

2,2'-Disubstituted 5,5'-Bipyrimidines

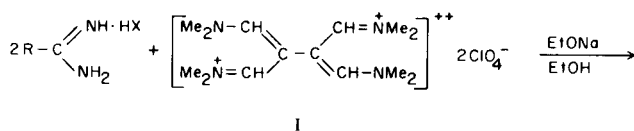
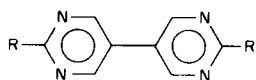
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Syntheses of 2,2'-bis(methylthio)-, 2,2'-diamino-, 2,2'-dihydroxy-, 2,2'-dichloro-, and 2,2'-diethoxy-5,5'-bipyrimidines are described.

In connection with a research program concerning certain polyaza analogs of *p*-quaterphenyl, it became necessary to explore the chemistry of 2,2'-disubstituted 5,5'-bipyrimidines. Two representatives of this class of compounds were prepared *via* a one-step condensation involving *S*-methylisothiurea or guanidine and a precursor (I) of 1,1,2,2-ethanetetra-carboxaldehyde prepared according to a method of Arnold (1). The reactions were carried out

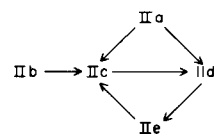
R = CH₃S, H₂N

IIa, R = CH₃S
 b, R = H₂N

in the presence of sodium ethoxide and produced 2,2'-bis(methylthio)-5,5'-bipyrimidine (IIa) and 2,2'-diamino-5,5'-bipyrimidine (IIb). The former compound (IIa) was recently prepared by an Ullmann reaction of 5-bromo-2-(methylthio)pyrimidine-4-carboxylic acid (2). The structure of IIa was supported by the pmr spectrum in deuteriochloroform (chemical shifts downfield from TMS as an external standard): singlets at 2.66 ppm due to methyl groups (6 protons) and at 8.77 ppm due to 4 protons of the pyrimidine rings. Ir spectrum of 2,2'-diamino-5,5'-bipyrimidine (IIb) was similar to that of 2-aminopyrimidine (3) in the region of characteristic absorption bands. Strong bands due to N-H stretching occurred at 3,140 and 3,300 cm⁻¹ (at 3,150 and 3,350 cm⁻¹ for 2-aminopyrimidine).

N-H bending gave rise to a strong band at 1,658 cm⁻¹ (at 1,650 cm⁻¹ for 2-aminopyrimidine).

The various reactions carried out in the system of 2,2'-disubstituted 5,5'-bipyrimidines are illustrated in the following figure. The objective was to synthesize 2,2'-dichloro-5,5'-bipyrimidine (IIe). Although a direct con-



IIa, R = CH₃S
 b, R = H₂N
 c, R = HO
 d, R = Cl
 e, R = C₂H₅O

version of 2-amino to 2-chloropyrimidine is known (4), 2,2'-diamino-5,5'-bipyrimidine (IIb) failed to react with nitrous acid in concentrated hydrochloric acid at -15° to produce the desired dichloro derivative (IIe). Treatment of the diamino compound (IIb) with 10 *N* sodium hydroxide solution under conditions similar to those for converting 2-amino to 2-hydroxypyrimidine (5) was found to be unsuited for the preparation of 2,2'-dihydroxy-5,5'-bipyrimidine (IIc). The latter compound, however, was produced in a good yield on treatment of a suspension of IIb in 10% aqueous sulfuric acid with excess nitrous acid at 0-5°. It was a colorless, nonmelting solid soluble in dilute sulfuric acid or sodium hydroxide solutions, and insoluble in the great majority of organic solvents. It was felt that caution had to be exercised in assigning the dihydroxy structure (IIc) to the above product in view of the past experience of Johnson and Joyce (6) who had erroneously (5) assigned the 2-hydroxypyrimidine structure to a water-

insoluble, nonmelting compound. Thus, other routes to the deamination product obtained from IIb were sought to characterize it more fully. Heating the bis(methylthio) derivative (IIa) with concentrated hydrochloric acid at reflux for two hours resulted in the formation of a minor product crystallized from water (m.p. 285-288°; ir peak at $3,450\text{ cm}^{-1}$) and a major, nonmelting product sparingly water-soluble and identical (solubilities, ir spectrum) to the deamination product described above. The matching ir spectra of the nonmelting compounds, to which the 2,2'-dihydroxy-5,5'-bipyrimidine structure (IIc) is assigned, did not display any ir absorption above $3,300\text{ cm}^{-1}$ and, in this respect, were similar to an ir spectrum of 2-hydroxypyrimidine which showed no band at frequencies greater than $3,200\text{ cm}^{-1}$ (3). A broad, medium-intensity band fell between $2,600$ and $3,100\text{ cm}^{-1}$. In the region of $1,600$ - $1,800\text{ cm}^{-1}$, there were two weak peaks at $1,805$ and $1,738\text{ cm}^{-1}$ and a strong, broad band centered around $1,633\text{ cm}^{-1}$. A band, corresponding to the latter, was found in the ir spectrum of 2-hydroxypyrimidine in the region of $1,620$ - $1,650\text{ cm}^{-1}$. According to Short and Thompson (3), this could be cited in support of a lactam tautomeric form for the compound. Its appearance at such high frequencies in the spectra of 2-hydroxypyrimidine and 2,2'-dihydroxy-5,5'-bipyrimidine (IIc) would be very difficult to explain in terms of a ring vibration or an O-H deformational vibration which, even in the hydrogen-bonded state, was not likely to rise to such a high value. It would appear that such properties of IIc as lack of solubility in water and melting point could be reconciled with the proposed structure. Polyhydroxypyrimidines are known to exhibit very low solubilities in water and high melting points. For instance, although 2-hydroxypyrimidine (m.p. 180°) is readily soluble in water (5), 2,4-dihydroxypyrimidine (m.p. ca. 340° with decomposition) is not (7).

When the hydroxy derivative IIc was allowed to react with a phosphorus pentachloride-phosphorus oxychloride mixture at temperatures of 150 - 200° , 2,2'-dichloro-5,5'-bipyrimidine (IIId) formed in 30% yield. Its pmr spectrum in deuterated dimethyl sulfoxide was consistent with the proposed structure and showed a single peak at 9.26 ppm downfield from TMS (internal standard). The same compound (IIId) was obtained directly from the bis(methylthio) derivative (IIa) and phosphorus pentachloride, albeit in a low yield. Reaction of the dichloro derivative (IIId) with sodium ethoxide in ethanol produced 2,2'-diethoxy-5,5'-bipyrimidine (IIe) in a high yield. Its pmr spectrum in deuteriochloroform showed methyl-group protons at 1.47 ppm, methylene-group protons at 4.50 ppm, and pyrimidine-ring protons as a singlet at 8.67 ppm downfield from TMS as an internal standard; the peak-area ratio was found to be 6:4:4. Heating the diethoxy derivative

(IIe) with concentrated hydrochloric acid at 100° gave a high yield of 2,2'-dihydroxy-5,5'-bipyrimidine (IIc) whose ir spectrum matched those of IIc prepared from IIa and IIb.

EXPERIMENTAL

2,2'-Bis(Methylthio)-5,5'-bipyrimidine (IIa).

A sodium ethoxide solution, prepared from 0.92 g. (0.04 g.-atom) of sodium and 30 ml. of absolute ethanol, was added dropwise (15-20 minutes) to a suspension of 4.51 g. (0.01 mole) of [2,3-bis(dimethylaminomethylene)butanediylidene]bis(dimethylammonium perchlorate) (I) (1) and 2.80 g. (0.01 mole) of S-methylisothiurea sulfate in 25 ml. of refluxing absolute ethanol. The mixture was heated under reflux for two hours, cooled to room temperature and filtered. The cake was washed with ice-cold ethanol and slurried in hot water (70°). The slurry was filtered, the cake washed with water and dried (0.65 g.). The crude product was sublimed (195 - 200° , 0.1 mm Hg) to give 0.57 g. (23% of theory) of a colorless sublimate, m.p. 209 - 212° . Two crystallizations from a 1:1 mixture of acetic acid and ethanol furnished a pure sample of the title compound, m.p. 214 - 215° , Lit. m.p. 210 - 212° (2).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_4\text{S}_2$: C, 47.98; H, 4.03; N, 22.37; S, 25.61. Found: C, 48.06; H, 4.29; N, 22.40; S, 25.46.

2,2'-Diamino-5,5'-bipyrimidine (IIb).

A sodium ethoxide solution prepared from 5.25 g. (0.228 g.-atom) of sodium in 100 ml. of absolute ethanol was added dropwise (20 minutes) to a suspension of 22.6 g. (0.05 mole) of [2,3-bis(dimethylaminomethylene)butanediylidene]bis(dimethylammonium perchlorate) (I) (1) and 12.2 g. (0.10 mole) of dry guanidine nitrate in 75 ml. of refluxing absolute ethanol. After addition of sodium ethoxide was complete, heating was continued for one hour. The mixture was cooled to room temperature and filtered. The cake was thoroughly washed with ethanol and slurried in 100 ml. of hot water (70°). The slurry was filtered, the cake washed with water and dried (7.50 g., 80% of theory). A small amount of the crude product was crystallized three times from acetic acid to give a colorless, nonmelting sample of 2,2'-diamino-5,5'-bipyrimidine.

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_6$: C, 51.06; H, 4.28; N, 44.65. Found: C, 50.72; H, 4.48; N, 44.31.

2,2'-Dihydroxy-5,5'-bipyrimidine (IIc).

Method A.

2,2'-Diamino-5,5'-bipyrimidine, 7.47 g. (0.039 mole), was suspended in 400 ml. of an aqueous sulfuric acid solution prepared by dissolving 40 ml. of concentrated ($\sim 96\%$) sulfuric acid in 360 ml. of water. The mixture was cooled in ice and stirred vigorously for 30 minutes. To the suspension was added (one hour) a solution of 10.76 g. (0.156 mole) of sodium nitrite in 30 ml. of water. The mixture was stirred for 30 minutes and subsequently treated with an additional 0.34 g. of sodium nitrite in 5 ml. of water. The stirring was continued for one hour. Most of the starting material went into solution which was filtered through a sintered glass funnel containing a layer of a filter aid (Celite). The cake was washed with 25 ml. of 3% aqueous sulfuric acid solution. The sulfuric acid in the filtrate was neutralized with 10 N sodium hydroxide solution and the pH was then adjusted to about 4 with acetic acid. The precipitated 2,2'-dihydroxy-5,5'-bipyrimidine was filtered and washed thoroughly with ice-cold water. The product, after drying at 100° under reduced pressure (25 mm Hg),

weighed 5.98 g. (80% of theory). A small amount of the above material was suspended in hot water and treated with an excess of 5% aqueous sodium hydroxide solution to dissolve most of the solid. The solution was filtered hot. The filtrate was acidified with acetic acid to pH 4 to precipitate the product. After filtering, washing with cold water and drying at 100° *in vacuo*, a colorless, nonmelting solid resulted.

Anal. Calcd. for C₈H₆N₄O₂: C, 50.52; H, 3.18; N, 29.46. Found: C, 50.54; H, 3.35; N, 29.65.

Method B.

2,2'-Bis(methylthio)-5,5'-bipyrimidine (0.44 g.) was heated in 2 ml. of boiling, concentrated hydrochloric acid for two hours. Evolution of methyl mercaptan was noted. Hydrochloric acid was evaporated under reduced pressure. The residue was slurried in 15 ml. of water and the insoluble material was filtered and washed with water. The aqueous filtrate was neutralized with 5% aqueous sodium hydroxide solution to precipitate a slightly yellow solid which, following a crystallization from water, melted at 285-288° (ir band at 3,450 cm⁻¹). The water-insoluble material was treated with 5% aqueous sodium hydroxide solution as described in the preceding preparation. This gave 0.15 g. of a colorless, nonmelting product whose ir spectrum matched that of the compound obtained according to Method A.

Method C.

2,2'-Diethoxy-5,5'-bipyrimidine (prepared as described below), 0.13 g. (0.00053 mole), and concentrated hydrochloric acid, 1.5 ml., were placed in a small test tube which was heated in a boiling-water bath for 2½ hours. The diethoxy compound went into solution. The liquid was cooled and neutralized with 10 N sodium hydroxide solution and the pH adjusted to 4 with acetic acid. The precipitate was filtered, washed with water and dried. Yield of a colorless compound, which neither shrunk nor melted below 400°, was 0.08 g. (84% of theory). The ir spectrum of this material matched those of 2,2'-dihydroxy-5,5'-bipyrimidine prepared according to Methods A and B.

2,2'-Dichloro-5,5'-bipyrimidine (IIc).

Method A.

2,2'-Dihydroxy-5,5'-bipyrimidine, 5.98 g. (0.0331 mole), phosphorus pentachloride, 35 g. and phosphorus oxychloride, 3 ml., were placed in a dry, three-necked flask equipped with a reflux condenser, a calcium chloride drying tube and a thermometer. The reaction mixture was heated at reflux for two hours. Phosphorus oxychloride was distilled until the pot temperature reached 205°. The reaction mass was held at this temperature for 30 minutes and then cooled to room temperature. It was cautiously decomposed with ice and water to give a solid which was filtered, washed with ice-cold water and quickly dried *in vacuo*. The crude product

weighed 6.80 g. It was sublimed at 200-220° (0.25 mm Hg) to give 2.75 g. (37% of theory) of a colorless 2,2'-dichloro-5,5'-bipyrimidine, m.p. 260-262°. The material was crystallized twice from a benzene-hexane mixture to furnish an analytical sample, m.p. 265-266°.

Anal. Calcd. for C₈H₄Cl₂N₄: C, 42.31; H, 1.77; N, 24.67; Cl, 31.23. Found: C, 42.03; H, 1.62; N, 24.83; Cl, 30.92.

Method B.

2,2'-Bis(methylthio)-5,5'-bipyrimidine, 0.16 g. (0.0006 mole), and phosphorus pentachloride, 1.0 g., were placed in a 10 ml., round-bottom flask. The reaction was carried out as described in Method A except that, after phosphorus oxychloride was distilled, the pot temperature was allowed to increase to 240°. This was accompanied by evolution of an additional minute quantity of phosphorus oxychloride. The reaction mixture was worked up as described in Method A. The ir spectrum of a crystallized product showed it to be 2,2'-dichloro-5,5'-bipyrimidine.

2,2'-Diethoxy-5,5'-bipyrimidine (IIe).

2,2'-Dichloro-5,5'-bipyrimidine, 0.57 g. (0.0025 mole), was added to a stirred solution of sodium ethoxide prepared from 0.12 g. (0.005 g.-atom) of sodium and 10 ml. of absolute ethanol. The mixture was allowed to react at room temperature for 5½ hours and then at reflux for ½ hour. It was cooled and drowned in a mixture of ice and water. The precipitate was filtered, washed with water and dried *in vacuo* to give 0.58 g. (94.5% of theory) of a colorless compound, m.p. 160-163°. The crude material was sublimed *in vacuo* and crystallized from benzene to give a sample of pure 2,2'-diethoxy-5,5'-bipyrimidine, m.p. 164°.

Anal. Calcd. for C₁₂H₁₄N₄O₂: C, 58.52; H, 5.73; N, 22.75. Found: C, 58.85; H, 5.88; N, 23.04.

REFERENCES

- (1) Z. Arnold, *Collect. Czech. Chem. Commun.*, **27**, 2993 (1962); see S. Trofimenko, *J. Org. Chem.*, **29**, 3046 (1964), for an alternative synthesis of 1,1,2,2-ethanetetracarboxaldehyde.
- (2) M. P. L. Caton, D. T. Hurst, J. F. W. McOmie, and R. R. Hunt, *J. Chem. Soc. (London)*, C, 1204 (1967).
- (3) L. N. Short and H. W. Thompson, *J. Chem. Soc. (London)*, 168 (1952).
- (4) C. G. Overberger and I. C. Kogon, *J. Am. Chem. Soc.*, **76**, 1066 (1952).
- (5) D. J. Brown, *Nature*, **165**, 1010 (1950).
- (6) T. B. Johnson and A. W. Joyce, *J. Am. Chem. Soc.*, **37**, 2163 (1915).
- (7) D. J. Brown, "The Pyrimidines," in the *Chemistry of Heterocyclic Compounds*, Interscience Publishers, New York, 1962, p. 249.