p-NITROBENZENESULFONYL CHLORIDE AS A RAW MATERIAL FOR THE MANUFACTURE OF SULFANILAMIDE PREPARATIONS

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In the manufacture of sulfanilamide preparations the first stage is the preparation of an arylsulfanilic acid chloride. Of the various derivatives of arylsulfonyl chlorides [1] the N-acyl derivatives of sulfanilic acid are used most in industry. In the domestic pharmaceutical chemical industry N-carbomethoxysulfanilyl chloride, also known as phenylurethylansulfonyl chloride, (I), is used exclusively.

The process of preparing (I) is simple enough and consists of the interaction of N-carbomethoxyaniline (phenylurethylane) (II) with chlorosulfonic acid (III) [2].

In spite of the technological simplicity of preparing (I) its manufacture is complicated by the following circumstances:

1) To obtain a sufficiently high (81-85%) yield of (I) it is necessary to use 5.5 moles (III) for 1 mole (II), in other words 3.3 tons (III) for 1 ton (I);

2) to isolate the final product and decompose the excess of (III) it is necessary to dilute the reaction "sulfomass" with a tenfold amount of water;

3) the process of chlorosulfonation is accompanied by the separation of a significant quantity of gaseous hydrogen chloride;

4) the obtained product is not adequately stable and is decomposed under the action of moisture, forming carbomethoxysulfanilic acid and hydrogen chloride, which, in particular, hinders the drying process, transportation, and storage of (I).

Of the enumerated deficiencies the main are first the unjustifiably large consumption of the difficultly available (III) the use of which is gradually increasing in connection with the rise in the range of sulfanilamide preparations, and also with the increase in the rate of manufacture of antipyretics, saccharin, etc., and secondly the presence of a large quantity of highly contaminated industrial effluent.

When preparing 1 ton (I) more than 50 m^3 of acidic waste water is formed containing 1750 kg sulfuric acid, 520 kg hydrogen chloride, 170 kg carbomethoxysulfanilic acid, and 127 kg other organic contaminants. In addition to this up to 160 kg gaseous hydrogen chloride is released into the atmosphere, requiring absorption by water in special installations.

Considering that the manufacture of (I) reaches several thousand tons per year the indicated effluent represents a serious danger to the surrounding environment, the more so since no rational means of utilizing or rendering it harmless has been found up to the present.

Investigations carried out in recent years directed towards reducing the consumption of (III), for example by partial replacement of it with sulfur trioxide or oleum [3] or by reducing the amount of industrial waste water by decomposing the sulfomass with waste sulfuric acid [4], have only partially solved the problem. With the aid of creating a more ideal technology with less effluent in the manufacture of the arylsulfonyl chloride we decided to choose p-nitrobenzenesulfonyl chloride (IV). This selection was made on the grounds that its preparation may be based on an available and cheap raw material viz. p-nitrochlorobenzene (V).

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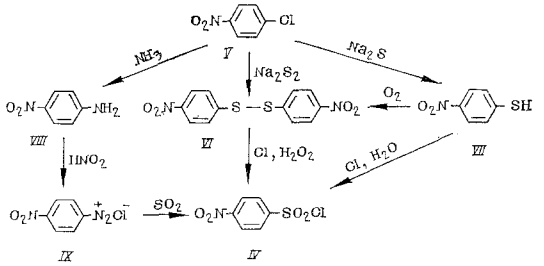
Routes for the synthesis of (IV) and (V) are shown in the scheme:



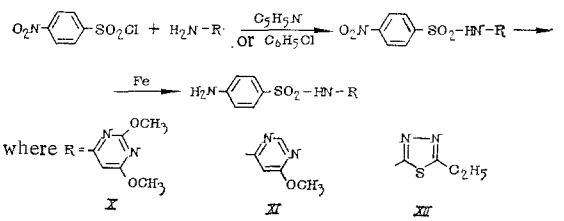
The preparation of (IV) from (V) may be carried out by treating (V) with an aqueous or aqueous-alcoholic solution of sodium sulfide with subsequent oxidation of the resulting p-nitrothiophenol (VII) with chlorine in an aqueous solution of acetic acid [5, 5a] or by treating (V) with sodium disulfide in alcoholic medium and oxidation of the obtained p,p-dinitrodiphenyl disulfide (VI) to (IV) with chlorine and hydrogen peroxide in a medium of acetic acid [6]. Both quoted variants have overall drawbacks viz. low yields of the desired product (from 20 to 50%), the formation of by-products, the use of organic solvents, and a significant quantity of harmful effluent.

The most interesting from our point of view was the preparation of (IV) from (V) by converting the latter into the intermediate p-nitroaniline (VIII) (the manufacture of VII on a large scale occurs in the Minkhimprom SSSR organization), diazotization of (VIII), and treatment of the obtained p-nitrophenyldiazonium chloride (IX) with sulfur dioxide. This reaction, discovered by Sandmeyer, was appreciably modified after 50 years by Meerwein [7, 7a]. The work of this author served as a basis for developing a pilot plant method for making (IX) and (VIII). The essence of the method consists in diazotizing (VIII) in a medium of concentrated hydrochloride acid and a solution of the diazonium salt (IX) was mixed with a solution of sulfur dioxide in acetic acid containing a divalent copper salt as catalyst. After diluting the reaction mass with water, (IV) was isolated in 82-85% yield. It was established by us that the process of preparing (IV) proceeded readily and in high yield on observing the following conditions. The amount of reagents must be as follows: (VIII) 1 mole, sodium nitrite 1.1 mole, hydrogen chloride (as hydrochloric acid) 4.65 mole, sulfur dioxide 5.3 mole, and copper salt 0.125 mole. It was important to carry out the diazotization reaction in a medium of hydrochloric acid of concentration not below 35%, at 0°C, and using a saturated solution of sodium nitrite. The concentration of sulfur dioxide in acetic acid must not be less than 27 g in 100 ml solution. As catalyst we used copper sulfate in place of the recommended cuprous chloride. Nonfulfillment of the indicated conditions reduced the yield of (IV) and led to the formation of side products such as p-nitrochlorobenzene, p-nitrobenzenesulfinic acid, p,p-dinitrodiphenylazoamine, etc.

The proposed method of preparing (IV) has little waste. Only 7 liters weakly contaminated effluent containing mainly sodium chloride is formed per kg of final product. Acetic acid and sulfur dioxide are regenerated and used once again in the same process. It was noted that the obtained (IV) possessed an adequately high stability in comparison with (I). The shelf life of (IV) was determined by special investigations as being 1 year 6 months.

Considering that the cost of the initial (VIII) was close to three times greater than the cost of (II), the economic expediency of using (IV) was confirmed experimentally in the synthesis of many known sulfanilamide preparations (sulfanilamide, sulfaguanidine, sulfathiazole, sulfadimezine, etc.), since their cost increases significantly depending on the raw material. At the same time the synthesis of new sulfanilamides of prolonged action, where a high relative contribution to cost is made by the synthesis of the complex heterocyclic fragment, is economically justified.

On this basis methods were developed for obtaining the preparations sulfadimethoxine (X), sulfamonoethoxine (XI), and ethazole (XII) by the general scheme



The synthesis of ethazole using (IV) is justified when carrying out the process in a chlorobenzene medium [8]. All the general methods of transforming a nitro group into an amino group were applicable when converting the nitro derivatives of sulfonamides into the final products. We selected a variant of the reduction with iron as the cheapest and safest, giving no harmful effluent.

EXPERIMENTAL

The synthesis of (IV) was carried out in an enameled steel apparatus. Technical products manufactured by the chemical industry were used as raw materials.

The intermediates 4-amino-2,6-dimethoxypyrimidine (XIII), 4-amino-6-methoxypyrimidine (XIV), and 2-amino-5-ethyl-1,3,4-thiadiazole (XV), manufactured by the pharmaceutical industry, were used for the synthesis of the sulfanilamide preparations.

p-Nitrobenzenesulfonyl Chloride (IV). Into a 10-liter enameled apparatus with a jacket for cooling with brine and fitted with a stirrer (80 rpm), thermometer, and hopper, was placed 35% hydrochloric acid (3.95 liters), then 98% (VIII) (1.48 kg) was introduced during 5 min. After stirring for 2 h 37% sodium nitrite solution (1940 ml) was poured in from the hopper during 30-35 min with cooling to −6°C. A solution was obtained which contained the partially separated diazonium salt and sodium chloride as a suspension.

A solution of sulfur dioxide in acetic acid containing 98% acetic acid (8.93 kg), sulfur dioxide (3.4 kg), and copper sulfate (0.3 kg) was first made.

The solution was loaded into an enameled apparatus, of 40-liter capacity, fitted with a jacket for cooling with brine, stirrer (60 rpm), thermometer, and linked with a system of traps filled with acetic acid to absorb sulfur dioxide.

The diazonium salt reaction mixture was gradually poured into this solution at 6-10°C at such a rate that the evolution of nitrogen was not too violent and the temperature gradually rose to 20°C. After evolution of nitrogen had finished the reaction mixture was diluted with 12 liters water, and the precipitate of (IV) which had separated was filtered off on a sealed pressure filter and washed with water.

A paste (2.15 kg) of (IV) was obtained having moisture content 15% or 1.82 kg dry substance. The yield was 82% calculated on (VIII) of content 95-96% and mp 77-80°C.

Regeneration of Sulfur Dioxide and Acetic Acid. The mother liquor after isolation of (IV) (approximately 12 liters) was placed in an enameled apparatus linked with a system of traps filled with acetic acid, heated gradually to boiling, and heated until complete cessation of sulfur dioxide evolution. The acetic acid solution of sulfur dioxide from the traps was used once again in the following operation. In this way 65% sulfur dioxide was regenerated. The aqueous solution of acetic acid remaining in the apparatus was treated with the calculated amount of sodium hydroxide solution to neutralize the hydrogen chloride contained in it (determined analytically), the apparatus was connected with a straight condenser, and a fraction (25.4 liters) was distilled at 102-107°C (in the vapor) which contained 31.5 g acetic acid in 100 ml liquid (or 8 kg 100% acetic acid in all).

To strengthen the aqueous acetic acid distillate it was subjected to rectification on a column packed with Raschig rings using dichloroethane as azeotrope forming agent. After complete removal of water the still residue consisting of 97.5% acetic acid was purified by redistillation.

The yield of regenerated acetic acid was 7.27 kg or 81.4% of the initial amount taken for saturation with sulfur dioxide.

4-Sulfanilamido-2,6-dimethoxypyrimidine (sulfadimethoxine) (X). Compound (XIII) (32.0 g, 0.2 mole) was dissolved in pyridine (100 ml) at 40-45°C. The solution was cooled to 18°C and (IV) (56.1 g, 0.24 mole) was added during 30-35 min. The mixture was stirred for 2 h at 56-58°C. The reaction mixture was diluted with water (200 ml), acidified to pH 1.0 with hydrochloric acid, and the solid filtered off.

The yield of dry (XVI) was 62.0 g or 91.5% calculated on (XIII).

For purification, technical (XVI) was dissolved in 5% sodium hydroxide solution, the solution decolorized with carbon, filtered, and the final product isolated by acidification with hydrochloric acid to pH 1.0.

The yield was 84.2% calculated on (XIII), mp 156-158°C.

Dry (or as paste) (XVI) (61.2 g) suspended in water (50 ml) was introduced gradually into a boiling mixture consisting of water (300 ml), ammonium chloride (21.7 g), and cast iron filings (46.4 g). The mixture was boiled for 8-10 h, cooled to 80°C, 40% sodium hydroxide solution (20 ml) added, then carbon (6 g), and the mixture was stirred for 30-40 min. The iron slurry was filtered off, washed with water (20 ml), filtered, and the filtrate was acidified with 3% hydrochloric acid solution after adding sodium hydrosulfite (0.4 g). After cooling, the precipitate of technical (X) was filtered off, washed with water, and dried.

The yield was 45.4 g, or 87% calculated on (XVI) and 73.4% calculated on (XIII).

To obtain a pharmacopoeic product technical (X) (45.4 g) was dissolved with boiling in 70% isopropanol (720 ml) containing activated carbon (4.5 g), boiled for 15 min, and filtered. The filtrate was cooled to 10°C; after 2 h crystals of (X) were filtered off and dried at 50-60°C.

Yield was 42.3 g or 81.3% calculated on (XVI) and 63.5% calculated on (XIII), mp 198-201°C.

4-Sulfanilamido-6-methoxypyrimidine (sulfamonomethoxine) (XI). The preparation was obtained by the method described for (X). Yield of 4-nitrobenzenesulfonamido-6-methoxypyrimidine (XVII) was 90-92% calculated on (XIV), mp 227-228°C (with decomposition) after purification by reprecipitation from a solution in sodium hydroxide.

The yield of pure (XI) was 84-86% calculated on (XIV), mp 203-206°C.

2-Sulfanilamido-5-ethyl-1,3,4-thiadiazole (ethazole) (XII). A mixture of (IV) (73.5 g, 0.33 mole), (XV) (87.4 g, 0.676 mole), and chlorobenzene (235 ml) was heated with stirring at 115-120°C for 2 h. After cooling to 90°C water (265 ml) was poured into the mixture. The isolated precipitate of 2-4-nitrobenzenesulfonamido)-5-ethyl-1,3,4-thiadiazole, (XVIII) was filtered off, washed with water, and dried at 50-60°C. Compound (XVIII) (93.3-97.7 g) of purity 98% was obtained. Yield was 89-94% based on (IV), mp 179-180°C. After purification by reprecipitation from alkaline solution it had mp 188-189°C. Compound (XVIII) is not described in the literature.

Technical (XVIII) (96.1 g) was introduced gradually into a boiling mixture consisting of water (720 ml), ammonium chloride (25.6 g), and iron filings (92 g), and boiling was continued for 7 h. After cooling the mixture to 80°C, 40% sodium hydroxide solution was poured in to pH 9.0, activated carbon (2 g) was added, the mixture stirred for 30 min, and the iron slurry was filtered off. The filtrate was acidified with hydrochloric acid to pH 4.0-4.5; after cooling to 20°C the precipitate of technical (XII) was filtered off and dried. Yield was 78.1-84.4 g and 94.2-95.5% calculated on (XVIII).

To obtain a pharmacopoeic product technical (XII) (81.6 g) was dissolved in a mixture of water (255 ml) and and 40% sodium hydroxide solution (25 ml), heated to 80°C, carbon (2.6 g) was added, and, after keeping for 30 min, the solution was filtered. Sodium chloride (90 g) was added to the filtrate which was cooled to 10°C for 10-12 h. The sodium derivative of (XII), which had separated, was filtered off, washed with saturated sodium chloride solution, and dissolved in water (810 ml). The solution was treated at 80°C with carbon (8.1 g) and sodium hydrosulfite (0.3 g), filtered, and acidified with hydrochloric acid at 55-60°C to pH 4.0-4.5. Pure (XII) (69.7-79.9 g) was obtained. The yield was 78.4-81.1% mp 186-190°C based on (IV).

For the regeneration of (XV) the aqueous mother liquor (360 ml) from (XVIII), after separation from the chlorobenzene layer, was decolorated with carbon (4 g), heated to 80°C, sodium hydrosulfite (0.2 g) was added, the solution filtered, and the filtrate made alkaline with 40% sodium hydroxide solution to pH 8.5-9.0. The precipitate of (XV) was separated and dried. Yield was 40.6 g of mp 178-180°C. Yield on regeneration was 97.1%. The product was used in the following operation of making (XVIII). Chlorobenzene was purified by redistribution.

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NEW METHOD OF RESOLVING RACEMIC LIPOIC ACID INTO ANTIPODES

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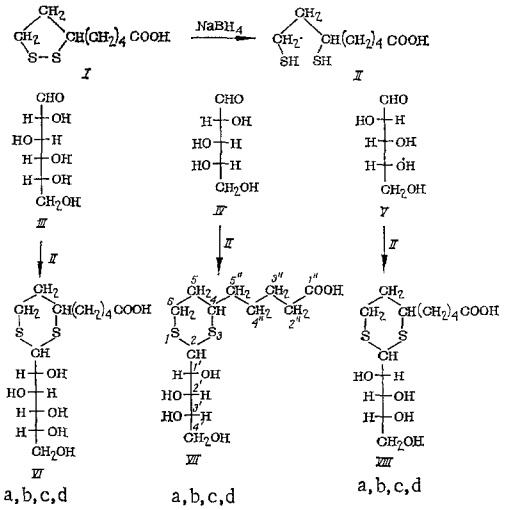
Lipoic acid (I) is 1,2-dithiolanyl-3-valeric acid (thioctoic acid, protogen A) and enters into the composition of the prosthetic group of the enzyme effecting the decarboxylation of pyruvic acid. Racemic lipoic acid obtained by synthesis is half as active as the natural (+) form. The 1,2-dithiolane ring determines the reactivity of this compound and is readily split on reduction, giving dihydrolipoic acid.

It seemed of interest to study the interaction of dihydrolipoic acid with monosaccharides having in view the formation of cyclic mercaptals of the corresponding sugars. Further, owing to the large selection of optically active monosaccharides, it may be considered that the introduction of a new asymmetric center would permit the preparation of readily separable diastereoisomers. After their separation and the removal of monosaccharides the lipoic acid may be isolated in optically active form. This in its turn should be a new route in principle for obtaining optically active acids. In known methods [1, 2] the preparation of optically active lipoic acid uses the classical means of separating acids based on the formation salts of the carboxylic acid with optically active amines.

Racemic dihydrolipoic acid (II), obtained by the reduction of (I) with sodium borohydride, was reacted with the appropriate sugar: D(+)-glucose, L(+)-arabinose (IV), or D(−)-arabinose (V) in a medium of concentrated hydrochloric acid.



As a result of the condensation a new asymmetric center is generated at C2 on forming thioacetals in addition to that existing at C4, which leads to a mixture of four isomers provisionally named fractions a, b, c, d obtained in a total yield of 73.5% (for VIa-d), 66.9% (for VIIa-d), and 58.9% (for VIIIa-d). The yield of fraction a which was isolated first from the mixture after reaction in the form of an oil varied depending on the temperature of the process. At 14-18°C the yield of fraction a was 14-17%, and at 2-4°C it fell to 3-4%; simultaneously the amount of isolated unreacted dihydrolipoic acid grew. Substances (VI-VIIIa) were not as a rule subjected to further purification since they were not investigated further. For the separation of the mixture of fractions b, c, and d their differing solubility in ethyl alcohol (for derivatives of D(+)-glucose) and in water (for derivatives of L(+)- and D(−)-arabinose) was used. As a result it turned out that fractions b, c, and d, corresponded according to analytical data to the isomeric 2-polyhydroxyalkyl-1,3-dithianyl-4-valeric acids (VI-VIIIb-d).

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