Preparation of Some Arylpyrimidines (1a)

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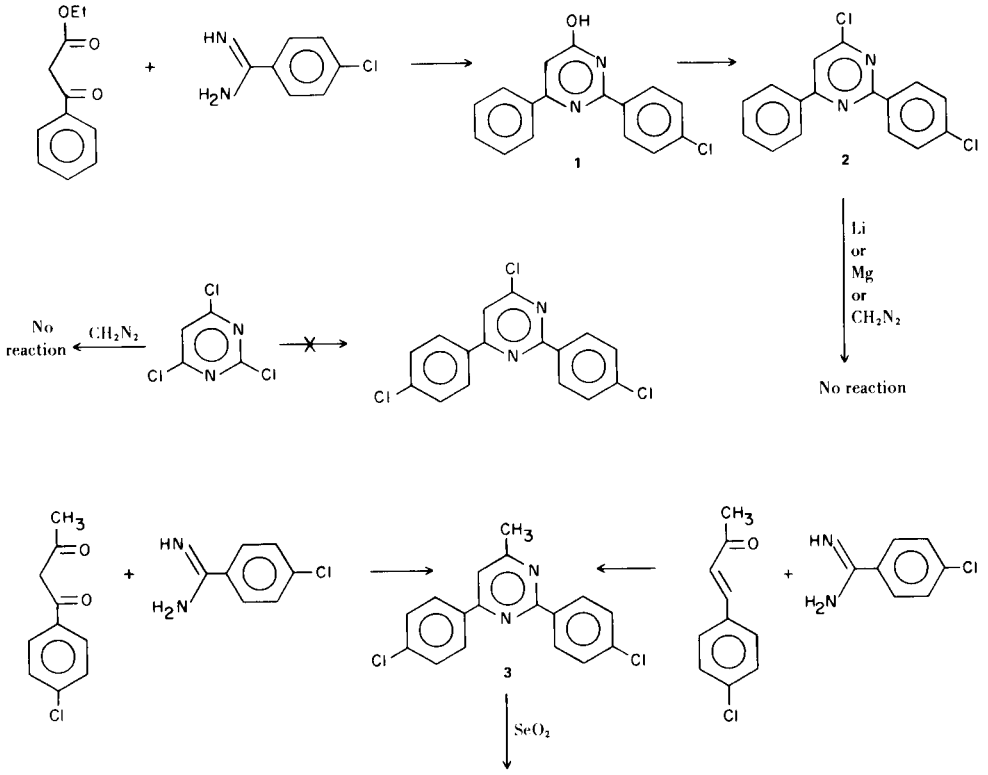
As part of a continuing program of preparation of potential antimalarials we have prepared several new arylpyrimidines and studied a few of their reactions. The compounds were made during attempts, thus far unsuccessful, to synthesize 2,6-bisaryl-α-(dialkylaminomethyl)-4-pyrimidinemethanols. None of the compounds prepared was active *vs Plasmodium berghei* in mice. 2-(4-Chlorophenyl)-4-hydroxy-6-phenylpyrimidine, **1**, was lethal to mice at 120 mg./kg. (2).

Compound **1**, prepared by the method of Snyder and Foster (3), was converted into 4-chloro-2-(4-chlorophenyl)-6-phenylpyrimidine (**2**) with thionyl chloride and phosphorus oxychloride. Compound **2** did not form a Grignard reagent under the usual conditions, nor did it undergo exchange with butyllithium. As may be inferred from Grundmann's work with diaryl-*s*-triazines (4) it did not react with diazomethane.

The preparation of the symmetrically substituted chloropyrimidine, 2,6-bis(4-chlorophenyl)-4-chloropyrimidine, from 2,4,6-trichloropyrimidine and 4-chlorophenyl magnesium bromide, a method used by us to prepare 2,4-bis(4-chlorophenyl)-6-chloro-*s*-triazine (5), was unsuccessful. 2,4,6-Trichloropyrimidine did not react with diazomethane as does the corresponding *s*-triazine derivative (5).

2,6-Bis(4-chlorophenyl)-4-methylpyrimidine (**3**) was prepared from 4-chlorobenzamidine and 4-chlorobenzoylacetone (method A). The yields were low, and from the reaction mixture 4-chlorobenzamide was isolated, indicating that the water formed in the reaction hydrolyzed the 4-chlorobenzamidine under the acidic conditions necessary for the reaction. Compound **3** was also prepared from 4-chlorobenzamidine and 4-(4-chlorophenyl)-3-butene-2-one (method B) (6). In this reaction there was evidence of polymerization of the unsaturated ketone, and the



Selenium Complexes

yield of **3** was consequently poor. Compound **3** could not be converted to the corresponding 4-aldehyde by reaction with selenium dioxide. Only intractible selenium complexes resulted.

In the preparation of 4-(4-chlorophenyl)-3-butene-2-one (7) we isolated and characterized 1,5-bis(4-chlorophenyl)-1,4-pentadiene-3-one (**4**).

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A60 spectrometer. The mass spectrum was obtained on a Hitachi RMU-6H spectrometer. Microanalyses were performed by Microanalysis, Inc., Wilmington, Delaware.

2-(4-Chlorophenyl)-4-hydroxy-6-phenylpyrimidine (**1**).

4-Chlorobenzamidine (15 g.), ethyl benzoylacetate (20 g.), sodium carbonate (15 g.) and water (30 ml.) were mixed and the mixture was made homogeneous by adding ethanol. It was stirred at room temperature for 16 hours. The thick mixture was diluted with water (50 ml.) and the solid was collected and washed with ethanol. It was crystallized from glacial acetic acid, yield 9 g. (30%), m.p. 305-307°; nmr (trifluoroacetic acid): δ 7.03 (s, 1, C_5-H).

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; Cl, 12.54; N, 9.90. Found: C, 67.62; H, 4.03; Cl, 12.24; N, 9.50.

4-Chloro-2-(4-chlorophenyl)-6-phenylpyrimidine (**2**).

Compound **1** (15 g.) was dissolved in thionyl chloride (100 ml.) and phosphorus oxychloride (25 ml.) and refluxed for 5 hours. Solvents were removed under reduced pressure. The residue was extracted with ether. The solution was charcoaled and concentrated to give 6 g. (37%) of the compound, m.p. 126.5-127.5°.

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2$: C, 63.81; H, 3.35; Cl, 23.54; N, 9.30. Found: C, 63.52; H, 3.29; Cl, 23.55; N, 9.14.

2,6-Bis(4-chlorophenyl)-4-methylpyrimidine (**3**).

Method A.

4-Chlorobenzamidine (5 g., 32 mmoles) and 4-chlorobenzoylacetone (7 g., 36 mmoles) were dissolved in absolute ethanol (200 ml.) and hydrogen chloride in ethanol was added until the solution was acidic. Ethanol was evaporated and the residue was heated to a melt (250°). The temperature was maintained for 15 minutes. Ethanol (100 ml.) was added, evaporated, and the residue again was melted. This process was repeated and the cooled mass was washed with petroleum ether (30-60°). The solid was suspended in water and the suspension was made basic. The solid was collected and crystallized from chloroform, yield 2.5 g. (25%), m.p. 143-144°.

Method B.

4-Chlorobenzamidine (3 g., 19.5 mmoles) and 4-(4-chlorophenyl)-3-butene-2-one (4 g., 22.2 mmoles) were heated to 110° and stirred for 2 hours. Concentrated hydrochloric acid was added, followed by 20 ml. of ethanol. The reaction mixture was refluxed for 2 hours, ethanol was distilled, and 50 ml. of water was added. The hydrochloric acid was neutralized with sodium bicarbonate. The solid was collected, washed with water, dissolved in ethanol, and the solution was filtered and concentrated. The precipitate obtained on cooling was triturated with ether. The ether solution on concentration gave 1 g. (16%) of 2,6-bis(4-chlorophenyl)-4-methylpyrimidine (**3**), m.p. 142-144°; nmr (benzene-d_6): δ 2.21 (s, 3, CH_3), 6.65 (s, 1, C_5-H), 7.72 (d, 2, C_6-phenyl, *o*-H's), 8.57 (d, 2, C_2-phenyl, *o*-H's).

Anal. Calcd. for $C_{17}H_{12}Cl_2N_2$: C, 64.78; H, 3.84; Cl, 22.50; N, 8.89. Found: C, 64.68; H, 4.01; Cl, 22.25; N, 8.51.

1,5-Bis(4-chlorophenyl)-1-4-pentadiene-3-one (**4**).

The residue from the distillation of 4-(4-chlorophenyl)-3-butene-2-one was washed with ether, and the remaining solid was crystallized from chloroform, m.p. 193-195°; mol. wt. 302 (mass spec.).

Anal. Calcd. for $C_{17}H_{12}Cl_2O$: C, 67.35; H, 3.99. Found: C, 67.11; H, 3.82.

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REFERENCES

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