302. *Chemotherapeutic Agents of the Sulphone Type. Part IV.*

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4-*γ-Diethylaminopropylamino*-2-p-*methylsulphonylphenyl*-6-*methylpyrimidine dihydrochloride* has been synthesised from *p*-methylsulphonylbenzamidine hydrochloride, and a number of thiazoles have been prepared from α-halogenated ketones and p-*methylsulphonylbenzthioamide*. None of the products possessed antimalarial activity.

p-Methylsulphonylbenzamidine hydrochloride (I) has been shown to have definite prophylactic activity and a slight therapeutic action in *P. gallinaceum* infections in chicks (Fuller, Tonkin, and Walker, *J.*, 1945, 633). It was also shown that prophylactic activity was retained in low degree by the amidoxime corresponding to (I) and by the *NN*-dimethyl derivative of (I), but lost, for example, on introducing a γ-diethylaminopropyl substituent into the amidine

group of (I). A few exploratory experiments have been carried out in attempts to develop antimalarial compounds from (I) and from its precursor, *p*-methylsulphonylbenzonitrile, by way of p-*methylsulphonylbenzthioamide* (II), and these are now reported.

Condensation of (I) with ethyl acetoacetate in the presence of enough alkali to liberate the free base gave 4-*hydroxy*-2-p-*methylsulphonylphenyl*-6-*methylpyrimidine*, which afforded 4-*chloro*-2-p-*methylsulphonylphenyl*-6-*methylpyrimidine* (III) on treatment with phosphoryl chloride. Condensation of (III) with γ-diethylaminopropylamine then gave 4-γ-*diethylaminopropylamino*-2-p-*methylsulphonylphenyl*-6-*methylpyrimidine dihydrochloride* (IV) in good yield. Addition of the elements of hydrogen sulphide to *p*-methylsulphonylbenzonitrile afforded *p*-methylsulphonylbenzthioamide (II) quantitatively. With phenacyl bromide and ethyl α-chloroacetoacetate, (II) afforded 4-*phenyl*-2-p-*methylsulphonylphenylthiazole* (V) and *ethyl* 2-p-*methylsulphonylphenyl*-4-*methylthiazole*-5-*carboxylate* (VI) respectively, while 1 : 12-dichloro-2 : 11-diketododecane and 1 : 14-dichloro-2 : 13-diketotetradecane yielded, on condensation with (II), 1 : 8-*bis*-2′-p-*methylsulphonylphenyl*-4′-*thiazolyl*-n-*octane* (VII) and 1 : 10-*bis*-2′-p-*methylsulphonylphenyl*-4′-*thiazolyl*-n-*decane* (VIII) respectively.

None of the above substances (IV), (V), (VI), and (VII) showed any antimalarial activity when tested in *P. gallinaceum* infections in chicks. Curd and Rose (*J.*, 1946, 343) have examined a short series of 4-β-diethylaminoethylamino-2-aryl-6-methylpyrimidine dihydrochlorides and again no antimalarial activity was observable.

Experimental.

4-*Hydroxy*-2-p-*methylsulphonylphenyl*-6-*methylpyrimidine*.—A mixture of *p*-methylsulphonylbenzamidine hydrochloride (20 g.) and ethyl acetoacetate (13 g.) was warmed to about 40° and treated with a solution of sodium hydroxide (4 g.) in water (40 c.c.). The clear solution which resulted soon began to deposit crystals. After 2 days at 37° the product was collected, dissolved in excess of dilute aqueous sodium hydroxide, and reprecipitated by acetic acid after filtration. On recrystallisation from alcohol, the *compound* separated in colourless needles (22 g.), m. p. 260° (Found : C, 54·5; H, 4·5; N, 10·4. $C_{12}H_{12}O_3N_2S$ requires C, 54·5; H, 4·5; N, 10·6%).

4-*Chloro*-2-p-*methylsulphonylphenyl*-6-*methylpyrimidine* (III).—The above hydroxy-compound (21 g.) was refluxed for 30 minutes with phosphoryl chloride (50 c.c.). Excess of reagent was removed under reduced pressure and the residue was treated with ice and left overnight. The precipitate was collected, and, on crystallisation from absolute alcohol, the *product* separated in pale yellow needles (17 g.), m. p. 139° (Found : C, 51·2; H, 3·9; N, 9·8. $C_{12}H_{11}O_2N_2ClS$ requires C, 51·0; H, 3·9; N, 9·9%).

4-γ-*Diethylaminopropylamino*-2-p-*methylsulphonylphenyl*-6-*methylpyrimidine Dihydrochloride* (IV).—The preceding chloro-compound (10 g.) was heated at 115—125° for 6 hours with γ-diethylaminopropylamine (6 g.; 1·25 mols.). The mixture was then cooled and dissolved in 2N-hydrochloric acid, and the solution was filtered. The solution was made alkaline with sodium hydroxide and the base was taken up in ether. The ethereal solution, in turn, was extracted with dilute acetic acid. The acid extract was then basified and the mixture was again extracted with ether. After being dried (K_2CO_3), the ether extract, on evaporation, afforded a thick brown syrup which was dissolved in benzene and treated with dry hydrogen chloride; a semi-solid precipitate then formed. The benzene was decanted and the residue dissolved in hot alcohol and treated with an equal volume of ethyl acetate. On cooling, the *product* separated in clumps of colourless needles (12 g.), m. p. 247° (Found : C, 50·6; H, 6·9. $C_{19}H_{28}O_2N_4S,2HCl$ requires C, 50·9; H, 6·7%).

p-*Methylsulphonylbenzthioamide* (II).—*p*-Methylsulphonylbenzonitrile (20 g.), alcoholic ammonia (30 c.c.; 10%), and alcohol (33 c.c.) were placed in a pressure bottle and the mixture was then saturated with hydrogen sulphide and heated in a boiling water-bath for 1½ hours. The solvent was removed under reduced pressure and the residue was washed with ammonium sulphide solution. The *product* separated from a large volume of water in pale yellow needles (21 g.), m. p. 205—206°, varying somewhat with the rate of heating (Found : C, 44·9; H, 4·1; N, 6·7. $C_8H_9O_2NS_2$ requires C, 44·6; H, 4·2; N, 6·5%).

4-*Phenyl*-2-p-*methylsulphonylphenylthiazole* (V).—A solution of the above thioamide (3 g.) and phenacyl bromide (3 g.) in alcohol (100 c.c.) was refluxed for 2 hours; the thioamide dissolved completely and then colourless crystals separated. The solution was cooled, and the product (4·2 g.) collected. The *compound* crystallised from alcohol in colourless hexagonal plates, m. p. 186° (Found : C, 60·5; H, 4·3; N, 4·3. $C_{16}H_{13}O_2NS_2$ requires C, 61·0; H, 4·2; N, 4·4%).

Ethyl 2-p-*Methylsulphonylphenyl*-4-*methylthiazole*-5-*carboxylate* (VI).—A mixture of *p*-methylsulphonylbenzthioamide (5 g.), ethyl α-chloroacetoacetate (5 g.), and spirit (100 c.c.) was refluxed for 2 hours. The process was repeated after addition of a further quantity (3 g.) of chloro-ester. The crystalline *product*, obtained on cooling, was collected and recrystallised from alcohol; colourless rectangular plates (6·5 g.) separated, m. p. 151° (Found : C, 51·5; H, 4·7; N, 4·0. $C_{14}H_{15}O_4NS_2$ requires C, 51·7; H, 4·6; N, 4·3%).

1 : 8-*Bis*-2′-p-*methylsulphonylphenyl*-4′-*thiazolyl*-n-*octane* (VII).—A mixture of 1 : 12-dichloro-2 : 11-diketododecane (4·1 g.), *p*-methylsulphonylbenzthioamide (6·7 g.), and absolute alcohol (100 c.c.) was refluxed for 4 hours, and, after cooling, the product (8·8 g.; m. p. 125—130°) was collected. Extraction with hot alcohol left a residue (4·2 g.; m. p. 152°), and concentration of the extract afforded more of the same material (3·3 g.; m. p. 148—150°) and finally unchanged thioamide (0·5 g.). The *product* separated from glacial acetic acid in tiny needles (6·3 g.), m. p. 152·5° (Found : C, 57·2; H, 5·4. $C_{28}H_{32}O_4N_2S_4$ requires C, 57·2; H, 5·4%).

1 : 10-*Bis*-2′-p-*methylsulphonylphenyl*-4′-*thiazolyl*-n-*decane* (VIII).—In the same manner, 1 : 14-dichloro-2 : 13-diketotetradecane (2·7 g.) and *p*-methylsulphonylbenzthioamide (4 g.) afforded a crude product (5·1 g.; m. p. 105—115°), similarly purified by extraction with alcohol. The *compound* (3 g.) separated from glacial acetic acid in small needles (2·2 g.), m. p. 150° (Found: C, 58·8; H, 5·9. $C_{30}H_{36}O_4N_2S_4$ requires C, 58·4; H, 5·8%).

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