# CHEMOTHERAPY OF TUBERCULOSIS

## Part V. Synthesis of Some $N^4$-Acyl-$N^1$-Aryl Sulphanilhydroxamides

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OF the numerous derivatives of sulphanilamide which have exhibited marked activity in experimental chemotherapy but have however not received adequate attention since their synthesis, the $N^4$-acyl sulphanilhydroxamides constitute an interesting group. The first members of this group were synthesised by Kharasch and Reinmuth[1] and, more extensively, by Moore, Miller and Miller.[2] Among the large number of homologous $N^4$-acyl sulphanilhydroxamides, the $N^4$-*n*-butyryl-, $N^4$-*n*-valeryl-, $N^4$-*n*-hexanoyl-, $N^4$-*n*-heptanoyl-, and $N^4$-*n*-octanoyl sulphanilhydroxamides were found to be more effective antistreptococcal agents than sulphanilhydroxamide, sulphanilamide or sulphapyridine,[2, 3, 4] while the toxicity of the active members was greatly below that of sulphanilamide. Hampil, *et al.* (*loc. cit.*) also found these compounds to be effective against meningococci. More recently, Goldfarb[5] synthesised $N^1$-*o*-methyl-, and $N^1$-*o*-benzyl sulphanilhydroxamides and found their bacteriostatic activities to be midway between those of sulphanilamide and sulphathiazole as expected on the basis of their pKa values in accordance with the Bell-Roblin theory.[6] One of the most promising member of this series, $N^4$-*n*-caproylsulphanilhydroxamide or "sulphabenamide", has been studied at some length by Hansen and Kreidler[7] who confirmed its therapeutic usefulness in $\beta$-hæmolytic streptococcal infections of rabbits.

The hope that the sulphanilhydroxamides may be of some value in the chemotherapy of mycobacterial infections was stimulated by an announcement by Gubner[8] that sulphabenamide was definitely beneficial in human tuberculosis. Gubner reported that five cases of advanced bilateral pulmonary tuberculosis, treated over ten months, gave absence of the tubercle bacilli from sputum and disappearance of the lesions. He also stated that no toxic effects developed when the drug was administered in quantities upto an ounce in 16 hours, or when given over a period of 10 months. However, sulphabenamide was pronounced too toxic by Smith and McClosky[9] on the basis of their chemotherapeutic studies in experimental guinea-pig tuberculosis. Another interesting feature about the $N^4$-acyl

sulphahydroxamides was their relative instability reported by Moore, *et al.* (*loc.cit.*) who stated that these compounds slowly dissolved at room temperature in dilute alkali with evolution of a gas and a formation of $N^4$-acylaminobenzenesulphinic acids. While assessing the antimycobacterial potentialities of the $N^4$-acyl sulphanilhydroxamides and ascertaining their exact mode of chemotherapeutic action, it was considered profitable to pay particular attention to $N^4$-acyl-$N^1$-substituted sulphanilhydroxamides which were expected to be more stable than those already available. Accordingly, the synthesis of $N^4$-acyl-$N^1$-aryl or heterocyclic sulphanilhydroxamides were undertaken. So far, only the preparation of a series of $N^4$-acyl-$N^1$-(mono- or dichloro-) phenyl sulphanilhydroxamides has been completed. The halogenated derivatives were especially attractive in view of the possibility of these being unantagonised by *p*-aminobenzoic acid similar to other halogenated sulphonamides recently disclosed.[10] The compounds synthesised are presented in the table.

The $N^4$-acyl-$N^1$-substituted sulphanilhydroxamides were obtained by the reaction of suitable $N^4$-acylsulphanilyl chlorides on freshly prepared specimens of the requisite halogenated β-phenylhydroxamides in pyridine medium.

*Substituted Sulphonamidohydroxamides*

| Serial No. | Name of the Compound | Molecular Formula | M.P./°C. | Nitrogen percentage | |
|---|---|---|---|---|---|
| | | | | Found | Required |
| 105 | $N^4$-*n*-Butyrylsulphanil-β-3-chlorophenyl hydroxamide | $C_{16}H_{17}O_4N_2SCl$ | 210–14 | 7·6 | 7·6 |
| 106 | $N^4$-*n*-Valerylsulphanil-β-3-chlorophenyl hydroxamide | $C_{17}H_{19}O_4N_2SCl$ | 195–97 | 7·6 | 7·3 |
| 107 | $N^4$-*n*-Caproylsulphanil-β-3-chlorophenyl hydroxamide | $C_{18}H_{21}O_4N_2SCl$ | 187–90 | 7·5 | 7·6 |
| 108 | $N^4$-*n*-Butyrylsulphanil-β-4-chlorophenyl hydroxamide | $C_{16}H_{17}O_4N_2SCl$ | 157–59 | 7·3 | 7·6 |
| 109 | $N^4$-*n*-Valerylsulphanil-β-4-chlorophenyl hydroxamide | $C_{17}H_{19}O_4N_2SCl$ | 216–17 | 7·3 | 7·3 |
| 110 | $N^4$-*n*-Caproylsulphanil-β-4-chlorophenyl hydroxamide | $C_{18}H_{21}O_4N_2SCl$ | 212–14 | 7·8 | 7·6 |
| 111 | $N^4$-*n*-Butyrylsulphanil-β-2:5-dichlorophenyl hydroxamide | $C_{16}H_{16}O_4N_2SCl_2$ | 143–44 | 6·7 | 7·0 |
| 112 | $N^4$-*n*-Valerylsulphanil-β-2:5-dichlorophenyl hydroxamide | $C_{17}H_{18}O_4N_2SCl_2$ | 140–42 | 6·9 | 7·0 |
| 113 | $N^4$-*n*-Caproylsulphanil-β-2:5-dichlorophenyl hydroxamide | $C_{18}H_{20}O_4N_2SCl_2$ | 141–42 | 6·8 | 7·0 |
| 114 | $N^4$-*n*-Butyrylsulphanil-β-3:4-dichlorophenyl hydroxamide | $C_{16}H_{16}O_4N_2SCl_2$ | 139–40 | 6·9 | 7·0 |
| 115 | $N^4$-*n*-Valerylsulphanil-β-3:4-dichlorophenyl hydroxamide | $C_{17}H_{18}O_4N_2SCl_2$ | 135–36 | 6·7 | 7·0 |

## EXPERIMENTAL

The simple substituted β-phenylhydroxylamines needed in this investigation were prepared by a further modification of the elegant method of Lapworth and his co-workers[11] based on the original preparative procedure of Willstatter and Kubli for β-phenylhydroxylamines.

The general procedure used for the synthesis of substituted β-phenylhydroxylamines is exemplified in the preparation of 4-chloro-β-phenylhydroxylamine.

*4-Chloro-β-phenylhydroxylamine.*—The reagent used for the reduction was prepared by adding drop by drop concentrated hydrochloric acid (105 c.c.) to a solution of anhydrous sodium sulphide (150 g.) dissolved in water (325 c.c.) with the aid of long dropping funnel, the lower end of which reaching to the bottom of the solution. This reagent was transferred to a glass stoppered bottle containing *p*-chloronitrobenzene (65 g.), toluene (75 c.c.) and a saturated solution of calcium chloride (50 g.). The mixture was shaken up vigorously for about one and a half hour to cause an emulsion keeping the temperature below 30° C. by occasional cooling. As the reduction proceeded liquid became thicker and the colour gradually darkened to deep orange. The reduction was completed in approximately two to two and a half hours and then ammonium chloride (60 g.) was added and the mixture was shaken to dissolve the inorganic matter. The precipitate of crystalline 4-chloro-β-phenylhydroxylamine was filtered, washed with water and finally with petroleum ether. The product thus obtained was crystallised from dilute alcohol, yield 42 g.

The substituted β-phenylhydroxylamines synthesised are tabulated as follows:—

| Compound | Formula | M.P./°C. | Yield % | Nitrogen percent. | |
|---|---|---|---|---|---|
| | | | | Found | Required |
| 3-Chloro-β-phenyl hydroxylamine | $C_6H_6ONCl$ | 98–100 | 60 | 9·73 | 9·75 |
| 4-Chloro-β-phenyl hydroxylamine | $C_6H_6ONCl$ | 99–100 | 55 | .. | .. |
| 2:4 Dichloro-β-phenylhydroxylamine | $C_6H_5ONCl_2$ | 77–78 | 70 | 7·7 | 7·9 |
| 3:4-Dichloro-β-phenylhydroxylamine | $C_6H_5ONCl_2$ | 135–37 | 30 | 5·7<br>5·65<br>(unstable) | 7·9 |

The N-acyl sulphanilyl chlorides used in these experiments were obtained by the methods already available in literature.[12, 13] The earlier workers had used the crude sulphochlorides on the ground that these were not very stable. It was now found to be advantageous to utilise in the present condensations stable acyl sulphanilyl chlorides which resulted by crystallisation from dilute acetone (charcoal).

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## Summary

A series of sulphanilamides derived from N-carbo and heterocyclic hydroxamides have been synthesised, since a number of $N^4$-acyl sulphanilhydroxamides have been favourably reported on in preliminary experimental bacterial infections. Among the latter was *sulphabenamide* or $N^4$-caproyl sulphanylhydroxamide, which was said to be effective clinically in streptococcal infections and tuberculosis. This is a new class of sulphanilamides involving the preliminary synthesis of some hitherto unknown substituted aryl- and heterocyclic hydroxamides. The compounds of this series so far prepared are the $N^4$-*n*-butyryl-, the $N^4$-*n*-valeryl-, and the $N^4$-*n*-caproyl-sulphanilyl derivatives of $\beta$-3-chlorophenyl-, $\beta$-4-chlorophenyl-, $\beta$-2:5-dichlorophenyl-, and $\beta$-3:4-dichlorophenyl-hydroxylamines.

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