CHEMOTHERAPY OF TUBERCULOSIS

Part II. Synthesis of N^4-Acyl-5-Alkylsulphathiazolones and 5: 5′-Alkylene *bis*-N^4-Acyl Sulphathiazolones

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ALTHOUGH it is eight years since Moore and Miller[1] first reported the synthesis of nine 5-alkyl sulphathiazolones and the promising chemotherapeutic activities exhibited by some of them in experimental bacterial infections, sulphathiazolones do not appear to have attracted attention from other workers in the field of chemotherapy. The one possible exception is sulphaethyl thiazolone which received passing notice from Cooper, Gross and Lewis[2] who found it to possess approximately the same antipneumococcal activity as sulphapyridine or sulphathiazole, an antistreptococcal action to that of sulphathiazole and antistaphylococcal activity of the same order as that of sulphathiazole or sulphadiazine. Cooper, *et al.*[2] were also of the opinion that whereas sulphaethyl thiazolone may perhaps cause fatal anæmia it was free from the serious defect in sulphadiazine of producing serious *urolithiasis* medicamenta in mice and rats. In the preliminary chemotherapeutic tests conducted, Moore and Miller[1] reported promising antistreptococcal activities for the 5-propyl-, 5-butyl-, 5: 5′-diethyl-sulphathiazolones and for the N^4-hexanoyl and heptanoyl derivatives of 5-butyl sulphathiazolone. Favourable antipneumococcal action was shown by 5-butyl, 5: 5′-dimethyl-, 5: 5′-diethyl-, and the N^4-hexanoyl substituted 5-butyl derivatives of sulphathiazolone, while 5-ethyl- and 5: 5′-diethyl sulphathiazolone were antistaphylococcal. Sulphaethyl thiazolone was absorbed as rapidly and its maximum concentration was higher on two dose levels than for sulfanilamide, sulphapyridine or sulphathiazole.

We were particularly interested in exploring the group of sulphathiazolones, carrying lipophilic alkyl radicals in the 5-position, for the treatment of tuberculosis and leprosy. Particular attention was paid to the synthesis of N^4-acylic compounds which were expected to be even more lipophilic than the free sulpha-alkylthiazolones. The inability in the early experiments to duplicate the higher yields reported by Moore and Miller[1] in the synthesis of the free 5-substituted sulphathiazolones by the acid hydrolysis of the corresponding N^4-acetyl derivatives, was also responsible for the election to synthesise exclusively N^4-acyl sulphathiazolones.

The 5-alkyl N^4-acyl sulphathiazolones and 5: 5′-alkylene-*bis*-N^4-acyl sulphathiazolones synthesised and which have not been reported hitherto, are tabulated. The N^4-acyl sulphathiazolones were prepared by the reaction of the appropriate acylsuphanilyl chloride with the requisite 2-amino-4-thiazolone in pyridine solution.

Substituted Sulphanilamidothiazolones

Serial No.	Name of the Compound	Molecular Formula	M.P./°C.	Nitrogen percentage	
				Found	Required
24	2:N^4-*n*-Butyryl sulphanilamidothiazolone	$C_{13}H_{15}O_4N_3S_2$	248–250	12·5	12·3
25	2-N^4-*n*-Valeryl sulphanilamidothiazolone	$C_{14}H_{17}O_4N_3S_2$	215–217	11·7	11·9
26	2-N^4-*n*-Caproyl sulphanilamidothiazolone	$C_{15}H_{19}O_4N_3S_2$	137–38	11·2	11·4
27	2-N^4-*n* Butyryl sulphanilamido-5-methylthiazolone	$C_{14}H_{17}O_4N_3S_2$	144–45	12·1	11·9
28	2-N^4-*n*-Valeryl sulphanilamido-5-methylthiazolone	$C_{15}H_{19}O_4N_3S_2$	135–36	11·0	11·4
29	2-N^4-*n*-Caproyl sulphanilamido-5-methylthiazolone	$C_{16}H_{21}O_4N_3S_2$	126–27	10·7	10·9
30	2-N^4-Acetyl-sulphanilamido-5-methylthiazolone	$C_{13}H_{15}O_4N_3S_2$	120–21	12·0	12·3
31	2-Sulphanilamido-5-ethylthiazolone	$C_{11}H_{12}O_3N_3S_2$	147–48	14·1	14·1
32	2-N^4-*n*-Butyryl sulphanilamido-5-ethylthiazolone	$C_{15}H_{19}O_4N_3S_2$	154–55	12·0	11·4
*33	2-N^4-*n*-Caproyl sulphanilamido-5-ethylthiazolone	$C_{17}H_2O_4N_3S_2$	178–72 Lit.,[1] 140–41	11·0	11·0
34	2-N^4-*n*-Butyryl sulphanilamido-5-*iso*-propylthiazolone	$C_{16}H_{21}O_4N_3S_2$	173–74	11·7	11·4
35	2-N^4-*n*-Caproyl sulphanilamido-5-*iso*-propylthiazolone	$C_{18}H_{25}O_4N_3S_2$	227–28	10·5	10·2
36	2-N^4-*n*-Butyryl sulphanilamido-5-*n*-hexylthiazolone	$C_{19}H_{27}O_4N_3S_2$	156–57	10·1	9·9
37	2-N^4-*n*-Valeryl sulphanilamido-5-*n*-hexylthiazolone	$C_{20}H_{29}O_4N_3S_2$	166–67	9·7	9·6
38	2-N^4-*n*-Butyryl sulphanilamido-5-phenylthiazolone	$C_{19}H_{19}O_4N_3S_2$	140–45	9·8	10·1
39	2-N^4-*n*-Valeryl sulphanilamido-5-phenylthiazolone	$C_{20}H_{21}O_4N_3S_2$	150–55	9·8	9·7
40	2-N^4-*n*-Caproyl sulphanilamido-5-phenylthiazolone	$C_{21}H_{22}O_4N_3S_2$	96–97 softg. at 70	9·4	9·9
41	5:5′-Diethylene-2:2′-*bis*-N^4-*n*-butyryl-sulphanilamidothiazolone	$C_{28}H_{32}O_8N_6S_4$	200–10 softg. at 180	11·4	11·8
42	5:5′-Hexamethylene-2:2′-*bis*-N^4-*n*-butyryl sulphanilamidothiazolone	$C_{32}H_{40}O_8N_6S_4$	125–45	10·9	11·0
43	5:5′-Hexamethylene-2:2-*bis*-N^4-*n*-valeryl sulphanilamidothiazolone	$C_{34}H_{44}O_8N_6S_4$	170–76 softg. at 155	11·0	10·6
44	5:5′Hexamethylene-2:2′-*bis*-N^4-*n*-caproyl sulphanilamidothiazolone	$C_{36}H_{48}O_8N_6S_4$	162–65	9·9	10·2

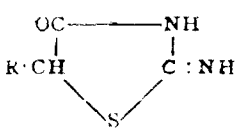
* This compound though differing in melting point from that of Moore and Miller (*loc. cit.*), gives correct analytical figure and exhibits marked activity in experimental streptococcal pneumococcal and *P. pestis* infections of white mice.[3]

Experimental

Pseudothiohydantoins.—The general procedure used for the synthesis of the 5-alkyl pseudothiohydantoins are exemplified in the preparation of 5-*iso*propyl-2-amino-4-thiazolone (No. 1). The 5: 5′-alkylenedipseudothiohydantoins (Nos. 5 and 6) were also prepared by a similar method, wherein the only modification adopted consisted in the use of the double the quantities of thionyl chloride, bromine and thiourea for each mole of the requisite dibasic acids.

5-iso*Propyl-2-amino-4-thiazolone.*—Isovaleric acid (55 c.c., 1 mol.) contained in a three-necked flask (750 c.c.) fitted with a reflux condenser, a dropping funnel and two calcium chloride guard tubes, was treated dropwise with thionyl chloride (50 c.c., 1·25 mols.). The reaction mixture was then heated on the water-bath for one hour when the evolution of the hydrochloric acid gas practically ceased. Bromine (27 c.c., 1 mol.), dried over concentrated sulphuric acid, was then added drop by drop to the hot reaction mixture. Heating on the boiling water-bath was continued for one hour after addition of all the bromine. The mixture was then cooled and cautiously treated with excess of alcohol (200 c.c.). The resulting solution of ethyl-α-bromo isovalerate was treated at room temperature with powdered thiourea (30 g., 1 mol.) and cautiously heated till the exothermic reaction set in. The reaction was moderated at this stage, by cooling if necessary, and completed by final refluxing for a further half an hour. The mixture was then diluted with excess of water, filtered and the aqueous acid solution of the hydrobromide basified with excess of ammonia. The resulting 5-*iso*propyl-2-aminothiazolone was crystallised from alcohol.

New pseudothiohydantoins synthesised now and numbered are set forth in Table II; pseudothiohydantoins not numbered are already known but prepared according to the procedure outlined above.



In the case of compounds Nos. 3 and 4, which were only feebly basic, the final purification through a dilute acid solution could not be adopted.

Compounds Nos. 1–4, crystallised from alcohol in colourless needles. Compounds Nos. 5 and 6 separated in colourless needles from alcohol, in which they were very sparingly soluble; these were advantageously purified by solution in dilute hydrochloric acid (charcoal) and reprecipitating by means

5-Substituted 2-amino-4-thiazolones

No.	Substituent (R) in position 5	Molecular Formula	M.P./°C.	Yield %	Nitrogen	
					Found	Required
	Methyl ..	..	..	67	..	..
	Ethyl ..	..	..	55	..	..
1	Isopropyl ..	$C_6H_{10}ON_2S$	224–25	35	18·0	17·7
	n-Butyl ..	..	..	75	..	..
2	*n*-Hexyl ..	$C_9H_{16}ON_2S$	187–89	68	14·2	14·0
3	*n*-Tetradecyl ..	$C_{19}H_{32}ON_2S$	167–72	60	8·9	9·0
4	Phenyl ..	$C_9H_8ON_2S$	228–29	84	14·8	14·5
5	Ethylene-5-pseudothiohydantoin	$C_8H_{10}O_2N_4S_2$	270 (dec.)	78	21·8	21·7
6	Hexamethylene-5-pseudothiohydantoin	$C_{12}H_{18}O_2N_4S_2$	249–51 (dec.)	72	17·5	17·8

of dilute ammonia in presence of appreciable amounts of alcohol when they separated as white needles and were analytically pure.

All the above substituted pseudothiohydantoins are soluble to varying extents in cold dilute sodium hydroxide from which they are regenerated with little change by dilute acetic acid.

The 5-alkyl-N^4-acyl sulphathiazolones (Nos. 24–30, 32–40) and the 5:5′-alkylene-*bis*-N^4-acylsulphathiazolones (Nos. 41–44) resulted by the action of 1·1 and 2·2 molecular proportions respectively of the requisite acylsulphanilyl chlorides on the suitable aminothiazolones in pyridine. The crude condensation products, obtained by dilution of the reaction mixtures with a large excess of water, were filtered, washed with water, and freed from traces of contaminating unreacted pseudothiohydantoins by thorough washing with dilute hydrochloric acid followed by water.

The final N^4-acyl sulphathiazolones were soluble in dilute ammonium hydroxide, the only exceptions being the 5-phenyl derivatives (Nos. 38–40). These were reprecipitated without change by dilute mineral acids. Occasionally, where the purity of the final product was in doubt, it was found to be advantageous to utilise the properties of the sulphathiazolones, *viz.*, dissolving in dilute ammonia. It was then possible to obtain pure samples by acidification of an ammonical solution (charcoal) of the acyl sulphathiazolones.

The yields of the purified acyl sulphathiazoles ranged between 30–40 per cent. of theory.

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Summary

An attempt has been made to explore the little investigated but chemically and biologically interesting group of 2-sulphanilamidothiazolones, mostly carrying lipophilic alkyl radicals in the 5-position, for members likely to prove useful in the treatment of tuberculosis and leprosy. In the synthesis of the candidate compounds, emphasis has been laid on the N^4-*n*-fatty acyl derivatives of 2-sulphanilamido-5-substituted thiazolones in the expectation that these would be even more lipophilic than the free sulphanilamidothiazolones themselves.

A preparative method for the intermediate 2-amino-5-substituted thiazolones, starting with the corresponding mono- and dibasic fatty acids, has been worked out. New 5-substituted pseudothiohydantoins, derived from monobasic acids, are 5-*iso* propyl-, 5-*n*-hexyl-, 5-*n*-tetradecyl-, and 5-phenyl-2-amino-thiazolones. Among new 5: 5′-alkylene-*bis*-pseudothiohydantoins are 5: 5′-ethylene-*bis*-2: 2′-aminothiazolone and 5: 5′-hexamethylene-*bis*-2: 2′-aminothiazolone, prepared from adipic and sebacic acids respectively.

The following sulphonamidothiazolones have been synthesised: N^4-*n*-butyryl-, N^4-*n*-valeryl-, and the N^4-*n*-caproyl sulphanilyl derivatives of 2-amino-, 2-amino-5-methyl-, 2-amino-5-ethyl-, 2-amino-5-*iso*propyl-, 2-amino-5-*n*-hexyl-, and 2-amino-5-phenyl-thiazolones; and *bis*-N^4-*n*-butyryl, *bis*-N^4-*n*-valeryl- and *bis*-N^4-*n*-caproyl-sulphanilyl derivatives of 5: 5′-ethylene-*bis*-2-amino and 5: 5′-hexamethylene-*bis*-2-aminothiazolones.

2-Sulphanilamido-5-ethylthiazolone, prepared in the course of this study, differs in its physical characteristics from that of sulphaethylthiazolone as reported by the earlier workers. However, the present sample affords good analytical values and is markedly active in some acute bacterial infections.

References

1. Moore and Miller .. *J. Amer. Chem. Soc.*, 1941, **64**, 2343.
2. Cooper, Gross and Lewis .. *Proc. Soc. Exp. Bio. Med.*, 1941, **47**, 538.
3. Chemotherapy Group of the Haffkine Institute Unpublished work.