

PHENOTHIAZINE SYNTHESSES. XVIII.* 2-AMINOPHENOTHIAZINE DERIVATIVES

S. V. Zhuravlev and A. N. Gritsenko

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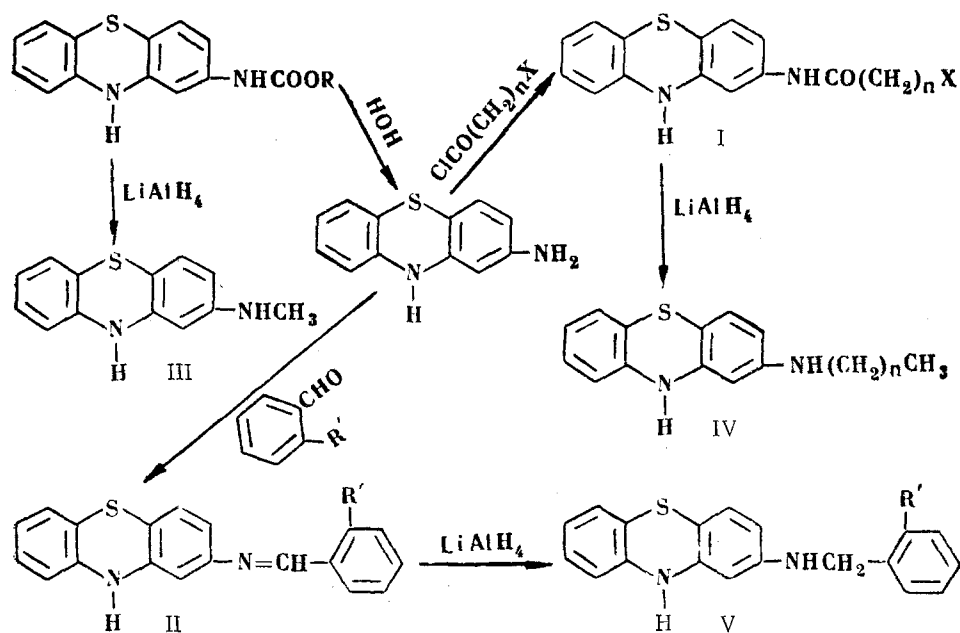
2-(α -chloroacetylamido)-2-(β -chloropropionylamido)-2-(benzylideneamino)- and 2-(*o*-hydroxybenzylideneamino)phenothiazines are synthesized and reduced by lithium aluminum hydride to 2-ethylamino-, 2-propylamino-, 2-benzylamino-, and 2-(*o*-hydroxybenzylamino)phenothiazine. Reduction of the methyl and ethyl esters of phenothiazinecarbamic-2 acid by lithium aluminum hydride gives 2-methylamino-phenothiazine.

The present paper is a continuation of investigations of substituted 2-aminophenothiazines, whose synthesis formed the subject of previous papers [2-6]. Apart from some previously described amino-substitution products of 2-aminophenothiazine, none of its other transformation products has been investigated. Only one compound of this series, 2-dimethylaminophenothiazine, is known. However, it was synthesized not by methylating 2-aminophenothiazine, but by cyclizing 2-amino-4-dimethylamino-2'-bromodiphenylsulfide. Attempts to synthesize 2-dimethylaminophenothiazine by thionation of 3-dimethylaminodiphenylamine were unsuccessful [7].

Treatment of 2-aminophenothiazine with acetic, chloroacetic and β -chloropropionic chloroanhydrides gave 2-acetylamido- (Ia), 2-chloroacetylamido- (Ib), and 2- β -chloropropionylamidophenothiazine (Ic).

2-Acylamido- and 2- ω -chloroacylamidophenothiazines were reduced using a fivefold excess of lithium aluminum hydride. The amide groups was converted to an alkylamino group, while with 2- ω -chloroacylamidophenothiazine reductive dechlorination was also observed. Available information [9, 10] indicates that the phenothiazine ring is unaffected by lithium aluminum hydride.

Reaction between 2-aminophenothiazine and benzaldehyde or salicylaldehyde proceeded smoothly in dilute ether solution. Raising the aldehyde concentration brought about resinification. The resultant 2-benzylideneaminophenothiazine (IIIa) and 2-(*o*-hydroxybenzylideneamino)phenothiazine (IIIb) are bright yellow, indicating that they contain a chromophore group conjugated to an aromatic ring. These colored Schiff's bases were decolorized by lithium aluminum hydride and converted into colorless 2-benzylaminophenothiazine (IVa) and 2-(*o*-hydroxybenzylamino)phenothiazine (IVb). Lithium aluminum hydride reduction of the previously obtained [3] esters of phenothiazinecarbamic-2 acid gave 2-methylaminophenothiazine (III) [8].



The ir spectra (UR-10, CCl₄, LiF)^{**} of the Schiff's bases IIa had a band at 3432 cm⁻¹ due to valence vibrations of the unsubstituted NH group of phenothiazine. The spectrum of the reduced substance, determined at the same molar

*For Part XVII see [1].

**Investigated by V. S. Troitskaya

concentration and same layer thickness, contains the same vibration frequency (3432 cm^{-1}) and, in addition, a band of lower intensity, but higher frequency at 3465 cm^{-1} . This band is ascribed to valence vibrations of an NH group of the diphenylamine type, formed by reduction of the —N=CH— group. These ir spectrum data confirm the way in which the reaction takes place, and the structure of the present compounds.

The 2-alkylamino- and 2-arylalkylaminophenothiazine bases are colorless, insoluble in water, and darken under the action of light and air. Their hydrochlorides are even less stable than the parent bases. Because of the low solubilities of the bases in water, and the slight stabilities of the hydrochlorides, pharmacological testing was of little interest.

EXPERIMENTAL

2-Acetylaminodiphenothiazine (Ia). 0.18 g acetyl chloride and a solution of 0.11 g sodium carbonate in 1 ml water are simultaneously added to 0.42 g 2-aminophenothiazine in 10 ml alcohol, which is stirred and cooled to $5\text{--}7^\circ$. When addition is complete, the reaction mixture is stirred for one hour, 5 ml water are added, and the precipitate is filtered off. 0.4 g material is obtained, mp $205\text{--}206^\circ$; recrystallized from toluene, mp 214° [2]. Identified by mixed melting point. Ib and Ic were prepared under the same conditions.

2-(α -Chloroacetylamido)phenothiazine (Ib). 3.8 g 2-aminophenothiazine in 50 ml alcohol, 2.24 g chloroacetyl chloride and 2.16 g sodium carbonate gives 3.7 g (72%) of material, mp $174\text{--}175^\circ$. Yellowish crystals, soluble in alcohol and acetone, mp 180° (from aqueous alcohol). Found: Cl 12.09; S 11.07; 11.10%. Calculated for $\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{OS}$: Cl 12.19; S 11.02%.

2-(β -Chloropropionylamido)phenothiazine (Ic). 2.14 g 2-aminophenothiazine in 30 ml alcohol, 1.3 g β -chloropropionyl chloride, and 1.06 g sodium carbonate gives 2.2 g (64%) material, mp 201° (decomp.). Yellowish crystals, quite soluble in dioxane, alcohol, moderately soluble in carbon tetrachloride and toluene. Mp 219° (from alcohol, then from dichloroethane). Found: S 10.29; 10.17%. Calculated for $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{OS}$: S 10.52%.

2-Benzylideneaminophenothiazine (IIa). 0.4 g benzaldehyde is added to a solution of 0.42 g 2-aminophenothiazine in 50 ml alcohol. The reaction mixture is stirred well for 30 min and left overnight for the reaction to proceed to completion. Next day the ether is distilled off until a precipitate begins to separate, and the reaction products are then left for 12-15 hr in a refrigerator. The precipitate is filtered off, and 0.5 g (77%) material obtained, mp $173\text{--}175^\circ$. After two recrystallizations from 80% isopropanol it melts at $174\text{--}175^\circ$. Yellowish plates, very soluble in acetone, dissolve in ethanol and isopropanol on boiling. Found: N 9.48, 9.53; S 10.56, 10.49%. Calculated for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{S}$: N 9.26; S 10.60%.

2-(*o*-Hydroxybenzylideneamino)phenothiazine (IIb). This is similarly prepared from 2.1 g 2-aminophenothiazine in 150 ml ether and 2.4 g salicylaldehyde. Yield 1.8 g (61%). After recrystallization from alcohol, mp $207\text{--}208^\circ$. Yellow crystals, soluble in acetone and toluene. Found: N 8.83; S 9.88, 9.79%. Calculated for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{OS}$: N 8.82; S 10.07%.

2-Alkylamino- and 2-arylalkylaminophenothiazines. 2-Methylaminophenothiazine (III). A solution of 2.73 g methyl ester of phenothiazinecarbamic-2 acid or of the equivalent amount of the ethyl ester in 15 ml dry tetrahydrofuran is added to a well-stirred ethereal solution of lithium aluminum hydride (5 mole) over 30 min. After the urethane has been added, the temperature is gradually raised. The reaction mixture is refluxed, with stirring, for 6 hr and, while cooling with ice water, wet tetrahydrofuran is added, followed by an aqueous solution of the same compound. The aluminum hydroxide is filtered off, and washed with tetrahydrofuran. The filtrate is distilled under a water pump vacuum to remove solvent, and the solid residue recrystallized from aqueous alcohol. 2.0 g (87%) of material is obtained, mp $130\text{--}132^\circ$. Colorless crystals, mp $135\text{--}136^\circ$ (from CCl_4), readily soluble in dichloroethane, alcohol, and acetone. Gradually darkens in the light. Found: N 12.31, 12.47; S 13.88, 13.81%. Calculated for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{S}$: N 12.27; S 14.04%.

2-Ethylaminophenothiazine (IVa). 0.51 g Ia or 1.3 g Ib gives, respectively, 0.25 g or 0.61 g substance, mp $142\text{--}143^\circ$ (from CCl_4). Colorless plates, darkening under the action of light and air, readily soluble in toluene, alcohol, and acetone. Found: N 11.30, 11.35; S 12.97, 12.93%. Calculated for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{S}$: N 11.56; S 13.21%.

2-Propylaminophenothiazine (IVb). Lithium aluminum hydride reduction of 1.52 g 2-(β -chloropropionylamido)-phenothiazine gives the hydrochloride of IVb, and treatment of this with alkali gives the base, mp $117\text{--}118^\circ$. Recrystallized from aqueous alcohol and then CCl_4 mp $124\text{--}125^\circ$. Yellowish crystals, very soluble in alcohols (methyl, ethyl, propyl), toluene, insoluble in water. Found: S 12.70, 12.72%. Calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{S}$: S 12.51%.

2-Benzylaminophenothiazine (Va). 0.39 g benzylideneaminophenothiazine is treated with excess lithium aluminum hydride in ether, and at the end of the reaction the products are decomposed, first with moist ether, then with water. The ethereal solution is separated from the aluminum hydroxide and the ether distilled off to give 0.3 g (77%) of colorless crystals, mp $161\text{--}162^\circ$ (from toluene), readily soluble in ether, chloroform, toluene, and alcohol. Found: C 74.86, 74.90; H 5.18, 5.20; S 10.59, 10.63%. Calculated for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{S}$: C 75.01; H 5.29; S 10.52%.

2-(o-Hydroxybenzylamino)phenothiazine (Vb). This is similarly prepared from 0.62 g 2-(o-hydroxybenzylamino)-phenothiazine, yield 0.4 g (62.5%). Forms clusters of colorless needles, mp 156-157° (from chloroform), readily soluble in acetone, hot chloroform, and alcohol. Found: C 71.39, 71.30; H 5.05, 4.99; S 10.14, 9.93%. Calculated for $C_{19}H_{16}N_2OS$: C 71.27; H 5.01; S 10.01%.

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Institute of Pharmacology and Chemotherapy AMS USSR, Moscow