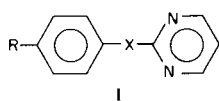


Antimalarial Agents IV. Some *p*-Aminophenyl *x*-(1, *y*-Diazinyl) Sulfones

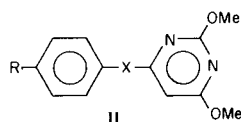
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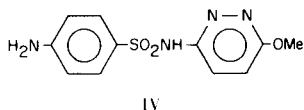
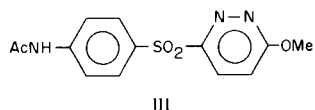
In view of the activity of heterocyclic sulfanilamides, such as IV, and bis(*p*-aminophenyl) sulfone (DDS) against *Plasmodium falciparum* (2 a,b), it was of considerable interest to synthesize some *p*-aminophenyl *x*-(1,*y*-diazinyl) sulfones for our program on synthetic antimalarial agents. The compounds selected for synthesis were *p*-aminophenyl 2-pyrimidinyl sulfone (Ia), *p*-aminophenyl 6-(2,4-dimethoxy)pyrimidinyl sulfone (IIa) and *p*-acetamidophenyl 6-(3-methoxy)pyridazinyl sulfone (III).



Ia, R = NH₂, X = SO₂
 Ib, R = NHAc, X = SO₂
 Ic, R = NO₂, X = SO₂
 Id, R = NO₂, X = S



IIa, R = NH₂, X = SO₂
 IIb, R = NO₂, X = S
 IIc, R = NO₂, X = SO₂



p-Acetamidophenyl 2-pyrimidinyl sulfone (Ib) was prepared as an intermediate for Ia. Base and acid hydrolysis of Ib, however, resulted in cleavage products only, and Ia was obtained by reduction of *p*-nitrophenyl 2-pyrimidinyl sulfone (Ic). *p*-Nitrophenyl 2-pyrimidinyl sulfide (Id), *p*-nitrophenyl 6-(2,4-dimethoxy)pyrimidinyl sulfide (IIb) and the sulfone IIc were needed as intermediates.

The sulfide IIb and the sulfones Ia-Ic, IIb, IIc and III did not have any activity against *Plasmodium berghei*. The sulfide Id was not tested.

EXPERIMENTAL

p-Acetamidophenyl 2-Pyrimidinyl Sulfone (Ib).

A stirred mixture of 6.4 g. of 2-bromopyrimidine, 8.8 g. of sodium *p*-acetamidobenzenesulfinate and 100 ml. of DMF was refluxed for 3 hours. The mixture was poured into 800 ml. of ice-water mixture. The resulting solid was collected and dried. It

was recrystallized from acetone-petroleum ether (b.p. 60-110°) to give 4.2 g. (37%) of the product, m.p. 237°. Attempts to hydrolyze Ib with acid and base to the sulfone Ia were not successful.

Anal. Calcd. for C₁₂H₁₁N₃O₃S (Ib): C, 51.97; H, 3.99; N, 15.15. Found: C, 52.13; H, 4.29; N, 15.23.

p-Nitrophenyl 2-Pyrimidinyl Sulfone (Ic).

To a solution of sodium ethoxide prepared by dissolving 2.3 g. of sodium in 250 ml. of absolute ethanol was added 16.5 g. of technical *p*-nitrothiophenol followed by 15.9 g. of 2-bromopyrimidine. The mixture was refluxed with stirring and under nitrogen blanket for 4 hours. The resulting solution was poured into 1.5 l. of ice water. The resulting solid was collected and washed with ice water until the washings were colorless. The solid was recrystallized from ethanol to give 11.2 g. (47%) of somewhat impure *p*-nitrophenyl 2-pyrimidinyl sulfide (Id), m.p. 108-113° (sintering at 95°).

To a stirred solution of 11.0 g. of crude Id in 150 ml. of glacial acetic acid was added a solution of 7.0 g. of potassium permanganate in 120 ml. of warm water (40°) and stirred for 30 minutes. The reaction mixture was treated with 9.0 g. of sodium bisulfite, cooled to 10°, and diluted with 300 ml. of ice water. The resulting solid was collected, washed well with ice water, air dried, and recrystallized from acetone to give 6.7 g. (84%) of the product, m.p. 209-212°.

Anal. Calcd. for C₁₀H₇N₃O₄S (Ic): C, 45.27; H, 2.66; N, 15.84. Found: C, 45.40; H, 2.86; N, 15.71.

p-Aminophenyl 2-Pyrimidinyl Sulfone (Ia).

A stirred mixture of 5.3 g. of *p*-nitrophenyl 2-pyrimidinyl sulfone, 21.5 g. of iron powder, 200 ml. of water and 2.5 ml. of glacial acetic acid was refluxed for 2 hours. After cooling in ice, the mixture was treated with 4.2 g. of sodium bicarbonate and filtered. The residue was washed with water, air dried, and extracted with boiling THF (6 X 50 ml.). The extract was treated with Darco, filtered, and concentrated to give 3.4 g. (72%) of the product, m.p. 201-203°. It was recrystallized from THF-petroleum ether (b.p. 60-110°) to obtain 3.2 g., m.p. 202-204°, dec. p. 208°.

Anal. Calcd. for C₁₀H₉N₃O₂S (Ia): C, 51.05; H, 3.85; N, 17.86. Found: C, 51.30; H, 4.21; N, 17.62.

Acetylation of *p*-Aminophenyl 2-Pyrimidinyl Sulfone.

Acetylation of *p*-aminophenyl 2-pyrimidinyl sulfone (Ia) with acetic anhydride and a few drops of pyridine resulted in 89% conversion to *p*-acetamidophenyl 2-pyrimidinyl sulfone (Ib), m.p. 236-237° dec. The melting point of a mixture of this product with *p*-acetamidophenyl 2-pyrimidinyl sulfone (Ib) prepared from sodium *p*-acetamidobenzenesulfinate and 2-bromopyrimidine was undepressed.

***p*-Nitrophenyl 6-(2,4-Dimethoxypyrimidinyl) Sulfide (IIb).**

To a stirred solution of sodium ethoxide prepared by dissolving 1.80 g. of sodium in 50 ml. of ethanol was added 12.9 g. of 2,4-dimethoxy-6-mercaptopyrimidine. To the solution were added 15.03 g. of *p*-bromonitrobenzene, 100 ml. of DMF, and a trace of copper powder. The mixture was refluxed for 4.5 hours. After addition of 100 ml. of 50% ethanol, it was cooled in ice. The resulting solid was collected, washed with 50% ethanol followed by water, and dried to obtain 10.14 g. of a solid, m.p. 122-124°. It was recrystallized from acetone-petroleum ether (b.p. 60-110°) to give 9.6 g. (44%) of the product, m.p. 127-128°.

Anal. Calcd. for C₁₂H₁₁N₃O₄S (IIb): C, 49.14; H, 3.75; N, 14.30. Found: C, 49.43; H, 4.23; N, 13.90.

***p*-Nitrophenyl 6-(2,4-Dimethoxypyrimidinyl) Sulfone (IIc).**

The sulfide IIb was oxidized as described in the preparation of Ic. The reaction time was 1.5 hours. The crude product was recrystallized from acetone-petroleum ether (Darco) to obtain IIc in 74% yield, m.p. 155.5-156.5°.

Anal. Calcd. for C₁₂H₁₁N₃O₆S (IIc): C, 44.31; H, 3.38; N, 12.92. Found: C, 44.63; H, 3.67; N, 12.57.

***p*-Aminophenyl 6-(2,4-Dimethoxypyrimidinyl) Sulfone (IIa).**

A solution of 3.25 g. of *p*-nitrophenyl 6-(2,4-dimethoxypyrimidinyl) sulfone (IIc) in 200 ml. of 1:1 dioxane-ethanol mixture was hydrogenated over Raney Nickel at 55 psig. The theoretical uptake of hydrogen was complete within 2 hours. The catalyst was filtered off, washed with ethanol (2 X 50 ml.) and the combined filtrates were evaporated to dryness *in vacuo*. The residue was recrystallized from acetone-petroleum ether to give 2.35 g. of the product, m.p. 198-200°. A second crop of 0.40 g., m.p. 189-191°, was obtained from the acetone-petroleum ether filtrate. The

higher-melting crop was recrystallized from acetone-petroleum ether to give 2.26 g. (77%) of the product, m.p. 198.5-200°.

Anal. Calcd. for C₁₂H₁₃N₃O₄S (IIa): C, 48.82; H, 4.41; N, 14.24. Found: C, 49.04; H, 4.68; N, 14.18.

***p*-Acetamidophenyl 6-(3-Methoxypyridazinyl) Sulfone (III).**

A mixture of 7.2 g. of 3-chloro-6-methoxypyridazine, 11.5 g. of sodium *p*-acetamidobenzenesulfinate and 150 ml. of methanol was heated for 3 days in a 300 ml. rocking autoclave at 120-125°. The mixture was cooled, washed out with methanol and filtered. The solid was washed well with cold water followed by methanol and dried to give 4.1 g. of the product, m.p. 240-242° dec. It was recrystallized from DMF-water (Darco) to give 3.2 g. (21%) of product, m.p. 239.5-240.5° dec.

Anal. Calcd. for C₁₃H₁₃N₃O₄S (III): C, 50.82; H, 4.22; N, 13.68. Found: C, 50.36; H, 4.77; N, 13.26.

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