PHENOTHIAZINE SYNTHESES

XXI. 3-Aminophenothiazine and some of its Transformation Products

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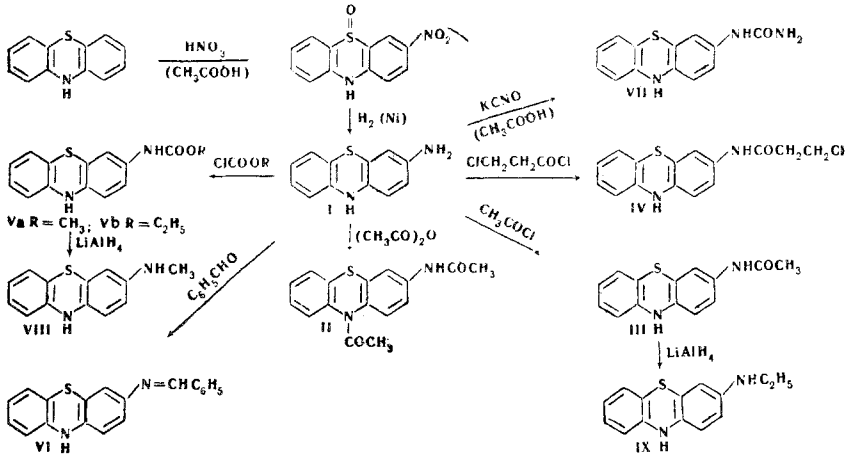
A new method of preparing 3-aminophenothiazine by hydrogenating 3-nitro-5-hydroxyphenothiazine in acetic acid or ethanol solution is developed. A number of derivatives of that amine are synthesized.

The need for 3-aminophenothiazine in amounts adequate for carrying out syntheses for obtaining potentially pharmacologically active compounds necessitated working out methods suitable for that purpose.

The method which we gave in one of the preceding communications [1] is based on protecting the amino group of 4-aminophenylamine with a phthaloyl group, and thionation of the 4-phthalimidodiphenylamine to 3-phthalimidophenothiazine, followed by removal of the phthaloyl group with hydrazine hydrate, proved inconvenient because of the large number of stages and the low yield of 3-aminophenothiazine.

It was found that hydrogenation in acetic acid or ethanol of 3-nitrophenothiazine-5-oxide, made by nitrating phenothiazine by a known method [2], gives a good yield of 3-aminophenothiazine, the isolation of the product being extremely simple, unlike that obtained with known methods. This made it possible to prepare 3-aminophenothiazine in any desired quantity, and of excellent quality. It was found that this compound, whether in the form of free base or as hydrochloride, was quite stable when dry. Obviously even small traces of side reaction products act catalytically on the further oxidation process, making it very difficult to isolate the required compound pure.

Preparation of pure 3-aminophenothiazine enabled some of its reactions, shown by the equations below,



to be investigated, and for the preparation of some new compounds, which can be used as starting materials for further syntheses.

The existing information about 3-aminophenothiazine [2–4] would readily lead one to conclude that both the compound itself and its derivatives are very unstable, but it unexpectedly proved that all the compounds obtained pure were quite stable in air, and rather more stable than the analogous derivatives of 2-aminophenothiazine [5, 6].

Comparison of the IR spectra of 3-aminophenothiazine and the isomeric 2-aminophenothiazine [5] in the 3200–3600 cm^{-1} region revealed the following. The spectrum of 3-aminophenothiazine has 3 absorption bands, at 3320, 3370 and 3400 cm^{-1}, while only two bands are found in the spectrum of 2-aminophenothiazine, viz. in the region 3325–3320 and at 3400 cm^{-1}. Obviously the more intense band in the 3-aminophenothiazine spectrum (at 3370 cm^{-1}) can be assigned to NH valance vibration of the phenothiazine ring, and the less intense one (at 3320 cm^{-1}) to NH_2 group symmetric valance vibrations. For 2-aminophenothiazine, the position of the band of NH of the phenothiazine ring is considerably lower, so that the NH_2 group symmetric valance vibrations band overlaps. The considerable lessening of ν_{NH} can be due to weakening of the conjugation effect between NH_2 group and ring since the NH_2 group is meta to the ring nitrogen.*

EXPERIMENTAL

3-Nitro phenothiazine-5-oxide. This was prepared by Shaposhnikov's [3] improvement of Bernthsen's method [2]. The product was purified by being recrystallizing twice from EtOH, its homogeneity being

*IR spectra were determined by V. G. Vinokurov, using a UR-10 instrument, and vaseline mulls

checked by TLC using unfixed alumina. Mp 273°–275° C. The compound formed yellow plates almost insoluble in water.

3-Aminophenothiazine (I). A flask of a hydrogenation setup, placed in a stirrer, was charged with a suspension of 14 g (0.054 mole) 3-nitrophenothiazine-5-oxide in 300 ml HOAc and 20 g moist Raney Ni, the air displaced by hydrogen, and hydrogenation effected by shaking for about 3 hr at room temperature, when about 4.5 *l* hydrogen were absorbed (theoretical 4830 ml, STP). As reaction proceeded, the 5-oxide dissolved, giving a color less transparent solution. At the end of the hydrogenation the solution was filtered as quickly as possible, contact with air coloring the solution blue. The solution was brought to pH 9 with dilute NaOH, the precipitate filtered off and dried in a desiccator. Yield 8 g (69%) dark material, which after two recrystallizations from toluene had mp 154°–155° C, glistening cream-colored plates, readily soluble in warm EtOH, acetone, $CHCl_3$, and insoluble in water. It darkens on exposure to light. Found: C 67.12; 67.58; H 4.72; 4.61; N 13.22; 13.23%, calculated for $C_{12}H_{10}N_2S$: C 67.26; H 4.70; N 13.08%.

The amine dissolved on heating with 2–3% HCl, and on cooling the hydrochloride came down as glistening colorless plates. On heating above 230° C it darkened without melting. Found: Cl 13.91; 14.03; S 12.51; 12.55%, calculated for $C_{12}H_{10}N_2S \cdot HCl$: Cl 14.03; S 12.76%. When the hydrogenation was run in EtOH the result was similar, though the reaction took longer (because 3-nitrophenothiazine-5-oxide is less soluble in EtOH).

3-Acetylamino-10-acetylphenothiazine (II). This was prepared by heating 3-aminophenothiazine in Ac_2O. Colorless crystals, mp 166°–167° C (ex toluene), soluble in EtOH and acetone, insoluble in water. Found: N 9.31; 9.20; S 10.37; 10.49%, calculated for $C_{16}H_{14}N_2O_2S$: N 9.39; S 10.75%.

3-Acetylamidophenothiazine (III). One dropping funnel was charged with 1.32 g (0.017 mole) acetyl chloride another with a solution of 0.94 g Na_2CO_3 in 5 ml water, and the two were added, dropwise, simultaneously to 2.14 g (0.01 mole) 3-aminophenothiazone in 80 ml EtOH which was stirred and held at 5°–7° C. When additon was complete, the mixture was stirred for 1 hr, 50 ml water added, and the precipitate filtered off. Yield 1.8 g (70%) substance with mp 203°–204° C, which was recrystallized from toluene, mp 206°–207° C (the literature gives [4] mp 208° C). Minute pale yellow needles, soluble in EtOH, dichloroethane, and $CHCl_3$. Found: N 11.04; 11.05; S 12.25; 12.28%, calculated for $C_{14}H_{12}N_2OS$: N 10.96; S 12.51%.

IV, Va, and Vb were obtained similarly.

3-(β-Chloropropionylamido)phenothiazine (IV). 2.14 g (0.01 mole) 3-Aminophenothiazine in 80 ml EtOH, 1.3 g (0.0102 mole) β-Chloropropionylchloride, and 1.06 g Na_2CO_3 gave 2.5 g (82%) substance mp 182°–184° C (ex toluene). Yellow crystals, readily soluble in dichloroethane, acetone, and EtOH. Found: Cl 11.25; 11.42%, calculated for $C_{15}H_{13}ClN_2OS$: Cl 11.63%.

Methyl phenothiazine-3-carbaminate (Va). 2.14 g (0.01 mole) 3-Aminophenothiazine in 80 ml EtOH, 1.6 g (0.017 mole) ethyl chloroformate, and 0.94 g Na_2CO_3 gave 2.45 g (90.5%) compound mp 154°–155° C (ex aqueous HOAc. Shining needles, soluble in hot toluene, readily soluble in ether, dichloroethane, acetone, and tetrahydrofuran. Found: N 10.68; 10.60; S 11.63; 11.59%, calculated for $C_{14}H_{12}N_2O_2S$: N 10.29; S 11.77%.

Ethyl phenothiazine-3-carbaminate (Vb). 4.28 g (0.02 mole) 3-Aminophenothiazine in 150 ml EtOH, 3.2 g (0.03 mole) ethyl chloroformate, and 1.88 g Na_2CO_3, when reacted together, on working up the products in the usual way, 5.28 g (92%) compound mp 144°–146° C. After being recrystallized twice from toluene, it had mp 151°–152° C. Undepressed mixed mp with a specimen of the same compound previously synthesized [1].

3-Benzylideneaminophenothiazine (VI). 0.7 g Benzaldehyde was added to a well-stirred solution of 0.5 g (2.33 mM) 3-aminophenothiazine in 80 ml ether, and the whole left for 2 hr. Much of the ether was distilled off, until crystallization began, then the products were left overnight in a refrigerator. The solid was filtered off, yield 0.58 g (about 83%) substance mp 223°–224° C. After recrystallizing from EtOH it had mp 227°–228° C. Bright yellow crystalline compound, soluble in acetone, and EtOH. Found: N 9.48; 9.35; S 10.81; 10.58%, calculated for $C_{19}H_{14}N_2S$: N 9.26; S 10.60%.

Phenothiazine-3-urea (VII). A solution of 0.15 g (1.85 mM) KCNO in 2 ml water was added to a solution of 0.32 g (1.5 mM) 3-aminophenothiazine in 3 ml 80% HOAc. The mixture was heated for 30 min on a steam bath, the precipitate filtered off, and washed with water. Recrystallization from EtOH gave 0.25 g (65.3%) shining pale yellow crystals; these darkened on heating above 250° C. Found: N 16.40; 16.44; S 12.34; 12.38%, calculated for $C_{13}H_{11}N_3OS$: N 16.40; S 12.51%.

3-Methylaminophenothiazine (VIII). 0.6 g (2 mM) Methyl phenothiazine-3-carbaminate in 5 ml dry tetrahydrofuran was added in portions to a well-stirred ether solution of 3.5 g (0.1 mole) $LiAlH_4$ over 30 min. After the urethane had been added, the temperature was gradually raised and the whole stirred and heated for 4 hr. After cooling dry ether was gradually added, the aluminum hydroxide filtered off, and washed with warm ether. The combined ether solutions were treated with ether saturated with HCl, when a precipitate of 3-methylaminophenothiazine hydrochloride formed, mass 0.38 g (72%). Recrystallization from EtOH gave shining mother-of-pearl like crystals, completely stable in air. Above 220° C they darkened. Found: Cl 13.44; 12.89; S 11.82; 11.90%, calculated for $C_{13}H_{12}N_2S \cdot HCl$, Cl 13.39; S 12.11%.

The free base was obtained from the hydrochloride in the usual way. After recrystallizing from aqueous EtOH it had mp 134°–135° C. Found: N 12.41; 12.35; S 13.97; 14.11%, calculated for $C_{13}H_{12}N_2S$: N 12.27; S 14.04%.

IX was prepared similarly.

3-Ethylaminophenothiazine (IX). A solution of 0.5 g (about 2mM) 3-acetylaminophenothiazine (III) in 5 ml tetrahydrofuran was added dropwise to an ether solution of 3.5 g (0.1 mole) $LiAlH_4$. When worked up in the usual way the products gave 0.4 g (72%) hydrochloride, which after recrystallizing from EtOH gave colorless needles with no characteristic mp, the compound darkening above 225° C. Found: Cl 12.31; 12.38%, calculated for $C_{14}H_{14}N_2S \cdot HCl$: Cl 12.12%.

The pure hydrochloride gave the free base mp 140°–141° C (ex EtOH). Glistening cream-colored plates. Found: N 11.62; 11.38; S 13.05; 13.24%, calculated for $C_{14}H_{14}N_2S$: N 11.56; S 13.23%.

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