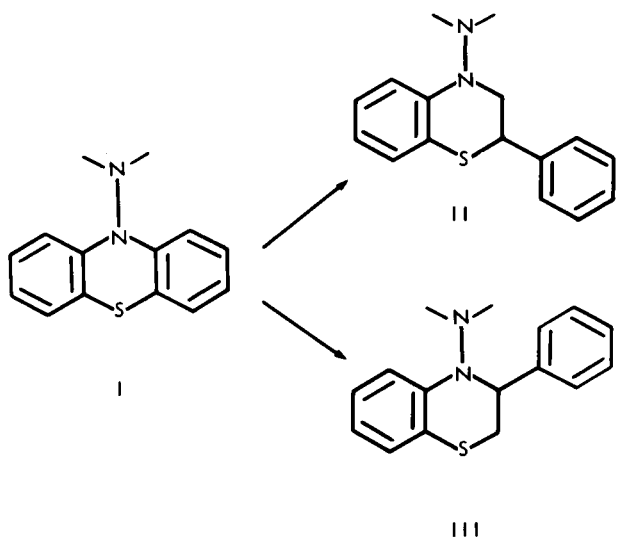
A Study of the Synthesis and Some Reactions of 3-Phenyl-1,4-benzothiazines (1)

Max Wilhelm and Paul Schmidt

Research Laboratories, Pharmaceutical Department, CIBA Limited

Condensation of *o*-aminothiophenol with 2-bromoacetophenone yields 3-phenyl-1,4-benzothiazine hydrobromide, which upon treatment with alkali gave a mixture of 3-phenyl-2*H*-1,4-benzothiazine (VIIa) and 3-phenyl-4*H*-1,4-benzothiazine (VIIb). Catalytic hydrogenation led to rearrangement of the benzothiazine (VIIa) to 2-phenyl-2-methyl-2,3-dihydrobenzothiazole (X), while reduction with lithium aluminium hydride resulted in 3-phenyl-2,3-dihydro-4*H*-1,4-benzothiazine (XVI). The latter was transferred to 3-phenyl-4-aminoalkyl-2,3-dihydro-4*H*-1,4-benzothiazines (XVII and XVIII).

Of all the drugs that exhibit potent psychotropic activity, the most important are the tricyclic compounds. These consist essentially of a tricyclic skeleton with an aliphatic side chain and a basic group substituted at the centre ring. To study the structure-activity relationships in the phenothiazine series, the most important group of all the psychopharmaceuticals, it was of interest to modify the skeleton (I) by untying one benzene ring and transferring it, so that instead of an anellated ring, a freely rotating phenyl substituent at the heterocyclic ring was obtained. A series of 2-phenyl-4-aminoalkyl-2,3-dihydro-4*H*-1,4-benzothiazine derivatives (II) was therefore prepared by Funke (2); in the present communication we shall report on the synthesis of 3-phenyl-1,4-benzothiazine derivatives (III).



I II III

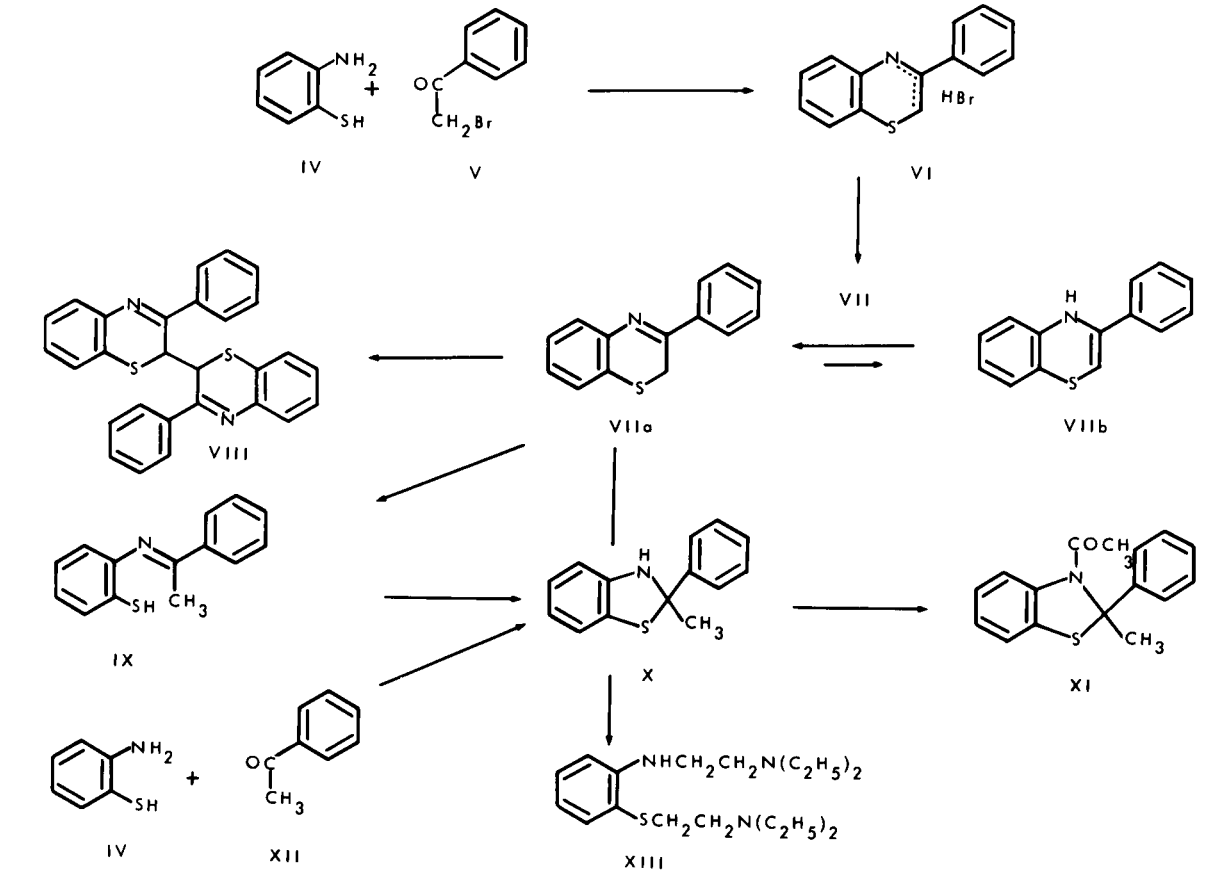
1,4-Benzothiazines with an aromatic group substituted in position 3 have been synthesized by Unger (3). Condensation of *o*-aminothiophenol with α-haloketones led to the hydrohalides of 3-phenyl-1,4-benzothiazines. Unger formulated these compounds as Schiff bases with a double bond in 3,4-position, whereas Friedrich, Kröhnke and Schiller (4) advanced the hypothesis that by way of Unger's synthesis the 4*H*-1,4-benzothiazines are formed.

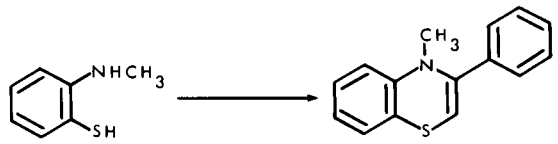
In order to investigate this structural problem, 3-phenyl-1,4-benzothiazine hydrobromide (VI) was prepared according to Unger's procedure by reaction of *o*-aminothiophenol (IV) with 2-bromoacetophenone (V). Treatment of the hydrobromide (VI) with alkali gave a mixture (VII) of the tautomeric 3-phenyl-2*H*-1,4-benzothiazine (VIIa) and 3-phenyl-4*H*-1,4-benzothiazine (VIIb). The proporation of these two isomers could be calculated by quantitative analysis of the nuclear magnetic resonance and ultraviolet spectra of VII.

One of the most important features of the nmr spectrum of VII is a S-CH_2 resonance at δ 3.38 ppm, which is consistent with structure VIIa. This assignment is supported by the C=N absorption at 6.37 μ in the infrared spectrum. However, in addition to the singlet at δ 3.38 ppm, the nmr spectrum of VII shows a rather weak NH signal at δ 3.9 ppm, which is due to the tautomeric 3-phenyl-4*H*-1,4-benzothiazine (VIIb). Integration of the two signals indicates a ratio of 80% of VIIa to 20% of VIIb. This relatively low content of 3-phenyl-4*H*-1,4-benzothiazine (VIIb) in the mixture (VII) of the tautomers explains the virtual lack of NH absorption in the infrared spectrum.

In order to estimate the ratio of the benzothiazine tautomers by analysis of the ultraviolet absorption curve of VII (Figure 1), it was necessary to know the absorption of a 3-phenyl-4*H*-1,4-benzothiazine derivative with a fixed double bond in the 2,3-position. 3-Phenyl-4-methyl-4*H*-1,4-benzothiazine (XV) was therefore synthesized by condensation of *o*-methylaminothiophenol (XIV) with 2-bromoacetophenone.

Compound XV shows two absorption maxima at 252 mμ and 300 mμ, while the ultraviolet spectrum of VII is





characterized by three maxima at 261, 300 and 320 mμ (Figure 1). The common absorption maximum of the two preparations at 300 mμ seems to indicate a minor concentration of 3-phenyl-4*H*-benzothiazine (VIIb) in VII, which is consistent with the interpretation of the nmr spectrum.

An attempt to separate the isomers (VIIa and VIIb) by distillation was unsuccessful and we isolated the unchanged mixture (VII) and the dimer (VIII) (5,6), whose structure was assigned by mass spectroscopy and by nmr analysis.

The first step towards the synthesis of 4-aminoalkyl-3-phenyl-2,3-dihydro-4*H*-benzothiazines would be the addition of hydrogen to the C=N bond in VII. However, hydrogenation of VII with palladium on charcoal or Raney nickel as a catalyst gave 2-phenyl-2-methyl-2,3-dihydrobenzothiazole (X). The structure of this compound was established by analysis of its nmr spectrum, which shows a CH_3 resonance at δ 1.98 ppm, by acetylation to 2-phenyl-2-methyl-3-acetyl-2,3-dihydrobenzothiazole (XI), as well as by identification with an independently synthesized sample. *o*-Aminothiophenol (IV) was condensed with acetophenone (XII) to yield 2-phenyl-2-methyl-2,3-dihydrobenzothiazole (X), which was found to be identical with the compound obtained by hydrogenation of 3-phenyl-2*H*-1,4-benzothiazine (VIIa).

Rearrangement of the benzothiazine ring (VII) to a benzothiazole system lends further support to the hypothesis that structure VIIa predominates. It may be assumed that in the first step of the reaction, the C-S bond of 3-phenyl-2*H*-1,4-benzothiazine (VIIa) is hydrogenated to form the intermediate thiophenol (IX), which then cyclizes to 2-phenyl-2-methyl-2,3-dihydrobenzothiazole (X). This reaction sequence is consistent with the mechanism postulated for a hydrogenolytic thiazine-thiazoline rearrangement (7).

Degradation of the dihydrobenzothiazole (X) took place upon treatment with sodium hydride and diethylaminoethyl chloride. In the course of this reaction we isolated 1-diethylaminoethylamino-2-diethylaminoethylmercaptobenzene (XIII).

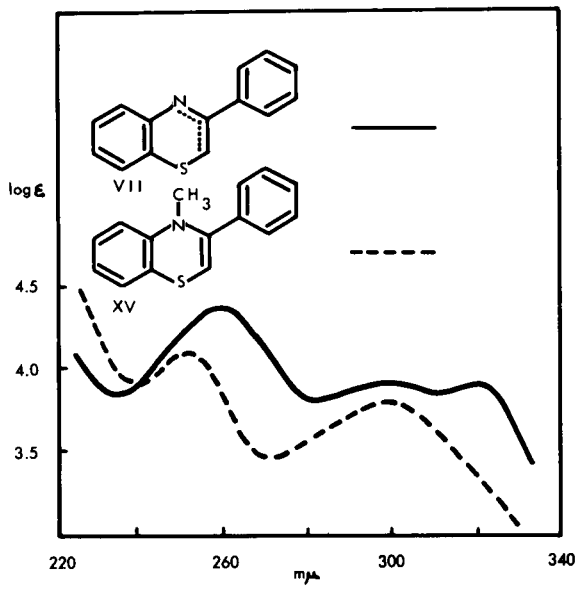
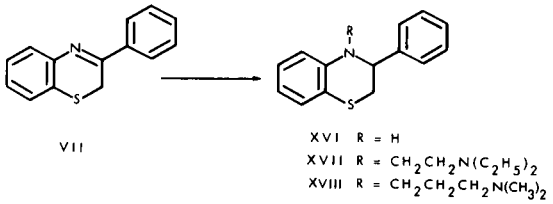


Figure 1. Ultraviolet Absorption Spectra of 3-Phenyl-1,4-benzothiazines.

The 3-phenyl-2,3-dihydro-4*H*-1,4-benzothiazine (XVI) could finally be prepared by reduction of 3-phenyl-1,4-benzothiazine (VII) with lithium aluminium hydride. Subsequent treatment of XVI with sodium hydride and dialkylaminoalkyl halides gave the desired 3-phenyl-4-alkylaminoalkyl-2,3-dihydro-4*H*-1,4-benzothiazines (XVII and XVIII).



Preliminary pharmacological screening showed that some of the basically substituted compounds described in the present communication possess a slight CNS activity. The compounds are, however, devoid of the neuroleptic properties of the phenothiazine derivatives (8).

EXPERIMENTAL

The melting points were taken on a Tottoli Melting Point Apparatus and are uncorrected. NMR spectra were determined on a Varian Associates A-60 spectrometer in carbon tetrachloride. The chemical shifts in ppm are relative to tetramethylsilane as an internal standard. Ultraviolet spectra were recorded on a Carry Spectrophotometer Model 15 using solutions in 95% ethanol.

3-Phenyl-1,4-benzothiazine Hydrobromide (VI).

A solution of 200 g. of 2-bromoacetophenone in 400 ml. of ether was slowly added to a solution of 125 g. of *o*-aminothiophenol in 400 ml. of ether. A yellow precipitate formed, which was recrystallized from methanol-ether to give 182 g. of yellow crystals, m.p. 213-215°.

Anal. Calcd. for $C_{14}H_{12}BrNS$: C, 54.91; H, 3.95. Found: C, 54.63; H, 3.89.

3-Phenyl-1,4-benzothiazine (VII).

A suspension of 150 g. of the hydrobromide (VI) in 600 ml. of 2 *N* sodium hydroxide was shaken with 400 ml. of chloroform until most of the solid had dissolved. After drying over anhydrous potassium carbonate, the chloroform was recovered and the residue was distilled to give 56 g. of an oil, b.p. (0.15 mm.) 152-155°; crystallization began after the oil had been allowed to stand for a few hours at room temperature, m.p. 45-48°. NMR δ 3.38 (singlet), 3.9 (singlet), 6.9-7.4 (multiplet), 7.75-8.00 (multiplet).

Anal. Calcd. for $C_{14}H_{11}NS$: C, 74.63; H, 4.92. Found: C, 74.52; H, 5.22.

2-[3-Phenyl-2*H*-1,4-benzothiazol-2-yl]-3-phenyl-2*H*-1,4-benzothiazine (VIII).

Recrystallization of the residue of the distillation of VII from dimethylformamide gave 32 g. of yellow crystals, m.p. 234-235°. NMR δ 3.45 (singlet), 6.9-7.4 (multiplet), 7.75-8.00 (multiplet).

Anal. Calcd. for $C_{28}H_{20}N_2S_2$: C, 75.00; H, 4.50. Found: C, 74.72; H, 4.63.

2-Phenyl-2-methyl-2,3-dihydrobenzothiazole (X).

A solution of 36.0 g. of 3-phenyl-1,4-benzothiazine (VII) in 300 ml. of ethanol was hydrogenated at 25° and 14 psi after addition of 3.0 g. of Raney nickel. After 15 hours, 3338 ml. of hydrogen had been absorbed, and the catalyst was removed by filtration. The filtrate was concentrated and the residue was distilled in high vacuum giving 27.0 g. of an oil boiling at 122-130° (0.05 mm.). NMR δ 1.98 (singlet), 3.98 (singlet), 6.4-7.7 (multiplet).

Anal. Calcd. for $C_{14}H_{13}NS$: C, 73.97; H, 5.76. Found: C, 74.28; H, 5.80.

A solution of 12.5 g. of *o*-aminothiophenol, 12.0 g. of acetophenone and 0.5 g. of *p*-toluenesulfonic acid in 200 ml. of benzene was boiled for 10 hours while the water was continuously separated. The reaction mixture was then evaporated. Distillation of the residue afforded 7.2 g. of an oil, b.p. (0.06 mm.) 130-137°. The infrared and nmr spectral data of this compound were identical with those of the compound (X) obtained by hydrogenation of VII.

Anal. Calcd. for $C_{14}H_{13}NS$. C, 73.97; H, 5.76. Found: C, 73.65; H, 5.54.

2-Phenyl-2-methyl-3-acetyl-2,3-dihydrobenzothiazole (XI).

A mixture of 8.0 g. of 2-phenyl-2-methyl-2,3-dihydrobenzothiazole (X) and 50 ml. of acetic anhydride was heated to 120° for 4 hours. Excess acetic anhydride was then evaporated. Recrystallization of the residue from ethanol gave 4.5 g. of colorless crystals, m.p. 81-82°.

Anal. Calcd. for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61. Found: C, 71.19; H, 5.60.

1-Diethylaminoethylamino-2-diethylaminoethylmercaptobenzene (XIII).

A suspension of 12.0 g. of 2-phenyl-2-methyl-2,3-dihydro-1,4-benzothiazole (X) and 2.3 g. of sodium amide in 100 ml. of

toluene was stirred at 90° for one hour. After addition of 9.0 g. of diethylaminoethyl chloride in 50 ml. of benzene, the reaction mixture was heated to 90° for 4 hours and then cooled to room temperature. Extraction with 2 *N* hydrochloric acid followed by addition of sodium hydroxide to the acid extract gave an oil that was extracted with ether. The combined ether extracts were dried over sodium sulfate and then concentrated to give 6.2 g. of an oil, b.p. (0.4 mm.) 125-134°.

To prepare the hydrochloride, 5.5 g. of the oil were dissolved in 3.5 ml. of 1 *N* hydrochloric acid and 20 ml. of water. This solution was evaporated to dryness and the solid residue was recrystallized from 2-propanol to give 2.1 g. of white crystals, m.p. 204-205°.

Anal. Calcd. for $C_{18}H_{35}Cl_2N_3S$: C, 54.53; H, 8.90; N, 10.60; Cl, 17.88; S, 8.09. Found: C, 54.77; H, 9.02; N, 10.58; Cl, 17.88; S, 8.24.

3-Phenyl-4-methyl-4*H*-1,4-benzothiazine (XV).

2-Bromoacetophenone (11.0 g.) was added in small portions to a solution of 7.0 g. of *o*-methylaminothiophenol and 2.9 g. of potassium hydroxide in 60 ml. of ethanol. The reaction mixture was boiled for 2 hours and then filtered. The filtrate was concentrated and the oily residue was distilled to give 5.3 g. of XV, b.p. (0.5 mm.) 171-180°.

Anal. Calcd. for $C_{15}H_{13}NS$: C, 75.21; H, 5.42; N, 5.87. Found: C, 75.02; H, 5.63; N, 5.80.

3-Phenyl-2,3-dihydro-4*H*-1,4-benzothiazine (XVI).

To a suspension of 15.0 g. of lithium aluminium hydride in 300 ml. of tetrahydrofuran was added a solution of 60.0 g. of freshly distilled 3-phenyl-1,4-benzothiazine (VII) in 300 ml. of tetrahydrofuran. The resulting mixture was stirred at 45° for 3 hours and then decomposed by consecutive addition of 20 ml. of water, 200 ml. of a 4 *N* solution of sodium hydroxide and finally of 60 ml. of water. The precipitate was collected by filtration and the filtrate was concentrated. Distillation of the residual oil yielded 26.0 g. of an oil, b.p. (0.1 mm.) 170-178°, which crystallized and was recrystallized from methanol to give white crystals of m.p. 58-59°.

Anal. Calcd. for $C_{14}H_{13}NS$: C, 73.97; H, 5.76. Found: C, 74.12; H, 5.87.

3-Phenyl-4-diethylaminoethyl-2,3-dihydro-4*H*-1,4-benzothiazine (XVII).

A mixture of 10.0 g. of 3-phenyl-2,3-dihydro-1,4-benzothiazine (VII) and 1.8 g. of sodamide in 150 ml. of toluene was stirred for 3 hours at 90°. A solution of 7.0 g. of diethylaminoethyl chloride in 50 ml. of toluene was then added, and the mixture was heated for a further 4 hours at 90°. The base was then extracted with 2 *N* acetic acid, and the combined extracts were made alkaline by addition of sodium hydroxide. Extraction of this alkaline solution with ether and evaporation of the solvent gave 5.6 g. of an oil, b.p. (0.5 mm.) 190-200°.

A maleate of XVII was obtained by addition of 1.2 g. of maleic acid in 20 ml. of ethanol to a solution of 3.5 g. of the oily base in 20 ml. of ethanol. Recrystallization from ethanol gave 4.0 g. of white crystals, m.p. 137-139°.

Anal. Calcd. for $C_{24}H_{30}N_2O_4S$: C, 65.13; H, 6.83. Found: C, 64.95; H, 6.82.

3-Phenyl-4-(3-dimethylaminopropyl)-2,3-dihydro-4*H*-1,4-benzothiazine (XVIII).

A mixture of 11.0 g. of 3-phenyl-2,3-dihydro-4*H*-1,4-benzothiazine (XVI) and 2.0 g. of sodium amide in 150 ml. of toluene was heated and stirred continuously for 2 hours at 90°. A solution of 7.0 g. of 3-dimethylaminopropyl chloride in 50 ml. of toluene was then added, and the mixture was heated at 90° for an additional 4 hours. After cooling to room temperature, 10 ml. of ethanol and then 200 ml. of 2 *N* acetic acid were added. The acid layer was separated and was made alkaline by addition of sodium hydroxide. Extraction with ether and evaporation of the solvent gave 9.2 g. of an oil.

To prepare the hydrochloride of XVIII, the oil was dissolved in 50 ml. of ethanol and 3.5 ml. of a 10 *N* solution of hydrogen chloride in ethanol were added. Crystallization began on addition of ether, and recrystallization of the precipitate from ethanol-ether afforded 4.5 g. of white crystals, m.p. 215-216°.

Anal. Calcd. for $C_{19}H_{25}ClN_2S$: C, 65.42; H, 7.21. Found: C, 65.58; H, 7.35.

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