THE SYNTHESIS OF PHENYL 2-PIPERIDINOETHYL SULPHIDE AND PHENYL 2-PIPERIDINOETHYL SULPHONE, AND THEIR QUATERNARY DERIVATIVES

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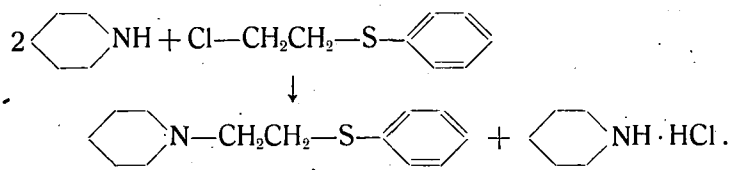
Phenyl 2-piperidinoethyl sulphide and sulphone, as well as their quaternary derivatives have been prepared with the purpose of investigating the physiological activity of the products. These compounds may be regarded as isosteres of phenyl 2-piperidinoethyl ether.

Aminoethyl phenyl ethers have been long since known as adrenaline-inhibiting agents. It is probable that the activity of this group of compounds should be explained by competetive mechanism [1]. By applying the principle of isosterism, we have synthesized phenyl 2-piperidinoethyl sulphide and the corresponding sulphone. The latter compound was made by oxidizing the sulphide with hydrogen peroxide.

These tertiary products were converted in absolute alcoholic medium to the corresponding quaternary derivatives.

The parent compounds were synthesized by condensing 2-chloroethyl phenyl sulphide or sulphone, respectively, with piperidine.



2 mols of piperidine were used for the reaction, since piperidine hydrochloride is formed as a by-product which may easily be filtered from the mixture after the condensation took place.

2-Chloroethyl phenyl sulphide was prepared from thiophenol and ethylene chlorohydrin in alkaline medium. 2-Hydroxyethyl phenyl sulphide, formed as a primary product, was converted to 2-chloroethyl phenyl sulphide by means of thionyl chloride [2] or phosphorus pentachloride [3]. Oxidation of the

sulphide with hydrogen peroxide gave the corresponding sulphone [2]. This oxidation was tried before and after condensing the sulphide with piperidine; the same product was obtained in both cases.

Experimental

Thiophenol (benzenethiol) was most easily prepared by means of chlorosulphonic acid [4].

Phenyl 2-piperidinoethyl sulphide

2-Chloroethyl phenyl sulphide (15 g) was slowly added, under continuous stirring, to 15 g of piperidine, and the mixture was refluxed for half an hour at 120° C. The precipitate which separated after cooling was filtered, and 20 ml of distilled water was added to the solution to dissolve the remainder of hydrochloride. The aqueous solution was then extracted with ether. The ethereal layer was dried over anhydrous sodium sulphate, the solvent was evaporated and the residue fractionated. B. p. 138° C. Yield 13 g. Analysis: Calculated C: 70,60; H: 9,01%. Found C: 70,61; H: 9,12%.

From this material the *picrate* was prepared. M. p. 146° C. Analysis: Calculated N 12,44%. Found N 12,60%.

The *hydrochloride* was obtained by treating the ethereal solution of the material with a solution of hydrogen chloride in ether, and the product was recrystallized from ethanol. M. p. 191° C. Analysis: Calculated Cl 13,77%. Found: 13,67%.

The *methoiodide* was prepared in ethanol solution with the calculated amount of methyl iodide. M. p. 165° C. Analysis: Calculated I 34,95%. Found I 34,56%.

Phenyl 2-piperidinoethyl sulphone

2-Chloroethyl phenyl sulphone (13 g) was dissolved in 20 ml of anhydrous benzene and under continuous stirring a solution of 18,8 g piperidine in 20 ml of benzene was gradually added. The mixture was then heated on the steam bath for 20 minutes, filtered and washed with benzene. The benzene solution was then concentrated to one fourth of its original volume under reduced pressure (water pump), and the residue was allowed to stand overnight in a refrigerator. The crystalline precipitate was filtered and recrystallized from benzene. Yield: 10,5 g. M. p. 86—87° C. Analysis: Calculated C 61,70; H 7,50%. Found C 61,75; H 7,55%.

M. p. of *picrate:* 186° C. Analysis: Calculated N 11,60%. Found N 11,70%.

The *hydrochloride* was prepared in ether by means of an ethereal solution of hydrogen. M. p. 213—214° C. Analysis: Calculated Cl 12,25%. Found Cl 12,28%.

The *methoiodide* was prepared in ethanol with the theoretical amount of methyl iodide. M. p. 175° C. Analysis: Calculated I 33,40%. Found I 33,49%.

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СИНТЕЗ ПИПЕРИДИНО β-ЭТИЛ-ТИОФЕНИЛЬНОГО ЭФИРА И ПРИПЕРИДИНО β-ЭТИЛЬНОГО СУЛЬФОНА И ЕГО ЧЕТВЕРТИЧНЫХ ПРОИЗВОДНЫХ

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Авторами были получены вышеупомянутые соединения а также их четвертичные производные, и они были подвергнуты фармакологическому исследованию. В упомянутых случаях — по сравнению с β-этил-фениловому эфиру пиперидина — был применен изостерный обмен.