

## 64. Sulphanilamide Derivatives.

By F. S. SPRING and E. P. H. YOUNG.

A number of sulphanilamide derivatives carrying an alkyl group substituent at N<sup>1</sup> have been prepared for test as tuberculocides. Preliminary results show that they are inactive in this respect.

ALTHOUGH there is considerable evidence showing that sulphanilamide drugs have no appreciable effect upon the spread of experimental tuberculosis in animals infected in various ways (Smithburn, *Proc. Soc. Exp. Biol. Med.*, 1938, **38**, 574; Kolmer, Raiziss, and Rule, *ibid.*, 1938, **39**, 581; Steinbach and Dillon, *ibid.*, 1939, **41**, 613; Dietrich, *Amer. Rev. Tuberc.*, 1938, **38**, 388; Flippin, Forrester, and Fitz-Hugh, *ibid.*, 1940, **42**, 821; Heise and Steenken, *ibid.*, p. 801), yet it has been repeatedly claimed that sulphanilamide in relatively large doses will retard the development of experimental tuberculosis (Rich and Follis, *Bull. Johns Hopkins Hosp.*, 1938, **62**, 77; 1939, **65**, 466; Buttle and Parish, *Brit. Med. J.*, 1938, ii, 776; Greey, Boddington, and Little, *Proc. Soc. Exp. Biol. Med.*, 1939, **40**, 418). It is also claimed that sulphapyridine retards the development of experimental tuberculosis, and similar claims have been made for various sulphanilamide derivatives and sulphones (Ballou, Guernon, and Simon, *Amer. Rev. Tuberc.*, 1942, **45**, 217; Ballou and Guernon, *ibid.*, p. 212; Barach, Molomot, and Soroka, *ibid.*, 1942, **46**, 268; Feldman, Hindshaw, and Moses, *Proc. Staff Meet. Mayo Clinic*, 1940, **15**, 695; 1941, **16**, 187; *Amer. Rev. Tuberc.*, 1942, **45**, 212, etc.).

In the present study, a group of sulphanilamide derivatives containing an alkyl group attached to N<sup>1</sup>\* have been prepared in order to test their tuberculocidal properties. It was hoped that the introduction of such an alkyl group would lead to greater penetration by the drug of the waxy structure of the tubercle bacillus (cf. Crossley, Northey, and Hultquist, *J. Amer. Chem. Soc.*, 1939, **61**, 2952; Robinson, J., 1940, 505; Steinbach and Duca, *Proc. Soc. Exp. Biol. Med.*, 1940, **44**, 133; Muschenheim, Forkner, and Duerschner, *ibid.*, 1940, **45**, 556; Bergmann and Haskelberg, *J. Amer. Chem. Soc.*, 1941, **63**, 2243). It was appreciated that the bactericidal properties of the parent sulphanilamide would be reduced by the introduction of an alkyl group, but it was hoped that this effect would be offset by the increase in lipid solubility.

N<sup>1</sup>-Heptadecylsulphanilamide and NN'-disulphanilyltetramethylenediamine were each prepared by the action of acetylsulphanilyl chloride upon the requisite amine, followed by hydrolysis of the N<sup>4</sup>-acetyl group, and also by the condensation of *p*-nitrobenzenesulphonyl chloride with the amine, followed by reduction of the nitro-group. Various derivatives of sulphapyridine of the general formula (I), in which R = *n*-C<sub>2</sub>H<sub>7</sub>, *n*-C<sub>5</sub>H<sub>11</sub>, *n*-C<sub>16</sub>H<sub>33</sub>, *n*-C<sub>18</sub>H<sub>37</sub>, and geranyl, together with N<sup>1</sup>-2-(6-methylpyridyl)-N<sup>1</sup>-octadecylsulphanilamide have been prepared. Not one of these sulphanilamides has any action upon the tubercle bacillus *in vitro*; furthermore, there appears to be a decline in their inhibitory action upon hæmolytic streptococci as the size of the alkyl group increases.

## EXPERIMENTAL.

NN'-Di-(*p*-nitrobenzenesulphonyl)tetramethylenediamine.—Adipamide (4.5 g.) was added to a solution prepared by addition of bromine (10 g.) to a mixture of sodium hydroxide (27.5 c.c.; 33%) and ice (50 g.). The mixture was heated on the steam-bath for 3 hours. The cold solution was then shaken with *p*-nitrobenzenesulphonyl chloride (13.85 g.) in ether (140 c.c.). The aqueous solution was separated, and acidified with 10% hydrochloric acid; the crude product was collected, washed with water, and purified by solution in hot potassium hydroxide solution (12%), followed by precipitation of the filtered solution with acid. After three crystallisations from aqueous acetone, NN'-di-(*p*-nitrobenzenesulphonyl)tetramethylenediamine was obtained as golden plates, m. p. 201° (Found: C, 41.9; H, 4.2. C<sub>16</sub>H<sub>18</sub>O<sub>8</sub>N<sub>4</sub>S<sub>2</sub> requires C, 41.9; H, 3.9%).

NN'-Disulphanilyltetramethylenediamine.—(a) A suspension of the nitro-compound (0.5 g.) in a mixture of alcohol (22.5 c.c.) and hydrochloric acid (*d* 1.15; 25 c.c.) was heated under reflux with tin (1 g.) for 1 hour. After standing overnight, the separated tin complex was collected and decomposed by heating with aqueous sodium carbonate solution (10%). The product was collected and crystallised from 80% alcohol (charcoal), yielding the disulphanilyl compound as needles, m. p. 205°, identical with the product prepared by method (b).

(b) A cooled solution of putrescine, prepared from adipamide (9 g.) as described above, was shaken with acetylsulphanilyl chloride (30 g.) in ether (300 c.c.). The solid separating at the interface was collected (5 g.) and crystallised from methyl alcohol, from which NN'-di(acetylsulphanilyl)tetramethylenediamine separated as platelets, m. p. 233° (sintering at 218°) (Found: C, 49.8; H, 5.6. C<sub>26</sub>H<sub>26</sub>O<sub>6</sub>N<sub>4</sub>S<sub>2</sub> requires C, 49.8; H, 5.4%). Hydrolysis was effected by heating under reflux for 1 hour with alcoholic hydrochloric acid (90 c.c. alcohol; 10 c.c. conc. acid). The hydrochloride was collected (microneedles, m. p. 241°), dissolved in aqueous acetone, and the solution neutralised by addition of sodium carbonate solution. Crystallisation of the product from 80% alcohol gave the disulphanilyl compound as needles, m. p. 205°, either alone or when mixed with the specimen prepared by method (a) (Found: C, 48.2; H, 5.5. C<sub>16</sub>H<sub>22</sub>O<sub>4</sub>N<sub>4</sub>S<sub>2</sub> requires C, 48.2; H, 5.5%).

N<sup>1</sup>-*n*-Heptadecylsulphanilamide.—(a) Heptadecylamine (5 g.) in ether (100 c.c.) was shaken with *p*-nitrobenzenesulphonyl chloride (4.75 g.) in ether (100 c.c.). After removal of the ether, the residue was crystallised from aqueous acetone, from which heptadecyl-*p*-nitrobenzenesulphonamide (3 g.) separated as cream-coloured plates, m. p. 90.5° (Found: C, 62.7; H, 9.2. C<sub>23</sub>H<sub>40</sub>O<sub>4</sub>N<sub>2</sub>S requires C, 62.7; H, 9.1%). Reduction of this compound (0.5 g.) with tin and hydrochloric acid as described above gave N<sup>1</sup>-*n*-heptadecylsulphanilamide (0.25 g.) as small needles, m. p. 118° either alone or when mixed with the specimen prepared by method (b).

(b) Condensation of heptadecylamine (25 g.) and acetylsulphanilyl chloride (23 g.) in ether gave N<sup>4</sup>-acetyl-N<sup>1</sup>-*n*-heptadecylsulphanilamide (22 g.), which separated as fine needles from alcohol, m. p. 128° (Found: C, 66.4; H, 9.8. C<sub>25</sub>H<sub>44</sub>O<sub>3</sub>N<sub>2</sub>S requires C, 66.4; H, 9.7%). Hydrolysis of this acetyl derivative with alcoholic hydrochloric acid, followed by treatment with sodium carbonate, gave N<sup>1</sup>-*n*-heptadecylsulphanilamide as needles, m. p. 118° (Found: C, 66.9; H, 9.9. C<sub>23</sub>H<sub>42</sub>O<sub>2</sub>N<sub>2</sub>S requires C, 67.3; H, 10.2%).

\* The nomenclature is that of Crossley, Northey, and Hultquist, *J. Amer. Chem. Soc.*, 1938, **60**, 2217.

**N<sup>1</sup>-2-Pyridyl-N<sup>1</sup>-n-propylsulphanilamide.**—A solution of freshly distilled 2-*n*-propylaminopyridine (Slotta and Franke, *Ber.*, 1930, **63**, 690) (10 g.) in dry pyridine (50 c.c.) was treated with acetylsulphanil chloride (17 g.), added during 30 minutes with stirring. The mixture was heated on the steam-bath for 3 hours and poured in water. The oil was collected and heated under reflux for 3 hours with aqueous-alcoholic sodium hydroxide solution (10%; 100 c.c.). The product was isolated by precipitation with water and crystallised from aqueous methylated spirit, N<sup>1</sup>-2-pyridyl-N<sup>1</sup>-n-propylsulphanilamide separating in needles, m. p. 108° (Found: C, 57.6; H, 6.2. C<sub>14</sub>H<sub>11</sub>O<sub>2</sub>N<sub>3</sub>S requires C, 57.7; H, 5.8%).

**N<sup>1</sup>-2-Pyridyl-N<sup>1</sup>-n-amylsulphanilamide.**—2-Aminopyridine (20 g.) in warm dry pyridine (20 c.c.) was treated with sodamide (8.2 g.). After the initial reaction had subsided, *n*-amyl bromide (37 g.) was added slowly, and the mixture set aside for 2 days, then heated under reflux for 3 hours. The cold mixture was poured into aqueous sodium carbonate solution, and the product isolated by means of ether. 2-*n*-Amylaminopyridine (22.2 g.), b. p. 130–135°/12 mm., solidified to a mass of colourless plates, m. p. 43° (Found: C, 73.5; H, 9.7; N, 16.85. C<sub>10</sub>H<sub>16</sub>N<sub>2</sub> requires C, 73.2; H, 9.8; N, 17.1%). The *picrate* separated in yellow needles from alcohol, m. p. 121° (Found: C, 48.9; H, 4.9. C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>.C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires C, 48.9; H, 4.8%). Freshly distilled 2-*n*-amylaminopyridine (15 g.) in pyridine (50 c.c.) was treated with acetylsulphanil chloride (21.5 g.), added during 30 minutes with stirring. The reaction was completed by heating for 2 hours on the steam-bath and pouring into water. N<sup>4</sup>-Acetyl-N<sup>1</sup>-2-pyridyl-N<sup>1</sup>-n-amylsulphanilamide was obtained as needles, m. p. 83°, from 50% aqueous acetic acid (Found: N, 11.3. C<sub>16</sub>H<sub>23</sub>O<sub>3</sub>N<sub>3</sub>S requires N, 11.6%). Hydrolysis of this acetyl derivative with aqueous-alcoholic sodium hydroxide (7.5%) gave N<sup>1</sup>-2-pyridyl-N<sup>1</sup>-n-amylsulphanilamide as needles from alcohol, m. p. 74–75° (Found: N, 13.5. C<sub>16</sub>H<sub>21</sub>O<sub>2</sub>N<sub>3</sub>S requires N, 13.2%).

**N<sup>1</sup>-2-Pyridyl-N<sup>1</sup>-cetylulphaniamide.**—2-Cetylaminopyridine, prepared by a modification of the method described for 2-*n*-amylaminopyridine, had b. p. 210–220°/12 mm. and solidified to a waxy solid, m. p. 67° (Schering-Kahlbaum, B.P. 265,167, give b. p. 215–225°/2 mm.; m. p. 65–66°). The *picrate* separated in yellow needles from alcohol, m. p. 84° (Found: C, 59.4; H, 7.4; N, 12.9. C<sub>21</sub>H<sub>35</sub>N<sub>2</sub>.C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires C, 59.2; H, 7.5; N, 12.8%). Condensation of 2-cetylaminopyridine (15 g.) with acetylsulphanil chloride (11 g.) in the manner described for the *n*-amyl analogue gave N<sup>4</sup>-acetyl-N<sup>1</sup>-2-pyridyl-N<sup>1</sup>-cetylulphaniamide (18 g.) as plates from light petroleum (b. p. 80–100°), m. p. 88° (Found: N, 8.6. C<sub>29</sub>H<sub>45</sub>O<sub>3</sub>N<sub>3</sub>S requires N, 8.2%). Hydrolysis of this acetyl derivative with aqueous-alcoholic sodium hydroxide (10%) gave N<sup>1</sup>-2-pyridyl-N<sup>1</sup>-cetylulphaniamide as needles, m. p. 77°, from aqueous alcohol (Found: C, 68.6; H, 9.1; N, 9.2. C<sub>27</sub>H<sub>43</sub>O<sub>2</sub>N<sub>3</sub>S requires C, 68.5; H, 9.1; N, 8.9%).

**N<sup>1</sup>-2-Pyridyl-N<sup>1</sup>-n-octadecylsulphanilamide.**—2-Octadecylaminopyridine, prepared from octadecyl chloride and 2-aminopyridine, was obtained as a colourless oil, b. p. 180–185°/0.01 mm., solidifying to a waxy solid, m. p. 66–67° (Found: C, 79.35; H, 12.1; N, 8.5. C<sub>23</sub>H<sub>42</sub>N<sub>2</sub> requires C, 79.8; H, 12.1; N, 8.1%). Condensation of the base with acetylsulphanil chloride, followed by hydrolysis of the acetyl derivative, yielded N<sup>1</sup>-2-pyridyl-N<sup>1</sup>-octadecylsulphanilamide as needles from aqueous alcohol, m. p. 70–71° (Found: N, 8.6. C<sub>29</sub>H<sub>47</sub>O<sub>2</sub>N<sub>3</sub>S requires N, 8.4%).

**N<sup>1</sup>-Geranyl-N<sup>1</sup>-2-pyridylsulphanilamide.**—2-Aminopyridine (10 g.), sodamide (4.15 g.), and xylene (50 c.c.) were heated for 1 hour on the steam-bath. The solution was cooled, treated with geranyl chloride (Forster and Cardwell, *J.*, 1913, **103**, 1339) (18.35 g.; b. p. 101°/12 mm.), and the reaction completed by 3 hours' heating at 150°. The cold reaction mixture was treated with water and extracted with xylene. Distillation gave 2-geranylaminopyridine as a yellow oil, b. p. 185–190°/12 mm. (Found: C, 78.2; H, 9.5; N, 12.1. C<sub>15</sub>H<sub>22</sub>N<sub>2</sub> requires C, 78.3; H, 9.6; N, 12.2%). The *picrate* separated from alcohol in fine yellow needles, m. p. 125° (Found: C, 54.8; H, 5.3; N, 15.0. C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>.C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires C, 54.9; H, 5.5; N, 15.25%). Condensation of this base with acetylsulphanil chloride in pyridine, followed by hydrolysis of the intermediate acetyl derivative with 10% alcoholic potassium hydroxide, gave N<sup>1</sup>-geranyl-N<sup>1</sup>-2-pyridylsulphanilamide as plates from alcohol, m. p. 75–76° (Found: C, 65.8; H, 6.8; N, 11.1. C<sub>21</sub>H<sub>27</sub>O<sub>2</sub>N<sub>3</sub>S requires C, 65.45; H, 7.0; N, 10.9%).

**N<sup>1</sup>-2-(6-Methylpyridyl)-N<sup>1</sup>-octadecylsulphanilamide.**—A mixture of *n*-octadecyl chloride (24 g.) and freshly prepared 6-amino-2-methylpyridine (27 g.) was treated with sodamide (10 g.). The flask and contents became warm and ammonia was evolved. After standing for 2 days, the mixture was decomposed by addition of water, and the product isolated by means of ether. The fraction, b. p. 170–230°/1 mm., was converted into the *picrate*, which separated in yellow platelets, m. p. 101° (15 g.) (Found: C, 60.8; H, 8.1. C<sub>24</sub>H<sub>44</sub>N<sub>2</sub>.C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires C, 61.1; H, 8.0%). Decomposition of the *picrate* gave the free base, b. p. 205°/0.25 mm., m. p. 46°, which was condensed with acetylsulphanil chloride in pyridine solution to give N<sup>4</sup>-acetyl-N<sup>1</sup>-2-(6-methylpyridyl)-N<sup>1</sup>-octadecylsulphanilamide in plates from light petroleum (b. p. 80–100°), m. p. 84° (Found: C, 68.4; H, 8.7; N, 7.6. C<sub>32</sub>H<sub>51</sub>O<sub>3</sub>N<sub>3</sub>S requires C, 68.9; H, 9.2; N, 7.5%). The acetyl derivative was hydrolysed by heating under reflux with aqueous-alcoholic sodium hydroxide solution (7.5%) for 2 hours. N<sup>1</sup>-2-(6-Methylpyridyl)-N<sup>1</sup>-octadecylsulphanilamide separated in waxy plates from aqueous alcohol, m. p. 77–78° (Found: C, 69.6; H, 9.35; N, 8.0. C<sub>30</sub>H<sub>49</sub>O<sub>2</sub>N<sub>3</sub>S requires C, 69.9; H, 9.5; N, 8.2%).

We are indebted to Messrs. I.C.I. (Dyestuffs), Limited, for their support of this investigation.

THE UNIVERSITY, MANCHESTER.

[Received, January 13th, 1944.]