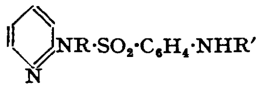
65. *Alkyl Derivatives of Sulphapyridine.*

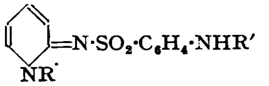
By W. Kelly and W. F. Short.

In agreement with Shepherd, Bratton, and Blanchard (*J. Amer. Chem. Soc.*, 1942, **64**, 2532) methylation of sulphapyridine or its N^4-acetyl derivative with methyl sulphate and alkali produces derivatives of 1-methyl-1 : 2-dihydropyridine as main product. Benzylation of sulphapyridine, however, produces either N^4-benzylsulphapyridine or 2-sulphanilimido-1-benzyl-1 : 2-dihydropyridine according to the experimental conditions employed.

Shepherd, Bratton, and Blanchard (*loc. cit.*) showed that methylation of sulphapyridine with diazomethane afforded 2-(*p*-aminobenzenesulphonmethylamido)pyridine, m. p. 86·5—87·5° (I; R = Me, R′ = H) and 2-sulphanilimido-1-methyl-1 : 2-dihydropyridine, m. p. 232—233° (II; R = Me, R′ = H), in the ratio 70 : 30, and when N^4-acetylsulphapyridine was methylated in the same way, the product contained the N^1-methyl derivative, m. p. 119·5—120° (I ; R = Me, R′ = Ac) and the dihydropyridine derivative, m. p. 239—240° (II; R = Me, R′ = Ac) in the ratio 60 : 40. Methylation of sulphapyridine and its N^4-acetyl derivative with methyl sulphate in aqueous solution was shown to yield 2-sulphanilimido-1-methyl-1 : 2-dihydropyridine (II; R = Me, R′ = H) and the corresponding N^4-acetyl derivative (II; R = Me, R′ = Ac) respectively, the yield being 40—50% in each case.

(I.)





(II.)

The experiments here described were completed in September, 1942, and since our conclusions are in substantial agreement with those of the American authors it is unnecessary to repeat the experimental details in cases where duplication has occurred. It is stated in B.P. 512,145 that a methyl group is introduced into the sulphimido-group when sulphapyridine or its N^4-acetyl derivative is methylated with methyl sulphate and alkali, the products melting at 225° and 231° respectively, and the acetyl compound also being obtained from 2-bromopyridine and *p*-acetamidobenzenesulphonamide. Repetition of the methylations as described in the patent afforded 2-sulphanilimido-1-methyl-1 : 2-dihydropyridine, m. p. 232—233°, in 57% yield and its constitution was established both by synthesis from and by degradation to 1-methyl-1 : 2-dihydropyridine. Methylation of N^4-acetylsulphapyridine with the same reagents afforded the corresponding acetyl derivative (II; R = Me, R'^4= Ac), m. p. 239—240°, in 93% yield and hydrolysis of the crude methylation product, m. p. 226—228°, afforded 2-methylaminopyridine in an amount which indicated the presence of 2—3% of the isomeric N^4-acetyl-N^1-methylsulphanilamidopyridine (I; R = Me, R' = Ac). Under these conditions methylation therefore occurs to some extent in the sulphamido-group, as suspected by the American authors. When 2-methylaminopyridine and *p*-acetamidobenzenesulphonyl chloride were condensed under the conditions prescribed in B.P. 512,145, 2-sulphanilamido-N^4-acetyl-N^1-methylpyridine (I; R = Me; R' = Ac), m. p. 117·4—118·4° (free amine, m. p. 87—88°), was obtained in 71% yield.

We find that benzylation of sulphapyridine results in the attachment of a benzyl group either at N^4 or at the pyridine nitrogen according to the experimental conditions employed. Thus, benzylation of sulphapyridine with benzyl chloride in alkaline *aqueous* solution is reported in B.P. 512,145 to yield 2-sulphanilamido-N^1-benzylpyridine (I; R = CH_2Ph, R' = H), m. p. 179°. Repetition of the experiment, however, gave a 38% yield of a compound, m. p. 186°, which must be N^4-*benzylsulphapyridine* (I; R = H, R' = CH_2Ph), since on hydrolysis it yields *benzylsulphanilic acid* and may also be obtained by condensing 2-bromopyridine with N^4-benzylsulphanilamide. Benzylation of sulphapyridine or N^4-acetylsulphapyridine in alkaline *aqueous-alcoholic* solution affords 2-sulphanilimido-1-benzyl-1 : 2-dihydropyridine (II; R = CH_2Ph, R' = H), m. p. 239—240°, and its acetyl derivative (II; R = CH_2Ph, R' = Ac), m. p. 213—214°, respectively. These compounds were prepared in the same way by Shepherd *et al.* (*loc. cit.*), who record m. p. 235° and 213—214° respectively. In agreement with them we find that the acetyl derivative prepared from 2-imino-1-benzyl-1 : 2-dihydropyridine and *p*-acetamidobenzenesulphonyl chloride melts at 213—214° and not at 188—190° as recorded by Polyakova and Kirsanov (*J. Appl. Chem. Russia*, 1940, **13**, 1215).* Finally, by condensing 2-benzylaminopyridine with *p*-acetamidobenzenesulphonyl chloride, we obtained 2-*sulphanilamido*-N^4-*acetyl*-N^1-*benzylpyridine* (I; R = CH_2Ph, R' = Ac), m. p. 186—187°, and this compound afforded 2-*sulphanilamido*-N^1-*benzylpyridine*, m. p. 134—135°, on hydrolysis.

EXPERIMENTAL.

N^4-*Benzylsulphapyridine*.—Benzyl chloride (40 c.c., 7 mols.) was added slowly with mechanical stirring to a solution of sulphapyridine (12·5 g.) in 2N-sodium hydroxide (30 c.c., 1·2 mols.) and water (40 c.c.), the mixture stirred for an hour, ether (100 c.c.) added, and the solid washed with dilute hydrochloric acid and recrystallised from alcohol. The crude solid (6·5 g. or 38%), m. p. 179—180°, on further recrystallisation from alcohol afforded N^4-*benzylsulphapyridine* in colourless plates, m. p. 186° (Found : C, 64·0; H, 5·2; N, 12·4. $C_{18}H_{17}O_2N_3S$ requires C, 63·7; H, 5·1; N, 12·5%). N^4-Benzylsulphanilamide (5·2 g.; Kelly, Robson, and Short, preceding paper), 2-bromopyridine (3·2 g.), potassium carbonate (2·8 g.), and copper powder (0·2 g.) gave the same compound in 21% yield when maintained at 200° for an hour. Hydrolysis of this compound (6 g.) by boiling for 4 hours with 36% hydrochloric acid (20 c.c.) gave *benzylsulphanilic acid* (3·7 g.), which was dried at 120° (Found : C, 58·8; H, 5·4; N, 5·0; *M*, by titration, 259. $C_{13}H_{13}O_3NS$ requires C, 59·3; H, 5·0; N, 5·3%; *M*, 263). This acid, which did not melt below 270°, was identical in properties with a specimen prepared from sulphanilic acid and benzyl chloride in aqueous alkaline solution.

2-*Sulphanilimido*-1-*benzyl*-1 : 2-*dihydropyridine*.—2-Imino-1-benzyl-1 : 2-dihydropyridine (3·7 g.), prepared as described by Tschitschibabin, Konowalowa, and Konowalowa (*Ber.*, 1921, **54**, 821), and *p*-acetamidobenzenesulphonyl chloride (2·4 g.; 0·5 mol.) afforded 2-sulphanilimido-N^4-acetyl-1-benzyl-1 : 2-dihydropyridine, which separated from alcohol in large colourless prisms, m. p. 213—214° (Found : C, 62·8; H, 5·2; N, 11·0. Calc. for $C_{20}H_{19}O_3N_3S$: C, 63·0; H, 5·0; N, 11·0%). The yield was 48·5% and a considerably lower yield (10%) was obtained when the condensation was effected in presence of pyridine. Addition of benzyl chloride (10 c.c.; 1·7 mols.) to a solution of sulphapyridine (15 g.) in 5N-sodium hydroxide (20 c.c.; 1·9 mols.) and alcohol (60 c.c.), followed by heating at 80° for 10 minutes and keeping for 16 hours, produced the same compound, m. p. and mixed m. p. 213—214°, in 53% yield. Hydrolysis of the acetyl derivative was effected by heating with alcohol and concentrated hydrochloric acid and crystallisation from alcohol gave 2-sulphanilimido-1-benzyl-1 : 2-dihydropyridine, m. p. 239—240° (Found : C, 63·9; H, 5·2; N, 12·5. Calc. for $C_{18}H_{17}O_2N_3S$: C, 63·7; H, 5·1; N, 12·4%). This compound was also obtained in 18% yield from sulphapyridine (15 g.), benzyl chloride (10 c.c., 1·5 mols.), 5N-sodium hydroxide (30 c.c., 2·5 mols.), and alcohol (70 c.c.) by heating on the steam-bath for 5 minutes.

2-*Sulphanilamido*-N^1-*benzylpyridine*.—*p*-Acetamidobenzenesulphonyl chloride (4·75 g.) was added to a solution of 2-benzylaminopyridine (3·7 g.), prepared as described by Tschitschibabin *et al.* (*loc. cit.*, p. 822), in dry pyridine (10 c.c.), and the mixture heated on the steam-bath for 15 minutes. The solid which separated on dilution of the cold reaction product with water (30 c.c.) was recrystallised from methyl alcohol, giving cubes or slender felted needles (3 g. or 39%) of 2-*sulphanilamido*-N^4-*acetyl*-N^1-*benzylpyridine*, m. p. 186—187° (Found : C, 62·7; H, 5·0; N, 11·1. $C_{20}H_{19}O_3N_3S$ requires C, 63·0; H, 5·0; N, 11·0%). Hydrolysis of the acetyl derivative (1 g.) was effected by boiling for an hour with alcohol (50 c.c.) and 5N-sodium hydroxide (5 c.c.). Crystallisation of the product from alcohol gave 2-*sulphanilamido*-N^1-*benzylpyridine*, m. p. 134—135° (Found : C, 63·6; H, 5·2; N, 12·3. $C_{18}H_{17}O_2N_3S$ requires C, 63·7; H, 5·1; N, 12·4%).

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* Only an abstract of this paper was available and the discrepancy may be due to a typographical error.