METHOD OF PREPARATION OF AZAPHENE

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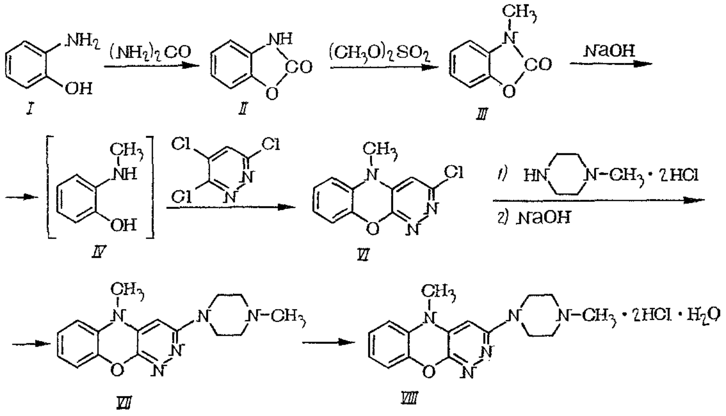
In earlier published work we reported the preparation of a new heterocyclic system, 3,4-diazaphenoxazine [1], the preparation of 10-alkyl- and 10-dialkylaminoalkyl-2-chloro-3,4-diazaphenoxazine [2, 3], 2-cycloalkylamino-3,4-diazaphenoxazine [4, 5], and certain other derivatives [6, 7, and 8]. In the present communication a method is described for the synthesis of a new original compound, azaphene, which is 2-(4methylpiperazinyl-1)-10-methyl-3,4-diazaphenoxazine dihydrochloride (VIII) [9].

The Ministry of Public Health of the USSR permits the use of azaphene as an antidepressant in medical practice. It is used in psychiatric practice in the medical treatment of ill-defined depressive states of different origins and during anxiety depressive states as a "curative" agent [10]. The high degree of tolerance for the compound permits it to be used in patients with serious somatic illness, for the elderly, and also in dispensing practice.

Azaphene is prepared according to the following scheme starting from 3,4,6-trichloropyridazine [1] and o-aminophenol (I).



EXPERIMENTAL

Bromomaleic Anhydride. To a mixture of 5.97 kg of 98.5% maleic anhydride and 0.06 kg of iron filings, 9.67 kg (3.1 liters) of bromine was added with stirring over 4 h at 80-90°C and the reaction mixture was maintained at this temperature for 8 h. The temperature was increased to 120-130° and after being kept at this temperature for 4 h the reaction mixture was cooled to 20-25°. This yielded 11 kg of technical bromomaleic anhydride which was distilled in vacuum at 98-108° (13 mm). The yield of bromomaleic anhydride of 90% purity was 9.44 kg and this comprises (on converting to 100% product) an 80% yield based on maleic anhydride..

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4-Bromopyridazin-3,6-diol. To a solution of 1.46 kg of 98% hydrazine sulfate in 10 liters of water 2.197 kg of 90% bromomaleic anhydride was added with stirring at 20-25° and the temperature was raised to 98-100°. The reaction mixture was maintained at this temperature for 3 h and then cooled to 15-20°, after 2 h the precipitate was filtered off, washed with water, and dried at 80-100°. This gave 1.79 kg of 4-bromopyridazin-3,6-diol as a white crystalline substance of 100% purity and with mp 247-252° (decomp.). The yield was 85%.

3,4,6-Trichloropyridazine (V). 4-Bromopyridazin-3,6-diol (2.865 kg) was added with stirring to 6.9 liters of phosphorus oxychloride, the reaction mixture was heated to boiling for 2-3 h (105° in the reaction mixture), boiled for 3.5 h, and cooled to 20°. The reaction mixture which contained V was poured into 15 liters of water and 26 liters of concentrated aqueous ammonia while stirring at 10-15°; the pH of the aqueous solution should not be below 6.0. Compound V was extracted from the solution with dichloroethane, the dichloroethane was distilled off and the residue dissolved in 11 liters of ethyl alcohol at 35-50°. This gave 12.44 liters of an alcoholic solution of V which contained 20 g of substance in 100 ml of solution. The yield of V was 2.48 kg and this was 90% calculated on the 4-bromopyridazin-3,6-diol. Compound V possesses a vesicant action on skin.

Benzoxazolone (II). A mixture of 1.637 kg of I, 1.82 kg of 99% urea, and 1.875 liters of 36% hydrochloric acid was heated with stirring to 80-90°. After being maintained for 1 h at this temperature the mixture was heated to boiling and boiled for 3 h, 2 liters of water was added over 30-40 min, then 0.357 liters of 36% hydrochloric acid and a further 1.65 liters of water. The reaction mixture was cooled to 20° and the precipitate filtered off and washed with water. This gave 2.451 kg of II as a paste. The yield of 100% substance was 1.681 kg which was 83% based on I.

N-Methylbenzoxazolone (III). The paste II (2.532 kg) was added to a solution of 0.93 liters of 42% sodium hydroxide in 7.85 liters of water and stirred until complete conversion into the sodium salt. Dimethyl sulfate (1.34 liters) was added over 1½ h to the obtained solution at 20-25°, the mixture was maintained at this temperature for 1 h, the precipitate was filtered off, washed with water, and dried at 35-45°. This gave 1.625 kg of 98.1% III with mp 83-85°. The yield of 100% substance was 83% based on II.

2-Chloro-10-methyl-3,4-diazaphenoxazine (VI). To a solution of 0.25 kg of 96% sodium hydroxide in 2 liters of 96% ethyl alcohol was added 0.304 kg of 98.1% III at 20-30° and the mixture boiled for 45 min. To the boiling reaction mixture which contained the sodium salt of N-methyl-o-aminophenol (IV) 1.835 liters of an alcoholic solution of V containing 0.367 kg of V was added with stirring over 30-40 min. The reaction mixture was boiled for 5 h, 1.8 liters of alcohol was distilled off, and the residue was cooled and left at 5° for 3 h. The precipitate of VI was filtered off, washed with 0.3 liter of 96% alcohol, and stirred with 7 liters of water; hydrochloric acid was added until a pH of 6.0-7.0, the mixture was stirred for 4 h, the solid was filtered off, washed with water, and dried. This gave 0.404 kg of VI of 90.4% purity. The yield of 100% substance was 78% calculated on III or V and the mp was 200-207° (within 2°).

2-(4-Methylpiperazinyl-1)-10-methyl-3,4-diazapenoxazine (The Base of Azaphene, VIII). About 0.6 liters of water was distilled azeotropically from a mixture of 4 liters of cyclohexanol and 1.112 liters of an aqueous solution of N-methylpiperazine dihydrochloride (0.718 kg of 100% substance). According to the degree of distillation of the water the temperature in the reaction mixture rose from 105 to 140°. The reaction mixture was cooled to 80°, 0.537 kg of 90.4% VI was added, the mixture was boiled for 5 h, cooled to 70°, and 7.5 liters of water was added in order to dissolve the dihydrochlorides of N-methylpiperazine and VII. The aqueous layer was separated from the cyclohexanol, treated with carbon, filtered, and while stirring at 10° 0.677 liters of 42.7% sodium hydroxide solution was added until pH 12.0. After maintaining at 5° for 9 h VII was filtered off, washed with water, and recrystallized from 50% aqueous acetone. This gave 0.47 kg of VII of 99.8% purity. The yield was 94% calculated on VI and the mp was 194-195°.

2-(4-Methylpiperazinyl-1)-10-methyl-3,4-diazaphenoxazine Dihydrochloride (Azaphene, VIII). To a solution of 0.47 kg of VII in 3.525 liters of ethyl alcohol was added 0.271 liter of 36% hydrochloric acid with stirring at 40-45°. After cooling and maintaining at 5° for 4-5 h the precipitate of VIII was filtered off, washed with alcohol, and dried to give 0.564 kg. The yield was 70% calculated on VI.

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