164. *The Preparation of* N^4*-Carboxyacylsulphonamides. Part II. The Synthesis of* N^4*-Phthalylsulphanilamide Derivatives.*

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p-Phthalimidobenzenesulphonyl chloride (I), which is obtained by the chlorosulphonation of either phthalanil (Dewar and King, *J.*, 1945, 114) or phthalanilic acid, has been caused to react with a number of amines and the resulting *p*-phthalimidobenzenesulphonamides have been hydrolysed to the corresponding N^4-phthalylsulphanilamides (III).

In Part I (Picard, Reid, and Seymour, *J.*, 1946, 751), the condensation of *p*-succinimidobenzenesulphonyl chloride and succinylsulphanilyl chloride with amines has been described. The work has been extended to cover similar condensations of *p*-phthalimidobenzenesulphonyl chloride, in view of the fact that some N^4-phthalylsulphanilamides, and more particularly N^4-phthalylsulphathiazole, have been shown to be superior to the succinyl analogues as intestinal antiseptics (Poth and Ross, *Proc. Amer. Soc. Pharmacol.*, Fed. Proc., Baltimore, 1943, **11**, 89; *J. Lab. Clin. Med.*, 1944, **29**, 785; Kirchof *et al.*, *J. Surg. Obst. Gynæcol.*, 1943, **51**, 419).

The phthalyl derivatives are usually obtained in a similar way to the succinyl derivatives, *i.e.*, by the action of the carboxylic acid or anhydride on the sulphanilamide (cf. Picard *et al.*,

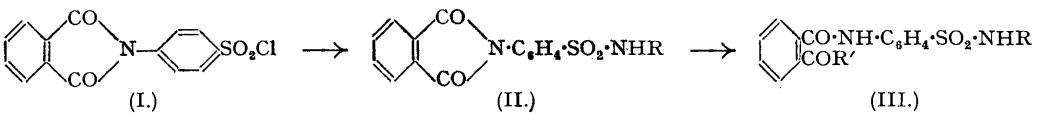
loc. cit.). *p*-Phthalimidobenzenesulphonyl chloride (I) has not been used previously as a starting material for these compounds, although its use as a possible substitute for acetylsulphanilyl chloride in the synthesis of N^1-substituted sulphanilamides was discussed by Dewar and King (*J.*, 1945, 114) in a paper which appeared whilst the present investigation was in progress.

We have prepared *p*-phthalimidobenzenesulphonyl chloride (I), essentially according to the method used by these authors, and have caused it to react with several amines, *viz.*, ammonia, methylamine, aniline, 2-aminopyridine, and 2-aminothiazole, using pyridine or a second mole of reacting amine as acid acceptor, to give the corresponding *p*-phthalimidobenzenesulphonamides (II). The phthalimido-compounds (II) were hydrolysed to the corresponding phthalylamino-compounds (III, R′ = OH) by means of hot dilute alkali. Hydrolysis with dilute mineral acid caused complete cleavage, yielding the free sulphanilamide.

It was found that, in general, the phthalylamino-derivatives do not possess a melting point distinct from that of their closed-ring analogues (II), no doubt owing to the fact that ring closure occurs on heating. In some cases, partial decomposition at a lower temperature was observed, followed by subsequent complete melting at a temperature near the melting point of the pure anil (II). N^4-*Phthalyl*-N^1-*phenylsulphanilamide* (III, R = C_6H_5, R′ = OH) was the only compound of this type examined which possessed a distinct melting point.

Treatment of *p*-phthalimidobenzenesulphonyl chloride (I) in dioxan solution with two molecular proportions of ammonia gave *p*-phthalimidobenzenesulphonamide (II, R = H), which appears to be identical with the product obtained by Vanags and Weinberg (*Ber.*, 1942, **75**, 1558) by heating sulphanilamide with excess of phthalic anhydride. In contrast to its succinimido-analogue, however, the sulphonyl chloride (I) was recovered substantially unchanged after treatment with excess of aqueous ammonia at 50° in a sealed tube. Reaction did occur with excess of ammonia in dioxan solution, but, instead of the expected *N*-(*p*-sulphamylphenyl)-phthalamide (III, R = H, R′ = NH_2) (cf. Picard *et al.*, *loc. cit.*), the products were phthalimide and sulphanilamide. Indications were obtained that similar decomposition took place on treatment of the sulphonyl chloride (I) with aqueous ammonia in a sealed tube at 75° and of the sulphonamide (II, R = H) with ammonia in dioxan. It is suggested that either *N*-(*p*-sulphamylphenyl)phthalamide (III, R = H, R′ = NH_2) or ammonium *p*-sulphamylphenylphthalamate (III, R = H, R′ = ONH_4) is formed as an intermediate which decomposes at the temperature employed to give phthalimide and sulphanilamide, the alternative route to phthalimidobenzenesulphonamide and ammonia being suppressed by the presence of excess ammonia. It is of interest to compare this reaction with the behaviour of *N*-methylphthalimide and *N*-ethylphthalimide on treatment with aqueous ammonia under mild conditions, whereby ammonium *N*-methylphthalamate and *N*-ethylphthalamate respectively were obtained which decomposed to *N*-methylphthalimide and *N*-ethylphthalimide under conditions favouring the removal of ammonia (Spring and Woods, *J.*, 1945, 625).

An attempt has been made to prepare phthalylsulphanilyl chloride by chlorosulphonation of phthalanilic acid by a method analogous to that used for obtaining succinylsulphanilyl chloride (cf. Picard *et al.*, *loc. cit.*). Under mild conditions chlorosulphonation did not occur, unchanged starting material being recovered; under more drastic conditions, chlorosulphonation took place accompanied by ring closure to phthalimidobenzenesulphonyl chloride (I).



(I.) (II.) (III.)

Experimental.

(All melting points are uncorrected.)

p-*Phthalimidobenzenesulphonamide* (II, R = H) *and* N^4-*Phthalylsulphanilamide* (III, R = H, R′ = OH).—Concentrated ammonia (*d* 0·88; 1·14 ml.; 0·02 mol.) was added to a solution of *p*-phthalimidobenzenesulphonyl chloride (I) (m. p. 241—242·5°; Dewar and King, *loc. cit.*, give m. p. 234—237°) (3·22 g.; 0·01 mol.) in dioxan (65 ml.) at 30°. After 15 mins.' shaking, and cooling, the solid (2·4 g., m. p. 316—317°) which had separated was removed and washed with water. Recrystallisation from 80% dioxan gave *p*-phthalimidobenzenesulphonamide as clusters of microcrystals, m. p. 334° (Found: C, 55·95; H, 3·6; N, 9·45. Calc. for $C_{14}H_{10}O_4N_2S$: C, 55·6; H, 3·35; N, 9·25%). *p*-Phthalimidobenzenesulphonamide (II, R = H) (0·91 g.) was hydrolysed by refluxing with sodium hydroxide (0·1N; 61 ml.) for 1 hour. The solution was acidified (Congo-red) by addition of hydrochloric acid, and the solid collected and crystallised from 80% ethanol to give N^4-phthalylsulphanilamide (III, R = H, R′ = OH) as needles, m. p. 320—328° on slow heating; if inserted into the bath at 265°, the compound decomposed immediately and subsequently melted at 320—328°; it is soluble in cold

sodium hydrogen carbonate solution (Found: C, 52·7; H, 3·75; N, 8·4. Calc. for $C_{14}H_{12}O_5N_2S$; C, 52·5; H, 3·8; N, 8·75%).

A solution of the *p*-phthalimidobenzenesulphonyl chloride (I) (3·22 g.; 0·01 mol.) in a mixture of concentrated ammonia (*d* 0·88; 30 ml.) and dioxan (125 ml.) was kept at 20—25° for 1½ hours and then at 40—50° for 2 hours. After concentration in a vacuum, the mixture was diluted with water to give a white crystalline precipitate (0·84 g.) which on recrystallisation from water gave phthalimide, m. p. 228—229°, undepressed on admixture with an authentic specimen. The mother-liquor on standing yielded a second crop (0·42 g.) which on recrystallisation from water gave sulphanilamide, m. p. 160—162°, undepressed when mixed with an authentic specimen.

p-*Phthalimidobenzenesulphonamidomethane* (II, R = CH_3) *and* N^4-*Phthalyl*-N^1-*methylsulphanilamide* (III, R = CH_3, R′ = OH).—A solution of the sulphonyl chloride (I) (6·44 g.; 0·02 mol.) in acetone (100 ml.) was treated at room temperature with methylamine solution (33%; 3·8 ml.; 0·04 mol.), added with shaking during 10 mins. The reaction mixture was shaken for a further 15 mins. and then refluxed on the steam-bath for 30 mins. The colourless product obtained after removal of solvent was triturated with cold water and recrystallised from 50% ethanol to give p-*phthalimidobenzenesulphonamidomethane* (II, R = CH_3) (3·8 g.) as small colourless needles, m. p. 241—242°; it is insoluble in cold sodium hydrogen carbonate solution (Found: C, 57·3; H, 3·45; N, 8·9. $C_{15}H_{12}O_4N_2S$ requires C, 57·0; H, 3·8; N, 8·85%).

The anil (II, R = CH_3) (3·16 g.; 0·01 mol.) was heated under reflux with potassium hydroxide solution (1·0N; 15 ml.) for 1½ hours; on neutralisation with hydrochloric acid (10%; 4·6 ml.), a white precipitate was obtained which yielded N^4-*phthalyl*-N^1-*methylsulphanilamide* (III, R = CH_3, R′ = OH) (2·3 g.) as small colourless needles from 30% aqueous ethanol, m. p. 241—242° (with preliminary softening at 180°); it dissolves in aqueous sodium hydrogen carbonate solution with evolution of carbon dioxide (Found: C, 54·1; H, 4·4; N, 8·05. $C_{15}H_{14}O_5N_2S$ requires C, 54·0; H, 4·2; N, 8·4%).

N^4-*Phthalyl*-N^1-*phenylsulphanilamide* (III, R = C_6H_5, R′ = OH).—*p*-Phthalimidobenzenesulphonanilide, m. p. 221—222° (0·6 g.), prepared as described by Dewar and King (*loc. cit.*), was boiled with potassium hydroxide solution (0·1N; 30 ml.) for 1 hour. The solid which separated after acidification to Congo-red with hydrochloric acid was recrystallised from glacial acetic acid to give N^4-*phthalyl*-N^1-*phenylsulphanilamide* as needles, m. p. 193—194°, soluble in cold aqueous sodium hydrogen carbonate (Found: C, 60·55; H, 3·9; N, 7·0. $C_{20}H_{16}O_5N_2S$ requires C, 60·6; H, 4·05; N, 7·05%).

2-(p-*Phthalimidobenzenesulphonamido*)*pyridine* (II, R = 2-pyridyl) *and* N^4-*Phthalylsulphapyridine* (III, R = 2-pyridyl, R′ = OH).—A solution of 2-aminopyridine (0·47 g.; 0·005 mol.) in pyridine (4·7 ml.) was heated at 100° for 30 mins. with *p*-phthalimidobenzenesulphonyl chloride (I) (1·61 g.; 0·005 mol.). After removal of the pyridine in a vacuum, the residue was triturated with water (5 ml.). and washed with dilute hydrochloric acid. The light brown powder (1·32 g.) was recrystallised from 80% dioxan to give 2-(*p*-phthalimidobenzenesulphonamido)pyridine as prisms, m. p. 278—278·5° (Found: C, 60·15; H, 3·65; N, 11·1. Calc. for $C_{19}H_{13}O_4N_3S$: C, 60·15; H, 3·45; N, 11·1%).

2-(*p*-Phthalimidobenzenesulphonamido)pyridine (0·94 g.) was refluxed for 2 hours with sodium hydroxide solution (0·1N; 50 ml.). Acidification of the solution with hydrochloric acid to Congo-red gave a precipitate (0·77 g.) which, after recrystallisation from 70% aqueous ethanol, yielded N^4-phthalylsulphapyridine (III, R = 2-pyridyl, R′ = OH) as prisms which decomposed immediately if inserted in the bath at 240° and subsequently melted at 273—274° (Found: C, 57·05; H, 3·85; N, 10·8. Calc. for $C_{19}H_{15}O_5N_3S$: C, 57·4; H, 3·8; N, 10·6%). Shapiro and Bergmann (*J. Org. Chem.*, 1941, **6**, 774) obtained the above compounds by the action of phthalic anhydride on sulphapyridine and recorded m. p. 276° for both the anil and the anilic acid.

2-(p-*Phthalimidobenzenesulphonamide*)*thiazole* (II, R = 2-thiazolyl) *and* N^4-*Phthalylsulphathiazole* (III, R = 2-thiazolyl R′ = OH).—2-Aminothiazole (1 g.; 0·01 mol.) in pyridine (1 ml.) and dioxan (25 ml.) was treated with the sulphonyl chloride (I) (3·4 g.; 0·01 mol.). The mixture was heated at 100° for 2 hours. After removal of the solvent mixture in a vacuum, the residue was triturated with water (15 ml.) and washed with dilute hydrochloric acid. The product (3·7 g.), on repeated recrystallisation from 95% dioxan, gave 2-(p-*phthalimidobenzenesulphonamido*)*thiazole* (II, R = 2-thiazolyl) as plates, m. p. 269—269·5° [Found (specimen dried at 55°/15 mm.): C, 53·4; H, 4·3; N, 8·95; (specimen dried at 55°/1 mm.): C, 53·1; H, 3·25; N, 10·7. $C_{17}H_{11}O_4N_3S_2$ requires C, 52·9; H, 2·9; N, 10·9. $C_{17}H_{11}O_4N_3S_2,C_4H_8O_2$ requires C, 53·25; H, 4·05; N, 8·85%].

2-*p*-(Phthalimidobenzenesulphonamido)thiazole was also obtained by using either benzene or excess of pyridine as solvent; or by using as acid acceptor an extra mole of aminothiazole in benzene or dioxan solution.

The anil (II, R = 2-thiazolyl) (1·15 g.) was hydrolysed in boiling potassium hydroxide solution (0·1N; 60 ml.) for 4 hours. The product isolated in the usual way was recrystallised from 80% aqueous ethanol to give N^4-phthalylsulphathiazole as prismatic needles which decomposed immediately if inserted in the bath at 220° and melted at 260—263° (Found: C, 50·5; H, 3·6; N, 10·7. Calc. for $C_{17}H_{13}O_5N_3S_2$: C, 50·6; H, 3·25; N, 10·4%). Moore and Miller (*J. Amer. Chem. Soc.*, 1942, **64**, 1572) reported m. p. 260—270° for this compound.

Chlorosulphonation of Phthalanilic Acid.—A solution of phthalanilic acid (24·1 g.; 0·1 mol.) in chlorosulphonic acid (58·3 g.; 0·5 mol.) was heated for 1 hour at 100° and poured on crushed ice. The solid was collected, washed with ice-water, and extracted with acetone. The acetone-insoluble fraction (13 g.) was recrystallised from chlorobenzene to give *p*-phthalimidobenzenesulphonyl chloride as plates, m. p. 241—242°.

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