SYNTHESES IN THE PHENOTHIAZINE SERIES

XIX. 3-Aminophenothiazine*

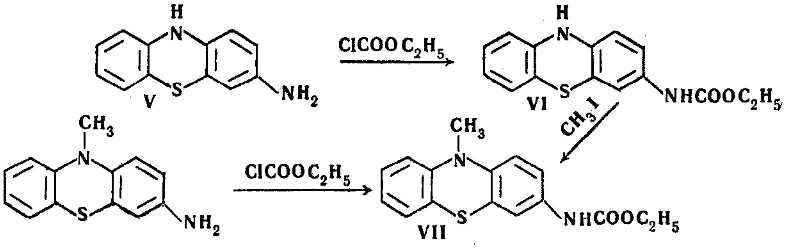
V. A. Skorodumov, S. V. Zhuravlev, and E. D. Panova

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 1, pp. 88–90, 1967

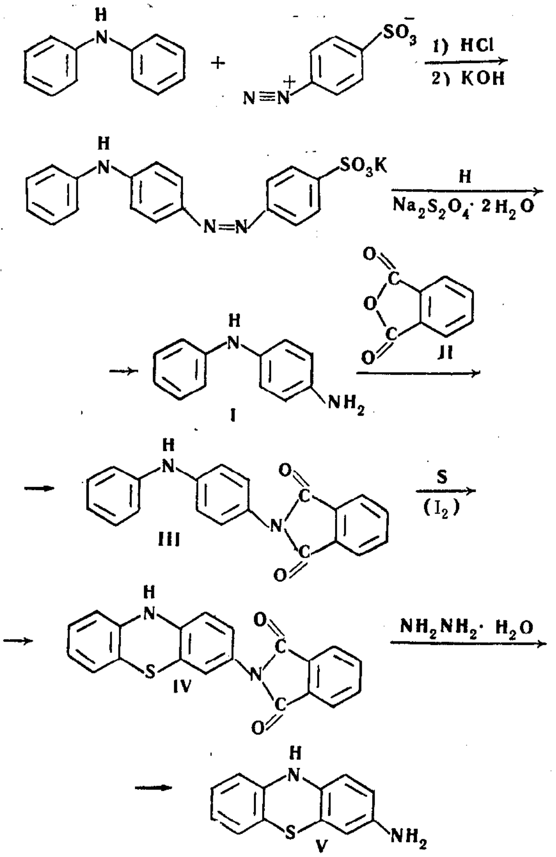
3-Aminophenothiazine is synthesized by hydrazinolysis of 3-phthalimidophenothiazine, prepared by thionating 4-phthalimidodiphenylamine. The structure of the compound is confirmed by preparation of derivatives.

The known methods of preparing 3-aminophenothiazine [2-7] are not such as to make it possible to obtain that compound pure, so that the literature lacks satisfactory figures for its melting point, and furthermore it has not been characterized by derivatives.

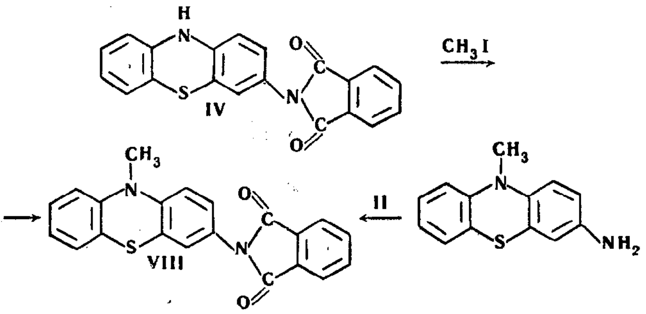
As expected, 3-aminophenothiazine proved to be unstable, and it did not give altogether satisfactory analytical data. Hence the structure had to be confirmed. Treatment with chloroformic ester converted it to ethyl phenothiazine-3-carbamate, methylation of which with methyl iodide gave ethyl 10-methylphenothiazine-3-carbamate, identical with the compound synthesized by reacting 10-methyl-3-aminophenothiazine with chloroformic ester:



We have been able to prepare 3-aminophenothiazine by a basically new route, hydrazinolysis of 3-phthalimidophenothiazine, prepared by thionation of 4-phthalimidodiphenylamine, the equations being:



Furthermore, treatment of 3-phthalimidophenothiazine with methyl iodide converted it to 10-methyl-3-phthalimidophenothiazine, which was also prepared by treating 10-methyl-3-aminophenothiazine with phthalic anhydride (II):



EXPERIMENTAL

4-Aminodiphenylamine (I). The K salt of tropeolin was prepared as described in [8], and 76 g (about 0.2 mole) reduced with sodium hydrosulfite as described in [9–11], to give 21 g (57.4%) I, as a white material which rapidly darkened, mp 67°–68°. The literature gives [11] mp 66°.

4-Phthalimidodiphenylamine (III). a) 5 g (0.0274 mole) I and 4.8 g (0.032 mole) II were carefully mixed together in a mortar, and the mixture heated for 4 hr in an oil-bath at 180°–190°. A dark-green powder obtained, insoluble in MeOH and EtOH, AcOH, ether, and benzene, slightly soluble in acetone. Yield 8.5 g (99%). It was recrystallized from dimethylformamide, when it formed yellow crystals mp 273°–274°. Found: C 76.03; 75.85; H 4.52; 4.52; N 8.83; 8.71%. Calculated for $C_{20}H_{14}N_2O_2$: C 76.42; H 4.49; N 8.91%.

b) A mixture of 10 g (0.067 mole) II, 12.3 g (0.067 mole) 4-aminodiphenylamine, and 8.6 g fused NaOAc in 120 ml AcOH was refluxed for 2 hr, cooled, the precipitate filtered off, washed with water, then with EtOH, and dried. Yield of III, mp 272°–273°, quantitative (21.2 g).

---

*For Part XVIII see [1]

3-Phthalimidophenothiazine (IV). 12 g (0.038 mole) III, 2.8 g (0.0875 g-at) S powder, and 0.6 g iodine in 40 ml o-dichlorobenzene were refluxed together in a flask with a stirrer and reflux condenser, in an oil-bath at 200°–210°, for 2 hr. Repeated recrystallization, from aqueous acetone, of the precipitate obtained on cooling, gave 4 g (30.8%) compound, mp 255°–257°. Yellow needles, soluble in benzene, and acetone, less soluble in EtOH. Found: N 7.84; 7.97; S 9.36; 9.14. Calculated for $C_{20}H_{12}N_2O_2S$: N 8.14; S 9.31.

3-Aminophenothiazine (V). 3.55 g (~0.01 mole) IV in 35 ml dry EtOH and 0.6 g (0.012 mole) hydrazine hydrate was held at 60°–70° for 2 hr 30 min, after cooling the precipitate of phthaloylhydrazine was filtered off, the ethanol completely distilled off from the filtrate, the dry residue extracted with ether, the ether extract filtered, and the ether evaporated off completely. The dry residue was recrystallized from toluene, the tarry part of the material being first separated. Further recrystallization gave 0.9 g (42%) 3-aminophenothiazine as minute white needle-shaped crystals, aggregated in clusters. Even when dry it darkened on standing for a few hours. Mp 139°–141°. Found N 12.45; 12.62; S 14.32; 14.34%. Calculated for $C_{12}H_{10}N_2S$: N 13.08; S 14.96%.

Ethyl phenothiazine-3-carbamate (VI). A 4-necked 250 ml flask was fitted with a stirrer, reflux condenser, and two dropping funnels. 0.9 g (0.0042 mole) V in 100 ml dry EtOH, was placed in the flask, the temperature was held at 10°–14°, and 0.44 g (0.004 mole) chloroformic ester in 10 ml dry EtOH added in 10–15 min, and simultaneously the same quantity of chloroformic ester, and a solution of 0.5 g NaOAc in 6 ml water were dropped in. The products were diluted with 30 ml water, and stirred for 1 hr at 10°–14°. The precipitate of NaCl was filtered off, and the solvent vacuum-distilled off. Three recrystallizations of the residue from aqueous acetone (1:1) gave 0.75 g white material with a bluish reflex, mp 150°–151°, yield 62.5%. Found: N 9.68; 9.71; S 11.41; 10.85%. Calculated for $C_{15}H_{14}N_2O_2S$: N 9.78; S 11.20%.

Ethyl 10-methylphenothiazine-3-carbamate (VII). a) 0.6 g (0.0021 mole) VI, 10 ml MeOH, and 5 ml MeI were heated together in a 25 ml steel bomb in a boiling water-bath for 8 hr. After cooling, the volatile materials were vacuum-distilled off, and the residue recrystallized from dry EtOH, to give 0.5 g (80%) colorless material, mp 133°–135°. Found: N 9.38; 9.30; S 10.94; 10.83%. Calculated for $C_{16}H_{16}N_2O_2S$: N 9.33; S 10.68%.

b) The method was similar to that used for VI. 1 g (0.0044 mole) 10-methyl-3-aminophenothiazine and two lots of 0.5 g chloroformic ester (1 g in all, or 0.009 mole) gave 0.8 g (61.5%) substance mp 133°–135°. Found: C 63.75; 63.54; H 5.43; 5.30; S 10.50; 10.62%. Calculated for $C_{16}H_{16}N_2O_2S$: C 63.98; H 5.37; S 10.68%;

The compounds prepared in a and b above had mps 134°–135°.

10-Methyl-3-phthalimidophenothiazine (VIII). a) 0.5 g IV and 3 ml MeI in 10 ml MeOH were charged into a small bomb which was then heated in a boiling water-bath for 8 hr. The products were worked up as described for VII, and 4 recrystallizations gave 0.2 g VIII, mp 196°–198°. Found: N 7.66; 7.52; S 9.25; 9.43%. Calculated for $C_{21}H_{14}N_2O_2S$: N 7.82; S 8.95%.

b) 2.3 g (0.01 mole) 10-methyl-3-aminophenothiazine and 1.5 g (0.01 mole) II were heated together at 180°–190° for 4 hr. Recrystallization from EtOH gave 2 g (58.3%) VIII, mp 204°–206°. Found: N 7.74; 7.55; S 9.29; 9.29%. Calculated for $C_{21}H_{14}N_2O_2S$: N 7.82; S 8.95%. Equal amounts of the products of a and b had mixed mp 203°–206°.

REFERENCES

1. S. V. Zhuravlev and A. N. Gritsenko, KhGS [Chemistry of Heterocyclic Compounds], 250, 1965.
2. A. Bernthsen, Chem. Ber., 17, 611, 1884.
3. A. Bernthsen, Ann., 230, 106, 1884.
4. F. Kehrmann, and O. Nossenko, Chem. Ber., 46, 2809, 1913.
5. S. Krishna and M. S. Jain, Proc. 15th Indian Sci. Congr., 153, 1928; C. A., 25, 3001, 1931.
6. V. G. Shaposhnikov, ZhRFKhO, 32, 230, 1900.
7. F. Kehrmann, Ann., 322, 1, 1902.
8. H. E. Fierz-David and L. Blangey, Basic Processes in Dye Chemistry [Russian translation], 246, IL, Moscow, 1957.
9. W. Hickinbottom, Reactions of Organic Compounds [Russian translation], GONTI, Moscow, 1939.
10. Preparative Organic Chemistry [Russian translation from Polish], edited by N. S. Vul'fson, 498, Goskhimizdat, Moscow, 1959.
11. R. Meyer, Chem. Ber., 53, 1273, 1920.

Institute of Chemotherapy and
Pharmacology, AMS USSR,
Moscow

11 June 1965