

SYNTHESIS AND INVESTIGATION OF SOME
10-BENZENESULFONYLPHENOTHIAZINE DERIVATIVES

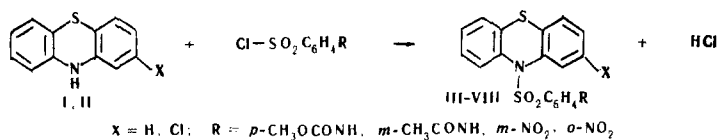
V. S. Karpinskii and L. V. Konovalova

UDC 547.869.2.07

A number of 10-sulfonyl derivatives of phenothiazine (I) and 2-chlorophenothiazine (II) were obtained by acylation of I and II with several sulfonyl chlorides. 10-(p-Aminobenzenesulfonyl)phenothiazine was alkylated.

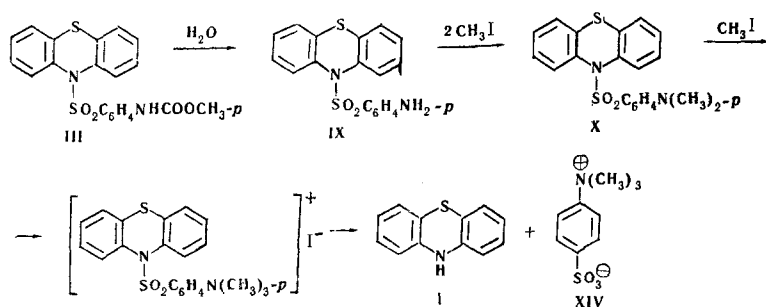
Many phenothiazine derivatives have biological activity; some of them are widely used in medical practice (methylene blue, promazine, chlorpromazine, etc.) [1]. Despite the abundance of literature data devoted to various derivatives of phenothiazine, its 10-sulfonyl derivatives have received comparatively little study [2,3]. There is no information on the biological activity of 10-(p-aminobenzenesulfonyl)phenothiazine. The psychotropic action of 10-dialkylaminoethylsulfonylphenothiazine is close to that of the corresponding dialkylaminoacyl derivatives of phenothiazines [2].

We have carried out the acylation of phenothiazine (I) and 2-chlorophenothiazine (II) with several sulfonyl chlorides in pyridine via the scheme



10-(p-Aminobenzenesulfonyl)phenothiazine (IX) was obtained by the hydrolysis of the methoxycarbonyl group in 10-(p-methoxycarbonylamino benzenesulfonyl)phenothiazine (III) in acidic and alkaline media.

Compound IX was alkylated by methyl iodide and dimethyl sulfate. Alkylation with methyl iodide in methanol gave 10-(p-dimethylaminobenzenesulfonyl)phenothiazine (X). Two successive processes occur in the exhaustive methylation of IX with methyl iodide in methanol: alkylation of the amino group and hydrolysis of the sulfamide bond (see scheme below):



The alkylation of IX with dimethyl sulfate gives initially 10-(p-methylaminobenzenesulfonyl)phenothiazine (XI), and subsequent alkylation leads to X. Considering the proximity of the melting points and the percentage of nitrogen in X and XI, we acylated XI with p-toluenesulfonyl chloride [4], as a result of which we obtained 10-[p-(N-methyl, N-tosyl)aminobenzenesulfonyl]phenothiazine (XII). This confirms the mono-methyl structure of XI.

Leningrad Pharmaceutical-Chemistry Institute. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 7, pp. 950-952, July, 1971. Original article submitted December 30, 1969.

© 1974 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$15.00.

EXPERIMENTAL

10-(p-Methoxycarbonylamino benzenesulfonyl)phenothiazine (III). A 2.62 g (0.0105 mole) sample of p-methoxycarbonylamino benzenesulfonyl chloride was added in the course of 30-40 min to a solution of 1.98 g (0.01 mole) of I in 5 ml of dry pyridine; the reaction mass warmed to 50-55° in the process. The reaction mixture was then heated to 85-90° and held at this temperature for 30 min. It was then allowed to stand at room temperature for 12 h. The resulting viscous mass was triturated with 15-20 ml of hot ethanol and cooled. The III was filtered and washed on the filter with 10 ml of ethanol.

Compounds I and II were similarly acylated with m-acetamidobenzenesulfonyl chloride, m-nitrobenzenesulfonyl chloride, and o-nitrobenzenesulfonyl chloride to give IV-VIII (Table 1).

10-(p-Aminobenzenesulfonyl)phenothiazine (IX). This was obtained in 90% yield by the method in [3] with III as the starting compound in place of 10-(p-acetamidobenzenesulfonyl)phenothiazine. It melted at 183-184° (from ethanol) (mp 182-184° [3]).

10-(p-Aminobenzenesulfonyl)-2-chlorophenothiazine (XIII). A mixture of 0.5 g (0.011 mole) of VII in 5 ml of dioxane and 0.4 ml of hydrochloric acid was heated for 1.5 h and cooled, and the resulting precipitate was filtered.

Alkylation of the Amino Group in IX. A. With methyl iodide. A mixture of 1.57 g (0.005 mole) of IX and 1.70 g (0.012 mole) of methyl iodide in 50 ml of methanol was heated for 1 h, neutralized with dry potassium carbonate, and heated for 40 min. The excess methyl iodide and methanol were removed by distillation, and the resulting precipitate of X was filtered. For exhaustive methylation, X was dissolved in methanol and heated with excess methyl iodide (50%) for 3 h. The methyl iodide and methanol were removed by distillation, 10 ml of distilled water was added, and the precipitate of phenothiazine was filtered (the phenothiazine thus obtained did not depress the melting point of genuine phenothiazine and had the correct percentage of nitrogen); evaporation of the aqueous filtrate gave a reaction product that was quite soluble in water and decomposed on melting at 300-320°. From the percentage of nitrogen and its properties, it corresponded to an inner salt of trimethylaminobenzenesulfonic acid (XIV). Found %: N 6.7. $C_9H_{14}NO_3S$. Calculated %: N 6.5.

B. With dimethyl sulfate. The methylation with dimethyl sulfate was carried out by the method in [5]. Crystallization from ethanol gave XI with mp 169-171° and X (Table 1).

Acylation of XI with p-Toluenesulfonyl Chloride. The acylation was carried out as in [4] to give XII, which was slightly soluble in diethyl ether and insoluble in water and alkali (Table 1).

LITERATURE CITED

1. V. V. Zakusov (editor), *New Data on the Pharmacology and Clinical Use of Phenothiazine Derivatives* [in Russian], Moscow (1958), p. 1.
2. N. V. Khromov-Borisov, M. L. Indenbom and E. V. Karpinskaya, *Zh. Organ. Khim.*, **3**, 1114 (1967).
3. H. I. Bernstein and L. R. Rothstein, *J. Am. Chem. Soc.*, **66**, 1886 (1944).
4. W. C. Johnson, R. J. Shennan, and R. A. Reed, *Organic Reagents for Organic Analysis* [Russian translation], IL, Moscow (1948), p. 109.
5. N. S. Vul'fson (editor), *Preparative Organic Chemistry* [in Russian], GKhI, Moscow (1959), p. 400.