CHEMOTHERAPY OF TUBERCULOSIS

Part I. Synthesis of Possible Lipophilic Chemotherapeuticals of the Sulphonamide and Sulphone Series derived from Fatty Acids, including those of the Chaulmoogra Group

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THE present state of our knowledge in the Chemotherapy of Tuberculosis, the significance of the results of testing the drugs *in vitro* and *in vivo*, and the peculiar pathological features of the disease have been described by us recently.[1] In accordance with the ideas, work has been undertaken to synthesise compounds that are likely to act powerfully on the tubercle bacilli both *in vitro* and *in vivo*.

For the discovery of drugs lethal to the tubercle bacilli, there are three methods that could be followed:—

(1) to start from a compound showing action on the tubercle bacilli and by introducing substituents attempt to arrive at a more powerful drug; (2) to examine a cross-section of compounds belonging to diverse groups and structures to detect the structural features associated with tuberculocidal activity and (3) to design inhibitors that could effectively interfere with any of the vital nutritional, metabolic or respiratory processes of the bacilli so as to cause death; these inhibitors could be designed only on the basis of the knowledge of the chemistry of the abovementioned processes. We have undertaken work employing all these methods and the compounds synthesised are presented in this and the succeeding communications. The testing of the compounds is under way.

Of the numerous compounds and substances tested so far for their curative action in experimental tuberculosis, only derivatives of sulfanilamide and 4:4′-diaminodiphenyl sulphone as well as the antibiotic streptomycin, have shown very significant protective action. But these compounds have not shown the same degree of protection in tuberculosis and leprosy clinically. The synthesis and study of lipophilic derivatives of sulphanilamide and 4:4′-diaminodiphenyl sulphone were undertaken to try out whether this would lead to any compound or compounds with better protective action.

The present communication is concerned with the synthesis of some simple *fatty* acyl derivatives of the sulfanilamides in clinical usage and 4:4′-disubstituted diphenyl sulphones. Among the fatty acids used in this exploratory study, hydnocarpic acid has been chosen as the representative

of the choulmoogra group. The twenty-three compounds now prepared are listed in Table I.

TABLE I

Serial No.	Name of the compound	Molecular Formula	M.P./°C.	Nitrogen percentage	
				Found	Required
1	N^4-Formyl-N^1-hydnocarpyl sulphanilamide	$C_{23}H_{34}O_4N_2S$	123–26	6·4	6·5
2	N^4-Acetyl-N^1-hydnocarpyl sulphanilamide	$C_{24}H_{36}O_4N_4S$	144–46	6·5	6·3
3	N^4-*n*-Butyryl-N^1-hydnocarpyl sulphanilamide	$C_{26}H_{40}O_4N_2S$	143–47	6·0	6·0
4	N^4-*n*-Caproyl-N^1-hydnocarpyl sulphanilamide	$C_{28}H_{44}O_4N_2S$	125–27	5·7	5·6
5	N^4:N^1-Dihydnocarpyl sulphanilamide	$C_{38}H_6\ O_4N_2S$	128–30	4·5	4·4
6	4-Nitro-4′-hydnocarpylamido-diphenyl sulphone	$C_{28}H_{36}O_5N_2S$	162–63	5·5	5·5
7	4:4′-Dihydnocarpylamido-diphenyl sulphone	$C_{44}H_{64}O_4N_2S$	132–34	3·9	3·9
8	4-Nitro-4′-formamidodiphenyl sulphone	$C_{13}H_{10}O_5N_2S$	229–30 lit.[5], 234–35	8·5	9·0
9	4-Nitro-4′-butyramido-diphenyl sulphone	$C_{16}H_{16}O_5N_2S$	179–80	7·6	8·4
10	4-Nitro-4′-*n*-valeramidodiphenyl sulphone	$C_{17}H_{18}O_5N_2S$	170–71 sintg. at 158	7·5	7·7
11	4-Nitro-4′-*n*-capramidodiphenyl sulphone	$C_{18}H_{20}O_5N_2S$	159–60	7·2	7·4
12	4-Nitro-4′-*n*-heptamidodiphenyl sulphone	$C_{19}H_{22}O_5N_2S$	161–63	7·0	7·2
13	4:4′-Di-*n*-butyramidodiphenyl sulphone	$C_{20}H_{24}O_4N_2S$	229–30	7·1	7·2
14	4:4′-Di-*n*-valeramidodiphenyl sulphone	$C_{22}H_{28}O_4N_2S$	207–08	6·6	6·7
15	4:4′-Di-*n*-capramidodiphenyl sulphone	$C_{24}H_{32}O_4N_2S$	186–87	6·3	6·3
16	4:4′-Di-*n*-heptamidodiphenyl sulphone	$C_{26}H_{36}O_4N_2S$	166–67	6·3	5·9
17	4:4′-*bis*-Chloroacetamido-diphenyl sulphone	$C_{16}H_{14}O_4N_2SCl_2$	191–92	6·5	7·0
18	4:4′-*bis*-Glycolylamidodiphenyl sulphone	$C_{16}H_{16}O_6N_2S$	245–55 softg. at 230	7·5	7·7
19	4:4′-*bis*-Adipylamidodiphenyl sulphone	$C_{24}H_{28}O_8N_2S$	131–33	6·0	5·6
20	4:4′-*bis*-Sebacylamidodiphenyl sulphone	$C_{32}H_2O_3N_2S$	141–43	4·3	4·5
21	2-(*p*-*n*) Caproylaminobenzene-sulphonamido)-pyrimidine	$C_{16}H_{20}O_3N_4S$	213–15	16·2	16·1
22	2-(*p*-*n*-Caproylaminobenzene-sulphonamido)-4-methylpyrimidine	$C_{17}H_{22}O_3N_4S$	165–68	15·7	15·5
23	2-(*p*-*n*-Caproylaminobenzene-sulphonamido)-4:6-dimethyl pyrimidine	$C_{18}H_{20}O_3N_4S$	202–03	14·8	14·9

Of the synthetical aliphatic diacyl derivative of 4 : 4'-diaminodiphenyl sulphone (Nos. 13–16), some of the lower members were investigated by Nitti, Bovet and Hamon[2] for their antibacterial action, but others do not appear to have been reported in the regular literature so far.

Experimental

Hydnocarpic and Chaulmoogric Acids.—The two acids were prepared from *H. Wightiana* oil by an adaptation of the methods of Cole and Cardosa[3] as follows:—

A mixture of *H. Wightiana* oil (700 c.c.), absolute alcohol (700 c.c.) and con. sulphuric acid (100 c.c.) was heated under reflux for 8 hours. It was cooled and freed from excess of alcohol, sulphuric acid, and glycerol by repeated washing with water. On filtration a clear brown liquid, with a faint fruity odour was obtained; yield, 775 c.c. which contained a mixture of esters.

The esters prepared from a number of batches (4 l.), after dehydration by heating under reduced pressure, were then fractionated. The fraction boiling between 180–230°/10–12 mm., containing most of the ethyl esters of chaulmoogric and hydnocarpic acids, was collected. A broad initial separation of the two esters was effected by subjecting the above fraction to redistillation in a 2 l. Claissen flask with a six-inch Vigreax column. Two main fractions (1) b.p. 190–205°/10–12 mm. and (2) b.p. 210–25°/10–12 mm. were thus collected; these on further fractionation separately, furnished two fairly constant boiling fractions of colourless liquid of b.p. 195–98°/11 mm. and b.p. 216–20°/11 mm., the yield of the two fractions being 1800 c.c. and 1200 c.c. respectively.

The lower boiling fraction (270 c.c.), alcohol (600 c.c.), and potassium hydroxide (65 g.) in water (65 c.c.) were gently refluxed for one hour, cooled and acidified with dilute sulphuric acid. The solid obtained was filtered, pressed well free from the adhering oily product, washed carefully with small amounts of cold 60 per cent. alcohol and crystallised five times from 80 per cent. alcohol. Pure hydnocarpic acid was thus obtained, m.p. 59–60°; yield, 35 g.

On saponifying the higher boiling ester (270 c.c.) and working up as described above, pure chaulmoogric acid, m.p. 67–68°; was obtained; yield, 82 g.

Pure hydnocarpic acid, unlike its ethyl ester, does not keep well (*cf.* Van Nagelli and Vogt-Markins[4]) and so was used up as early as possible for further operations.

N^4-acyl-N^1-hydnocarpyl sulphanilamides (Nos. 1–4),—were synthesised by the action of (1·12) molecular proportion of hydnocarpyl chloride on the appropriate N^4-acyl sulphanilamides in pyridine solution.

N^4, N^1-Dihydnocarpyl sulphanilamide (No. 5),—was obtained by the action of slightly more than two molar proportions of hydnocarpyl chloride on sulphanilamide in pyridine solution.

4-Nitro-4′-hydnocarpylamidodiphenyl sulphone (No. 6) and *4 : 4′-Dihydnocarpylamidodiphenyl sulphone* (No. 7),—were obtained by the action of a slight excess of hydnocarpyl chloride on 4-nitro-4′-aminodiphenyl sulphone and 4 : 4′-diaminodiphenyl sulphone respectively in pyridine solution.

4-Nitro-4′-formamidodiphenyl sulphone (No. 8),—was prepared essentially by the procedure of Heyman and Heidelberger.[5]

The other normal fatty acyl derivatives of 4-nitro-4′-aminodiphenyl sulphone (Nos. 9–12) and of 4 : 4′-diaminodiphenyl sulphone (Nos. 13–16) were easily obtained by the action of slightly more than the calculated amount of the requisite acid chloride on 4-nitro-4′-aminodiphenyl sulphone and 4 : 4′-diamino-diphenyl sulphone respectively in pyridine medium.

4 : 4′-bis-Chloroacetamidodiphenyl sulphone (No. 17),—was obtained in fair yields by the action of a slight excess of chloro-acetyl chloride on diaminodiphenyl sulphone suspended in cold water in the presence of sodium acetate or bicarbonate.

4 : 4′-bis-Glycolamidodiphenyl sulphone (No. 18),—resulted in almost quantitative yields by boiling *bis*-4 : 4′-chloroacetamido diphenyl sulphonte with 20 parts of sodium acetate solution for 12 hours.

The n-caproyl derivatives of sulphadiazine (No. 21), *sulphamerazine* (No. 22), and *sulphamethazine* (No. 23),—were obtained in excellent yields by reacting excess of *n*-caproyl chloride with the respective sulphanilamides in pyridine. These were initially purified by reprecipitation with excess of dilute hydrochloric acid from cold aqueous solutions of their sodium salts.

Of the caproyl derivatives prepared, caproyl sulphadiazine has recently been reported by Finkelstein[6] also. The yields of the aforementioned compounds were uniformly good, and ranged from 80–90% for the recrystallised samples.

4 : 4′-bis-Adipylamidodiphenyl sulphone (No. 19),—4 : 4′-Diaminodiphenyl sulphone (25 g.) and adipic acid (14·6 g.; 2 mols.) in a 100 c.c. long necked round bottom flask, were heated together in an oil-bath first at 130–50° for one hour, and later at 150–70° for 4 hours. The melt was cooled, purified

through a dilute alkaline solution (charcoal), and fractionally crystallised from alcohol or acetone, yield 6 g.

Although the corresponding diethyl ester of the above amide, *viz.*, 4 : 4′-*bis*-*o*-carboethoxyvaleraminodiphenyl sulphone, has been synthesised by Gray and Platt[7] by the action of *o*-carbethoxy valeryl chloride on 4 : 4′-diaminodiphenyl sulphone, these authors have converted their esters directly to the disodium salt of 4 : 4′-*bis*-adipylamidodiphenyl sulphone.

4 : 4′-*bis*-*Sebacylamidodiphenyl sulphone* (No. 20),—was obtained by fusion of diaminodiphenyl sulphone (9·3 g.) with sebacic acid (15·2 g.; 2 mols.) first at 130–50° for one hour, and then at 150–70° for four hours. The reaction product was purified through dilute alkali and then crystallised from alcohol, yield 9 g.

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Summary

Twenty-three compounds have been synthesised as possible lipophilic chemotherapeuticals of the sulphonamide and sulphone series. Among such compounds are the hydnocarpic acid derivatives of N^4-*n*-fatty acyl sulphanilamides, N^4, N^1-dihydnocarpylsulphanilamide, normal fatty-acyl derivatives of 4-nitro-4′-amino- and 4 : 4′-diamino-diphenylsulphones, 4 : 4′-*bis*-adipylamido- and 4 : 4′-*bis*-sebacylamido-diphenylsulphones, and the N^4-*n*-caproyl derivatives of 2-sulphanilamidopyrimidine, 2-sulphanilamido-4-methyl- and 2-sulphanilamido-4 : 6-dimethyl pyrimidines.

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