BACTERIAL CHEMOTHERAPY, III: SYNTHESIS OF POSSIBLE LIPOPHILIC CHEMOTHERAPEUTICALS OF THE SULPHANILAMIDE GROUP*

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ALTHOUGH the compounds of the sulphanilamide group already evolved have provided medical science with some of the most potent weapons for the effective conquest of many diseases of bacterial origin, there is still a long list of bacterial infections uninfluenced by the newer chemotherapeuticals; among the latter, leprosy and tuberculosis continue to constitute the major posers to chemotherapy. This justifies further exploratory work both on compounds closely related to the effective substances already known and on their structural allies but with other substituents. The present study is one of a series of such exploratory investigations in the sulphanilamide group undertaken at this Institute with the object of extending their range of therapeutic usefulness in bacterial infections, also including those caused by the acid-fast mycobacterium.

The newer reports of the effectiveness of the treatment of experimental tuberculosis in the guinea pig and the rabbit with members of the sulphanilamide group are still discordant. A number of workers have claimed that sulphanilamide,[2, 3] sulphapyridine,[4] prontosil soluble,[5] sulphathiazole[6, 7] and sulphadiazine[7] in high blood-levels may modify the course of experimental tuberculosis. However the results obtained so far do not appear to warrant clinical trial of any of the aforementioned compounds. The low antitubercular activity of the sulphonamides, notwithstanding their direct action on many pathogenic organisms,[8] has been put down as perhaps partly due to their inability to penetrate the lipoid layer of the bacteria. Consequently, an attempt has been made to achieve better results by introducing lipophilic radicals into the sulphonamides. On this basis, only a single compound, N^1-dodecanoyl sulphanilamide, has been prepared[9] and tested experimentally without, however, consistent success.[10, 11] On the ground that sulphathiazole is more active than sulphanilamide against most bacteria, the introduction of a lipophilic substituent in the heterocyclic part of the

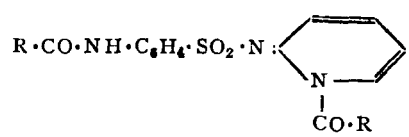
* A preliminary note covering part of the material embodied in this communication appeared in *Current Science*.[1]

former has been tried; a series of alkyl sulphathiazoles[12] as well as several sulphathiodiazoles[13] have been prepared but have not yet been tested against the tubercle bacillus. Thus the results secured so far can in no sense be called uniform.

Study of the numerous acyl derivatives of the sulphonamides hitherto synthesised has disclosed a few members effective in combating experimental coccal infections in mice associated with a low order of toxicity; some of them have also passed actual clinical trials.[14] However, with the exception of N^1-dodecanoyl sulphanilamide which is uncertainly reported, on[9, 10, 11] and the chaulmoogryl derivative[11] of sulphanilamide, none of the fatty acid derivatives of the sulphonamides appear to have been investigated as to their efficacy in tuberculosis or leprosy.

The present communication represents one of the many possible lines of attack for ascertaining whether or not the sulphonamides can be pressed to service in the conquest of mycobacterial infections by suitable synthetic operations on the molecule of sulphanilamide. Accordingly, a series of acyl derivatives of the sulphonamides have been synthesised in the expectation that these might exhibit a much greater ability to penetrate the lipoid layer of the tubercle and lepra bacilli as compared to the parent sulphonamides. The sulphonamides chosen for necessary modifications of their molecules in order to render them lipophilic were all previously known and reported to be active at least in some coccal infections. The final sulphonamides, prepared in this connection, are represented in Tabe I.

For purposes of convenience, the nomenclature of Crossley, Northey and Hultiquist[17] has been adopted. This does not however, exclude the alternative structure



for the N^4, N^1-diacyl sulphapyridines (Nos. 66–71 and 73) which is also possible.[18] In all probability they are equilibrium mixtures of the two isomeric forms. The compounds Nos. 86–92 have been assigned the structure represented in the table on the basis of their mode of preparation and in accordance with recent studies[18] on this type of compounds.

Besides the simple normal fatty acyl derivatives, a few branched-chain acyl sulphonamides (Nos. 71, 73, 79, 80, 84), of which Nos. 71, 79 and 84 contain the advantageous cyclohexyl group,[19] were also included in this study in view of the interesting results obtained by Robinson and Birch[20] with acids of the latter type.

TABLE I

Serial No.	Name	M.P./°C.	Nitrogen percentage	
			Found	Required
40	N^4-*n*, Caprylyl sulphanilamide*	198	9·6	9·7
41	N^4-Cyclohexoyl sulphanilamide	238	9·8	9·9
61	N^4-*n*, Butyryl sulphapyridine	206	12·9	13·2
63	N^4-*n*, Heptoyl sulphapyridine	193	11·6	11·6
64	N^4-*n*, Caprylyl sulphapyridine	213–14	10·8	11·2
66	N^4, N^1-Diacetyl sulphapyridine	194	11·8	12·6
67	N^4, N^1-Di (*n*, butyryl)-sulphapyridine ..	163	10·7	10·8
68	N^4, N^1-Di (*n*, caproyl)-sulphapyridine ..	155–57	10·1	9·5
69	N^4, N^1-Di (*n*, caprylyl)-sulphapyridine ..	135	8·5	8·4
70	N^4, N^1-Dibenzoyl sulphapyridine	217	9·2	9·2
71	N^4, N^1-Dicyclohexoyl sulphapyridine ..	193–95	8·6	9·0
73	N^4, N^1-Dicinnamoyl sulphapyridine ..	196–98	8·6	8·3
74	N^4-*n*, Butyryl sulphathiazole	244–46 dec.	12·4	12·5
75	N^4-*n*, Caproyl sulphathiazole	198–99	11·2	11·6
76	N^4-*n*, Heptoyl sulphathiazole	202–03	10·8	11·1
77	N^4-Palmityl sulphathiazole	140–47	8·3	8·5
78	N^4-Stearyl sulphathiazole	148–50	7·8	8·1
79	N^4-Cyclohexoyl sulphathiazole	222–23 dec.	11·5	11·5
80	N^4-Furoyl sulphathiazole	dec. above 240	12·0	12·0
81	N^4-*n*, Butyryl sulphathiazoline	224–25	12·1	12·5
82	N^1-*n*, Caproyl sulphathiazoline	181–82	11·2	11·5
83	N^4-*n*, Heptoyl sulphathiazoline	175–76	11·2	11·1
84	N^4-Cyclohexoyl sulphathiazoline	220	11·5	11·4
85	N^4-*n*, Caprylyl sulphanildimethylamide ..	79–82	8·4	8·6
86	1-Methyl, 2-(N^4-*n*, butyryl sulphanilimidio) 1 : 2-dihydro pyridine	213	12·6	12·6
87	1-Methyl, 2-(N^4-*n*, caproyl sulphanilimido) 1 : 2-dihydro pyridine	213–15	11·8	11·6
88	3-Methyl, 2-(N^4-*n*, caproyl sulphanilimido) 2 : 3-dihydro thiazole	215	11·5	11·4
89	3-Methyl, 2-(N^4-*n*, heptoyl sulphanilimido) 2 : 3-dihydro thiazole	173–74	11·3	11·0
90	3-Methyl, 2-(N^4-*n*, caprylyl sulphanilimido) 2 : 3-dihydro thiazole	153–54	10·4	10·6
91	3-Methyl, 2-(N^4-*n*, caproyl sulphanilimido) 2 : 3-dihydro thiazoline	201–03	11·1	11·4
92	3-Methyl, 2-(N^4-*n*, heptoyl sulphanilimido) 2 : 3-dihydro thiazoline	170	11·0	11·0
93	N^4-*n*, Butyryl, N^1-(*p*-nitrophenyl)-sulphanilamide	248–50 dec.	11·2	11·6
94	N^4-*n*, Caproyl, N^1-(*p*-nitrophenyl)-sulphanilamide†	152	10·3	10·7
95	N^4-*n*, Butyryl sulphanilyl sulphanilamide ..	235–36	10·6	10·6
96	N^4-*n*, Caproyl sulphanilyl sulphanilamide ..	184–86	9·4	9·9
	2-Sulphanilamido benzoic acid‡	ca. 215 dec.	9·4	9·6
97	2-(N^4-*n*, Butyryl sulphanilamido)-benzoic acid	226–28 dec.	7·3	7·7
	4-Sulphanilamido benzoic acid§	181–82	9·3	9·6
98	4-(N^4-*n*, Butyryl sulphanilamido)-benzoic acid	224–26	7·4	7·7

* Variously reported[15] to melt at 189° and 200°C.

† Literature[16] gives the m.p. 225°C.

‡ Reported by Kolloff[21] to melt at 225°C.

§ Kolloff[21] reports m.p. 202°C., Crossley *et al*[17] give m.p. 198–200°C.

Experimental

The N^4-acyl sulphonamides (Nos. 40, 41, 61, 63, 64, 74–84, 93–98) were prepared by condensation of molecular proportions of the requisite acid chlorides on the respective sulphonamides in the presence of pyridine. The condensation products, obtained by dilution of the reaction mixtures with excess of water, were severally purified through precipitation from their dilute sodium hydroxide solutions (decolorising carbon) by acidification with excess of dilute hydrochloric acid. They were finally recrystallised from either alcohol (Nos. 40, 41, 61, 63, 74–79, 93–98) or acetic acid (Nos. 64, 80–84) in colourless needles with the exception of Nos. 74, 75, 93 and 94, which were obtained as slightly pale plates or prismatic needles. The compound No. 97 was recrystallised from acetone in colourless needles.

Of the remaining N^4-acyl sulphonamides, the compounds, Nos. 85, 88–90 were prepared by operation of molecular proportions of the appropriate acid chlorides on the respective sulphonamides in pyridine medium; for the remaining compounds, *viz.*, Nos. 86, 87, 91, 92, the corresponding N^4-acyl but N^1-unsubstituted sulphonamides constituted the starting materials: aqueous alkaline solutions of these, on methylation with dimethyl sulphate, furnished the desired compounds. The compounds were first purified and freed from traces of the initial parent sulphonamides by suitable methods dictated by their differences in character when they were obtained as well defined, colourless crystals. The compound No. 85 was crystallised from acetone; the sulphathiazole derivatives, Nos. 88, 89 and 90, were obtained from acetic acid while the rest were crystallised from alcohol.

The N^4-N^1-disubstituted sulphapyridines (Nos. 66–71, 73) resulted directly by the operation of slightly more than 2 mols. of the appropriate acid chloride on sulphapyridine itself in pyridine solution. These products were isolated by taking advantage of their characteristic insolubility in both dilute mineral acids and alkalies. As hot polar solvents had the tendency to split off the acyl groups at the N^1-nitrogen of these compounds—in the case of the straight chain acid compounds, hot water broke them down to the corresponding N^4-acyl derivatives and the acids, while hot alcohol readily converted them to a mixture of the respective N^4-acyl derivatives and the acid esters—it was found advantageous to effect their recrystallisation by dilution of their solutions (charcoal) in acetone. These were then obtained as colourless plates and were dried *in vacuo* over anhydrous calcium chloride.

The yields of the final compounds reported herein, in all the instances, were good.

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Summary

On the ground that the sulphonamide group of drugs after suitable synthetic modifications of their molecules may probably be useful in mycobacterial infections, the possibility of rendering a few members, previously known to be active in coccal infections, lipophilic by the introduction of fatty acid residues in the latter has been explored. Accordingly, normal and branched chain acyl derivatives, thirty-seven in all, of sulphanilamide, sulphapyridine, sulphathiazole, sulphathiazoline, etc., have been synthesised.

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