}D$ 1.5415. The picrate was prepared in the usual manner, m.p. 169–171°. A mixed melting point with an authentic sample gave no depression, m.p. 170.5–171.5°, mixed m.p. 168.5–170°.

Preparation of 2-N-Dimethylamino-4-hydroxypyrimidine.—A solution of 125 ml. of technical fuming sulfuric acid (20% SO_3) was cooled to 0° and 26.8 g. (0.2 mole) of maleic acid was added over a period of 35 minutes. The reaction mixture was stirred for an additional 20 minutes. To this mixture at 0° was added 27.2 g. (0.1 mole) of *asym*-dimethylguanidine sulfate over a period of 15 minutes. The reaction mixture was then stirred for three hours until room temperature was reached and the temperature slowly raised to 95° and maintained at this temperature for 3 hours. The hot mixture was chilled in an ice-bath and carefully poured into 350 g. of ice. It was then carefully neutralized with ammonium hydroxide until basic to litmus, chilled in an ice chest and filtered. A yellow precipitate was obtained which after drying in a vacuum oven at 90° for 4 hours weighed 23 g. (83%), m.p. 160–170°. This was recrystallized twice from water using a small quantity of "Norite." A white crystalline product was obtained as long needles and after drying in a vacuum oven weighed 20 g. (72%), m.p. 175.5–176.5°. The compound fluoresces a blue color under ultraviolet light.

Anal. Calcd. for $C_6H_9N_3O$: C, 51.76; H, 6.52; N, 30.2. Found: C, 52.01; H, 6.47; N, 30.4.

The picrate was prepared in the usual manner, m.p. 220–222.5°; recrystallization from ethanol gave yellow crystals, m.p. 220.5–222.5°.

Anal. Calcd. for $C_{12}H_{12}N_8O_7$: N, 22.8. Found: N, 22.8.

Preparation of 2-Dimethylamino-4-chloropyrimidine.—A mixture of 13.9 g. (0.1 mole) of 2-dimethylamino-4-hydroxypyrimidine and 40 ml. of redistilled phosphorus oxychloride was refluxed for 2 hours. The brown solution was then poured into approximately 200 g. of an ice–water mixture, followed by addition of "Norite" to the solution. After several minutes, solid and "Norite" were removed from the reaction mixture and the filtrate chilled to 0° and carefully neutralized to litmus with ammonium hydroxide keeping the temperature between 0–5°. The creamy white precipitate was removed by filtration and washed with water, then dried at 30° for 24 hours in a vacuum oven, 12.4 g. (79%), m.p. 40–42°. The compound was sublimed at 35° (1 mm.) to obtain a crystalline product, 12 g. (78%), m.p. 41–42°.

Anal. Calcd. for $C_6H_8ClN_3$: C, 45.73; H, 5.11; N, 26.75. Found: C, 45.67; H, 5.06; N, 26.95.

The compound fluoresces a blue color under ultraviolet light.

The picrate prepared in the usual manner was recrystallized from ethanol, m.p. 144–145°.

Anal. Calcd. for $C_{12}H_{11}ClN_6O_7$: N, 21.5. Found: N, 21.4.

Preparation of 2-N-Dimethylaminopyrimidine by Dehalogenation of 2-N-Dimethylamino-4-chloropyrimidine.—To 50 ml. of a 1:1 ethanol–water solution was added 8.7 g. (0.0555 mole) of 2-N-dimethylamino-4-chloropyrimidine, 6.0 g. (0.15 mole) of magnesium oxide and 0.2 g. of 10% palladium on charcoal. After 6 hours the theoretical amount of hydrogen was adsorbed. The catalyst was filtered off, washed thoroughly with ethanol and the filtrate extracted with chloroform continuously for 4 hours. The solvent was removed after drying and the residue distilled to give a colorless liquid, b.p. 66–67° (12 mm.), 4.6 g. (67.5%), $n^{25}D$ 1.5419.

The picrate was prepared in the usual manner, m.p. 169–170.5°. A mixed melting point with an authentic sample showed no depression.

Reaction between *n*-Butyllithium and 2-N-Dimethylaminopyrimidine.—To a cooled solution (−20°) of 0.1 mole of *n*-butyllithium prepared by the method of Gilman[14] there was added dropwise under a nitrogen atmosphere, 12.3 (0.1 mole) of 2-N-dimethylaminopyrimidine over a period of 20 minutes. The mixture turned from a blue to a green color and was allowed to stir for 35 minutes, the reaction temperature rising to 18°. The mixture was then refluxed for 30 minutes and turned an orange color. The gummy mixture was then cooled and hydrolyzed with 30 ml. of water. The

(14) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, THIS JOURNAL, **71**, 1499 (1949).

ether layer was separated and the aqueous layer extracted with 6 portions of 25 ml. of ether. Removal of the solvent after drying gave a residue which was distilled to give a yellow liquid, b.p. 102–105° (4.5 mm.), 3.5 g. (20%). A large tarry residue was left in the distilling flask. Redistillation gave 3.0 g. (17%), $n^{25}D$ 1.5122, d^{25}_4 0.9646, of 2-N-dimethylamino-4-butylpyrimidine. On standing in a closed flask for 24 hours this compound turns red.

Anal. Calcd. for $C_{10}H_{17}N_3$: C, 67.00; H, 9.55; N, 23.4. Found: C, 66.71; H, 9.65; N, 23.2.

The picrate was prepared in the usual manner, m.p. 80–81° and was recrystallized from ethanol, m.p. 80.5–81.5°.

Anal. Calcd. for $C_{16}H_{20}N_6O_7$: N, 20.8. Found: N, 21.2.

The reaction was repeated using 0.9 mole of *n*-butyllithium and 36.9 g. (0.3 mole) of 2-N-dimethylaminopyrimidine. The reaction mixture was treated in the same fashion as described in the previous experiment. There was obtained a yellow liquid which turned red after 24 hours, b.p. 124–135° (2.5 mm.), 12 g. (17%). Redistillation of the liquid gave a yellow distillate, b.p. 140–145° (4.5 mm.), 9 g. (13%), $n^{25}D$ 1.5030, which is probably the dibutyl derivative, 2-N-dimethylamino-4,6-di-*n*-butylpyrimidine.

Anal. Calcd. for $C_{14}H_{25}N_3$: C, 71.43; H, 10.70; N, 17.8. Found: C, 71.69; H, 10.54; N, 17.6.

These compounds fluoresce a blue color under ultraviolet light.

Ultraviolet Absorption Spectra.—Ultraviolet absorption spectra were determined with a Beckman quartz spectrophotometer. An aqueous buffered solution, *p*H 7.0 ± 0.02, was used as the solvent in order to compare the curves with those reported by reference 3.

Acknowledgment.—We are grateful to Dr. Chester Stock and his group at the Sloan-Kettering Institute for testing these compounds for their effectiveness against sarcoma 180. We are also grateful to the National Health Institute for support.

BROOKLYN, N. Y.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

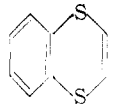
Heterocyclic Vinyl Ethers. IV. Benzo-1,4-oxathiadiene and Benzo-1,4-dithiadiene[1,2]

BY WILLIAM E. PARHAM AND JOHN D. JONES

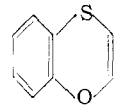
RECEIVED OCTOBER 2, 1953

The synthesis (three methods) and proof of structure of benzo-1,4-oxathiadiene (II) are described and the polymerization, ethanolysis, bromination, hydrolysis and electrophilic substitution of this ring system are compared to analogous reactions with benzo-1,4-dithiadiene (I). This paper describes a new synthesis and certain new reactions of I, and includes a study of osazone formation from β-oxy- and β-thiohydrazones.

A recent study[3] of the chemistry of benzo-1,4-dithiadiene (I) has shown that the sulfur-containing ring of this system exhibits the stability, and some of the reactions (*i.e.*, electrophilic substitution), usually associated with molecules possessing a considerable degree of resonance stabilization.



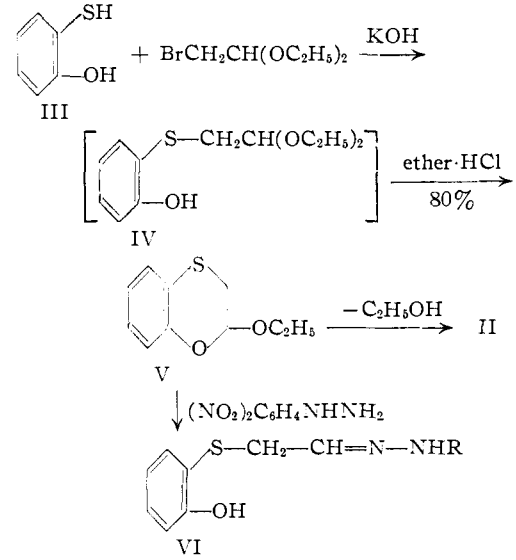
I



II

This report describes a study of the synthesis and reactions of an analogous system, benzo-1,4-oxathiadiene (II). Interest in this new heterocyclic system was twofold: (1) to compare the properties and stability of systems I and II, and (2) to accumulate data which will be of ultimate value in regard to a final clarification of the relative electronic effects of oxygen and sulfur.[4]

A study of the reaction sequence outlined in the following equations was chosen initially as a route to benzo-1,4-oxathiadiene for:



(1) the method had proved highly successful for the preparation of I,[3] and (2) use of this method would allow a direct comparison to be made concerning the relative ease of formation of the double bond in the heterocyclic rings of I and II.

2-Ethoxybenzo-1,4-oxathiene (V) was obtained in 80% over-all yield from the reaction of equimolar quantities of monothiocatechol (III), diethyl bromoacetal and potassium hydroxide in absolute ethanol solution. The intermediate phenolic acetal IV was not isolated, but instead was treated with

(1) This work was supported by the Office of Ordnance Research, Contract Number DA-11-022-ORD-571.

(2) From the Ph.D. Thesis of John D. Jones, University of Minnesota (1953).

(3) W. E. Parham, T. M. Roder and W. R. Hasek, THIS JOURNAL, **75**, 1647 (1953).

(4) *A priori* it seemed reasonable to assume that the type of resonance responsible for the greater stability of thiophene relative to furan (*i.e.*, valence shell expansion of sulfur) would make a greater contribution to the structure of I (two sulfur atoms) than to the structure of II (one sulfur atom); hence the dithia compound should be more stable than the oxathia compound. On the other hand, oxygen can release electrons in the direction of its covalent bonds more readily than sulfur, and a combination of resonance involving release of electrons from oxygen and sulfur and expansion of the valence shell of sulfur should impart a noticeable degree of stabilization to the 1,4-oxathiadiene system. *Cf.* W. E. Parham, J. Gordon and J. Swalen, *ibid.*, **74**, 1824 (1952).