155. *The Preparation of* N^4*-Carboxyacylsulphonamides. Part I. Reactions of Succinimidobenzenesulphonyl Chloride and Succinylsulphanilyl Chloride.*

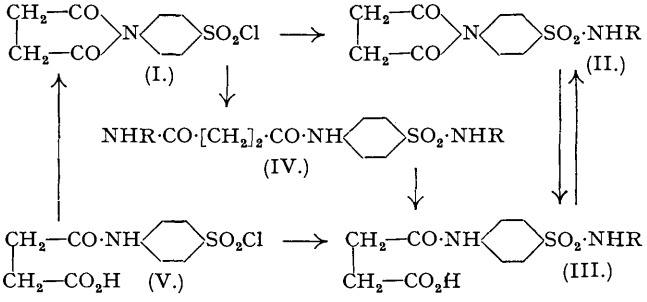
By C. W. Picard, E. Reid, and D. E. Seymour.

p-Succinimidobenzenesulphonyl chloride (I) has been condensed with a number of amines to yield the corresponding *p*-succinimidobenzenesulphonamides which have been hydrolysed to the corresponding N^4-succinylsulphanilamides. Succinylsulphanilyl chloride (V) has been prepared and condensed with ammonia, methylamine, and aniline to yield the corresponding N^4-succinylsulphanilamides (III). The condensation of succinylsulphanilyl chloride with aminoheterocyclic compounds does not proceed smoothly.

N^4-Succinylsulphanilamides are normally obtained by the reaction of succinic acid, anhydride, or ester with a sulphanilamide (*e.g.*, B.P. 515,412; B.P. 557,985; U.S.P. 2,323,651; Miller, Rock, and Moore, *J. Amer. Chem. Soc.*, **1939**, **61**, 1198; Shapiro and Bergmann, *J. Org. Chem.* **1941**, **6**, 774; Moore and Miller, *J. Amer. Chem. Soc.*, **1942**, **64**, 1572). The use of *p*-succinimidobenzenesulphonyl chloride (I) as a means of preparing such compounds has received little attention, and *succinylsulphanilyl chloride* (V) does not appear to have been previously described in the literature apart from a German patent (D.R.P. 731,912) which mentions the use of the crude sulphonyl chloride in a preparation of succinylsulphapyridine, but gives no details of its method of preparation or properties.

p-Succinimidobenzenesulphonyl chloride (I) (Adams, Long, and Jeans, *J. Amer. Chem. Soc.*, **1939**, **61**, 2346; Moore and Miller, *loc. cit.*) has been caused to react with amines under two series of conditions: (*a*) with one molecular proportion of amine (ammonia, methylamine, aniline, 2-aminopyridine, or 2-aminothiazole) in the presence of pyridine or a second mol. of the reacting amine acting as acid acceptor, to give the corresponding *p*-succinimidobenzenesulphonamide (II) in good yield. On hydrolysis with sodium hydroxide the imide ring was readily opened to give the corresponding N^4-succinylsulphanilamide (III); (*b*) with excess of ammonia or methylamine to give the diamide (IV, R = H or R = Me). *N*-(*p*-Sulphamylphenyl(succinamide (IV, R = H), which Adams *et al.* (*loc. cit.*) had previously obtained by this method, gave, on hydrolysis with sodium hydroxide, N^4-succinylsulphanilamide (III, R = H). The only product isolated from alkaline hydrolysis of N-(p-*methylsulphamylphenyl*)-N′-*methylsuccinamide* (IV, R = Me) was N^1-methylsulphanilamide, which suggests that the methyl group renders the succinamide group less resistant to alkali treatment. Reaction of (I) with excess of 2-aminothiazole in pyridine under the same conditions as those used by Moore and Miller (*loc. cit.*) gave in good yield 2-(*p*-succinimidobenzenesulphonamido)thiazole (II, R = 2-thiazolyl) instead of the expected diamide (IV, R = 2-thiazolyl); Moore and Miller (*loc. cit.*) had obtained a low yield of an unidentified product the nitrogen analysis of which (14·85%) would seem to preclude the diamide (IV, R = 2-thiazolyl. Calc.: N, 16·0%).

Succinylsulphanilyl chloride (V) has been obtained in 20% yield by the chlorosulphonation of succinanilic acid. Attempts to improve the yield by varying the temperature resulted in one instance in the formation of *p*-succinimidobenzenesulphonyl chloride (I) in low yield. Treatment of succinylsulphanilyl chloride with acetyl chloride gave *p*-succinimidobenzenesulphonyl chloride. The sulphonyl chloride (V) has been condensed with ammonia to give succinylsulphanilamide (III, R = H); with methylamine to give N^4-*succinyl*-N^1-*methylsulphanilamide* (III, R = Me); and with aniline to give N^4-*succinyl*-N^1-*phenylsulphanilamide* (III, R = Ph). In each case an excess of the condensing amine was used as acid acceptor. Satisfactory conditions for the condensation of succinylsulphanilyl chloride with amino-heterocyclic compounds have not so far been devised.



Experimental.

All m. ps. are uncorrected. Analyses by Drs. Weiler and Strauss.

p-Succinimidobenzenesulphonyl chloride (I) was prepared by chlorosulphonation of succinanil (Adams *et al.*, *loc. cit.*) and purified by dissolving the wet sulphonyl chloride in acetone and reprecipitating it (with cooling) by water. It separated from the aqueous acetone as white needles, m. p. 197·5—198·5° (yield 48%). Moore and Miller (*loc. cit.*) give 189—195° (Found: C, 44·05; H, 2·9; N, 5·2. Calc. for $C_{10}H_8O_4NClS$: C, 43·9; H, 2·95; N, 5·1%). When treated with excess of ammonia under the conditions of Adams *et al.* (*loc. cit.*) it gave *N*-(*p*-sulphamylphenyl)succinamide (IV, R = H) as needles from water, m. p. 237—237·5°. Adams *et al.* (*loc. cit.*) give m. p. 234—238° (Found: C, 44·3; H, 4·95; N, 15·5. Calc. for $C_{10}H_{13}O_4N_3S$: C, 44·3; H, 4·85; N, 15·5%). With excess of methylamine under similar conditions N-(p-*methylsulphamylphenyl*)-N′-*methylsuccinamide* (IV, R = Me), m. p. 204—205°, was obtained as needles from water (Found: C, 48·55; H, 5·8; N, 13·9. $C_{12}H_{17}O_4N_3S$ requires C, 48·2; H, 5·75; N, 14·05%).

N-(*p*-Sulphamylphenyl)succinamide (IV, R = H) (1·1 g.) was hydrolysed by boiling with aqueous potassium hydroxide (0·25 N; 16 ml.) for 2½ hours; on neutralisation with hydrochloric acid (Congo red), N^4-succinylsulphanilamide (0·35 g.) was obtained as needles from water, m. p. 207—209° (Found: C, 44·4; H, 4·4; N, 10·5. Calc. for $C_{10}H_{12}O_5N_2S$: C, 44·15; H, 4·45; N, 10·3%). Under similar conditions *N*-(*p*-methylsulphamylphenyl)-*N*′-methylsuccinamide gave a low yield of N^1-methylsulphanilamide as needles from water, m. p. 109—109·5° (cf. Mangini, *Chem. Abs.*, 1943, **37**, 98).

p-*Succinimidobenzenesulphonamide* (II, R = H).—A solution of the sulphonyl chloride (I) (2·75 g.; 0·01 mol.) in acetone (30 ml.) and pyridine (2 ml.) was shaken with ammonia (*d*, 0·88; 0·57 ml.; 0·01 mol.) for 15 minutes, and the solid which separated was removed and washed with water (0·58 g.; m. p. 279—283°). Recrystallisation from water gave *p*-succinimidobenzenesulphonamide as needles, m. p. 290—290·5° undepressed by admixture with a specimen (m. p. 290—290·5°) prepared according to the method of Miller, Rock, and Moore (*loc. cit.*) who give m. p. 280—282° (Found: C, 47·3; H, 4·0; N, 10·9. Calc. for $C_{10}H_{10}O_4N_2S$: C, 47·3; H, 3·95; N, 11·05%). The compound (II, R = H) (0·42 g.) was hydrolysed by heating under reflux for 1 hour with potassium hydroxide solution (0·5 N; 3·33 ml.). After being cooled, the solution was neutralised with hydrochloric acid and the precipitated solid (0·4 g.), m. p. 204—206°, recrystallised from water to give N^4-succinylsulphanilamide as needles, m. p. 209—211° undepressed with a specimen (m. p. 212—212·5°) obtained according to the conditions of Miller, Rock, and Moore (*loc. cit.*).

N-(p-*Methylsulphamylphenyl*)*succinimide* (II, R = Me).—*p*-Succinimidobenzenesulphonyl chloride (2·74 g.; 0·01 mol.) in acetone (50 ml.) was treated with methylamine solution (33% w/v; 1·88 ml.; 0·02 mol.). The mixture was shaken for 15 minutes and refluxed for 15 minutes, and the acetone was then removed and the residue triturated with water and crystallised from aqueous alcohol (1 : 1) to give N-(p-*methylsulphamylphenyl*)*succinimide* as needles (1·1 g.), m. p. 199—199·5° (Found: C, 49·05; H, 4·4; N, 10·3. $C_{11}H_{12}O_4N_2S$ requires C, 49·3; H, 4·5; N, 10·45%). The compound (0·7 g.) was hydrolysed by boiling for 1½ hours with potassium hydroxide solution (0·1 N; 50 ml.) to give N^1-methyl-N^4-succinylsulphanilamide (III, R = Me) as plates from alcohol (0·6 g.), m. p. 207—207·5° undepressed with a specimen prepared as described below.

p-*Succinimidobenzenesulphonanilide* (II, R = Ph).—*p*-Succimidobenzenesulphonyl chloride (4·09 g.; 0·015 mol.) was heated with aniline (1·4 g.; 0·015 mol.) in pyridine (13 ml.) at 100° for 1 hour. Excess of water was added and the product (4·3 g.), m. p. 246—246·5°, was recrystallised from glacial acetic acid to give p-*succinimidobenzenesulphonanilide* as needles, m. p. 248—249° (Found: C, 58·15; H, 4·6; N, 8·75. $C_{16}H_{14}O_4N_2S$ requires C, 58·25; H, 4·3; N, 8·5%). The sulphonanilide (0·33 g.) was refluxed with potassium hydroxide solution (0·1 N; 25 ml.) for 1 hour. Neutralisation with hydrochloric acid gave N^1-phenyl-N^4-succinylsulphanilamide (III, R = Ph) (0·25 g.), m. p. 223—224° undepressed when mixed with the specimen described below.

2-(p-*Succinimidobenzenesulphonamido*)*pyridine* (II, R = 2-pyridyl).—A solution of 2-aminopyridine (0·95 g.; 0·01 mol.) in pyridine (10 ml.) was heated for 30 minutes on the steam-bath with *p*-succinimidobenzenesulphonyl chloride (2·749 g.; 0·01 mol.). The mixture was cooled, and water (50 ml.) was added and the solid collected (2·8 g.; m. p. 262—271°). Recrystallisation from acetic acid (40%) gave 2-(*p*-succinimidobenzenesulphonamido)pyridine, m. p. 288—289°. Shapiro and Bergmann (*loc. cit.*) give m. p. 288—290° for the compound prepared by condensation of succinic anhydride with sulphapyridine (Found: C, 54·3; H, 4·1; N, 12·7. Calc. for $C_{15}H_{13}O_4N_3S$: C, 54·45; H, 3·95; N, 12·7%). The compound (II, R = 2-pyridyl) (0·83 g.) was refluxed for 2 hours with potassium hydroxide solution (0·1N; 50 ml.); N^4-succinylsulphapyridine was obtained as needles from alcohol (0·4 g.), m. p. 196—197° (Found: C, 51·65; H, 5·55; N, 10·4. Calc. for $C_{15}H_{15}O_5N_3S,C_2H_6O$: C, 51·65; H, 5·35; N, 10·65%). For comparative purposes, 2-(*p*-succinimidobenzenesulphonamido)pyridine was prepared as described by Shapiro and Bergmann (*loc. cit.*). The product separated as needles from alcohol, m. p. 195—196° undepressed when mixed with the specimen described above (Found: C, 51·7; H, 5·5; N, 10·8%). Shapiro and Bergmann obtained a product free from solvent of crystallisation, m. p. 145°; Moore and Miller give m. p. 135—140° rising to 191—194° after seven months, whilst D.R.P. 731,912 gives m. p. 191°. The solvent of crystallisation was not removed from our product by drying in a high vacuum at 80°.

2-(p-*Succinimidobenzenesulphonamido*)*thiazole* (II, R = 2-thiazolyl).—2-Aminothiazole (5 g.; 0·05 mol.) in pyridine (50 ml.) was treated with *p*-succinimidobenzenesulphonyl chloride (13·65 g.; 0·05 mol.) with shaking. The mixture was then heated at 100° for 1 hour and the pyridine removed under reduced pressure. The residue was triturated with water (100 ml.) to yield a brown powder, m. p. 252—255° (13·3 g.). The crude material was washed and recrystallised several times from aqueous dioxan (1 : 1) (charcoal) to yield white needles, m. p. 269·5—270·5° (2·2 g.). Moore and Miller (*loc. cit.*) give m. p. 266—267° for this compound prepared by a different method (Found: C, 46·4; H, 3·5; N, 12·5. Calc. for $C_{13}H_{11}O_4N_3S_2$: C, 46·35; H, 3·3; N, 12·5%). The same compound (II, R = 2-thiazolyl) was obtained when two equivalents of 2-aminothiazole were used (*a*) in pyridine solution (cf. Moore and Miller, *loc. cit.*) and (*b*) in benzene solution. The anil (II, R = 2-thiazolyl) was also obtained from N^4-succinylsulphathiazole by heating with acetyl chloride or by heating at its m. p. for 10 minutes. The anil was hydrolysed with boiling aqueous potassium hydroxide solution (2 equivs.; 0·1 N) to give N^4-succinylsulphathiazole as needles from aqueous alcohol, m. p. 186—187° [Found (for specimen dried at 80°/15 mm.): C, 42·2; H, 4·05; N, 11·5; (for specimen dried at 80° in high vacuum): C, 43·85; H, 3·8; N, 11·6. Calc. for $C_{13}H_{13}O_5N_3S_2,H_2O$: C, 41·85; H, 4·05; N, 11·25. Calc. for $C_{13}H_{13}O_5N_3S_2$; C, 44·0; H, 3·7; N, 11·85%].

Succinylsulphanilyl chloride (V) was prepared by adding succinanilic acid (19·3 g.) to chlorosulphonic acid (33 ml.) at 10—12°. The temperature was then maintained at 40—50° for 40 hours with agitation by means of nitrogen bubbles. The crude sulphonyl chloride was precipitated by pouring on crushed ice (200 g.). The product was washed and purified by dissolving in acetone (80 ml.) and reprecipitating with water (250 ml., added slowly with cooling). A crystalline solid, m. p. 142—143° (8 g.; 42%), separated which was recrystallised from acetone–benzene (1 : 9; 500 ml.) to give needles, m. p. 142—143° (3·8 g.; 20%) (Found: C, 41·7; H, 3·65; N, 5·15. $C_{10}H_{10}O_5NClS$ requires C, 41·2; H, 3·45; N, 4·8%). The sulphonyl chloride (5 g.) was refluxed with acetyl chloride (15 ml.) for 15 minutes to give *p*-succinimidobenzenesulphonyl chloride as needles from aqueous acetone, m. p. 197—198° (2·8 g.).

N^4-*Succinylsulphanilamide* (III, R = H).—Succinylsulphanilyl chloride (0·4 g.) was added to ice-cold ammonia (*d* 0·88; 5 ml.). An oil separated which redissolved on shaking. After being kept at 0° for 2 hours the solution was acidified with dilute hydrochloric acid and the solid (m. p. 188—191·5°; 0·4 g.) collected and crystallised from water to give needles, m. p. 209—210° (Found: C, 44·5; H, 4·6; N, 10·1. Calc. for $C_{10}H_{12}O_5N_2S$: C, 44·15; H, 4·45; N, 10·3%).

N^4-*Succinyl*-N^1-*methylsulphanilamide* (III, R = Me).—Succinylsulphanilyl chloride (1·47 g.; 0·005 mol.) was stirred for 2 hours with a solution of methylamine hydrochloride (6·75 g.; 0·1 mol.) in water (15 ml.) containing sodium carbonate (5·3 g.). The crystalline solid, m. p. 198—201° (1·0 g.), was collected and recrystallised from water to give N^4-*succinyl*-N^1-*methylsulphanilamide* as needles, m. p. 204—205° (Found: C, 46·55; H, 4·95; N, 10·1. $C_{11}H_{14}O_5N_2S$ requires C, 46·2; H, 4·95; N, 9·8%).

N^4-*Succinyl*-N^1-*phenylsulphanilamide* (III, R = Ph).—Succinylsulphanilyl chloride (1·47 g.; 0·005 mol.) was refluxed for 1 hour with a solution of aniline (1·16 g.; 0·0125 mol.) in benzene (15 ml.). The benzene was then removed and the residue triturated with water to yield a white solid (3 g.; m. p. 178—179°). Repeated crystallisation from aqueous alcohol gave needles of N^4-*succinyl*-N^1-*phenylsulphanilamide*, m. p. 223—224° (0·8 g.). (Found: C, 55·1; H, 4·8; N, 7·9. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·65; N, 8·05%).

The authors are indebted to Miss J. Reynolds for carrying out a considerable part of the experimental work and to Dr. F. S. Spring of Manchester University for his interest and advice. They also thank the Directors of Herts Pharmaceuticals Limited for permission to publish this work.

RESEARCH LABORATORY, HERTS PHARMACEUTICALS LIMITED,
WELWYN GARDEN CITY.

[*Received, December 12th*, 1945.]