On the Synthesis of 3-Amino-2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazine 5,5-Dioxide and of 3-Amino-1,2-dihydro-3*H*-dibenzo[*c*,*jk*]pyrido[2,1-*c*]-1,4-thiazepine 7,7-Dioxide

P. Catsoulacos*, M. Pelecanou and Ch. Camoutsis

Laboratory of Pharmaceutical Chemistry, Department of Pharmacy,
School of Health Sciences, University of Patras,
26500 Patras, Greece

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3-Amino-2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazine 5,5-dioxide and 3-amino-1,2-dihydro-3*H*-dibenzo-[*c*,*jk*]pyrido[2,1-*c*]-1,4-thiazepine 7,7-dioxide were synthesized from the corresponding 3-oxime acetates by reduction with the borane-tetrahydrofuran complex. Reduction was not successful in the case of 2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazine-3-oxime acetate.

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Introduction.

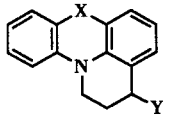
As an extension of our studies on sulfur-nitrogen heterocyclic compounds [1] the synthesis of 3-amino-2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazine (**1**) was attempted. Compound **1** may be considered as a phenothiazine tranquilizer derivative in which the alkylamino chain present on the heterocyclic nitrogen, is incorporated into a fourth ring [2]. This incorporation affects pharmacologically important structural features of the molecule such as the rotational freedom of the alkylamino chain and the stereochemistry of the phenothiazine ring system [3] and may result in derivatives with interesting properties.

Godefroi and Wittle [4] have attempted to obtain **1** by the reduction of 3,2-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one oxime (**5**) with lithium aluminum hydride and they obtained homopiperazino[3,2,1-*kl*]phenothiazine instead **5** while Harfenist and Magnien [5] have succeeded in obtaining **1** by the reduction of **5** by the Bouveault-Blanc (poor yield, impure preparation) and the Leuckart reaction (29% yield).

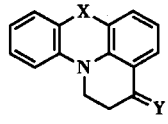
Since it is known that oxime acetates are reduced by diborane to the corresponding amines [6-8] we sought to obtain **1** by the reduction of the acetate of oxime **5** (**6**) in the presence of the borane-tetrahydrofuran complex. However, after 20 hours of reflux of **6** with the borane-tetrahydrofuran complex and subsequent basic hydrolysis of the reaction mixture, oxime **5** was recovered as the main product.

On the other hand, reduction of the oxidized derivative 2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one oxime acetate 5,5-dioxide (**9**) in the presence of the borane-tetrahydrofuran complex gave the desired corresponding amine **2** in high yield. In addition, a dihydrodibenzothiazepine derivative of related structure, bearing oxidized sulfur as well, the 1,2-dihydro-3*H*-dibenzo[*c*,*jk*]pyrido[2,1-*c*]-1,4-thiazepin-3,12-dione 3-oxime acetate 7,7-dioxide (**12**) was also reduced to the corresponding amine **13** in high yield (simultaneous reduction of the tertiary amide function to tertiary amine took place [9]).

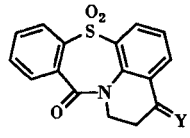
We attribute the difference in behavior towards the borane-tetrahydrofuran complex of the three oxime acetates, **6**, **9**, and **12** to the different electronic properties of the ring system rendered by the different oxidation state of the sulfur.



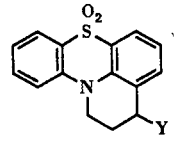
1 X = S Y = NH_2
2 X = SO_2 Y = NH_2
3 X = SO_2 Y = $NHCOCH_3$



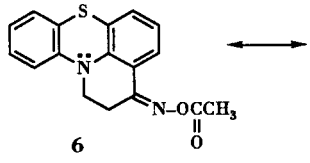
4 X = S Y = O
5 X = S Y = NOH
6 X = S Y = $NOCOCH_3$
7 X = SO_2 Y = O
8 X = SO_2 Y = NOH
9 X = SO_2 Y = $NOCOCH_3$



10 Y = O
11 Y = NOH
12 Y = $NOCOCH_3$



13 Y = NH_2
14 Y = $NHCOCH_3$



6 **6a**

21 **21a**

Results and Discussion.

Oxime acetate **6** was obtained by acetylation of the oxime **5** which was prepared according to the known synthetic scheme [10] given in Figure I. The synthetic procedure included cyanoethylation of the heterocyclic nitrogen of phenothiazine **15** to obtain **16**, followed by alkaline hydrolysis to the corresponding propionic acid **17**. The acid was subsequently cyclized to the ketone **4** which was transformed to the oxime **5** and acetylated to the corresponding oxime acetate **6**.

Compound **6** was allowed to react with excess of the borane-tetrahydrofuran complex under reflux (66°) for 20 hours and was subsequently treated with aqueous sodium hydroxide to give the oxime **5** as the main product (25% yield). Prolonged reflux did not succeed in reducing **6** to the corresponding amine.

The inability of the borane-tetrahydrofuran complex to reduce **6** prompted us to extend the investigation to the oxime acetate of the 5,5-dioxide derivative **9**.

For the preparation of **9**, oxidation of sulfur to sulfone was effected by treating the 10-cyanoethylphenothiazine **16** with 30% hydrogen peroxide in acetic acid [11]. Attempted alkaline hydrolysis of the 10-cyanoethylphenothiazine 5,5-dioxide (**16'**) to the corresponding acid **17'** however, as was previously done for the conversion of **16** to **17** (Figure I), afforded the de-cyanoethylated product, phenothiazine 5,5-dioxide. In order to obtain **17'** the propionitrile was first converted to the corresponding methyl propionate by the action of methanolic hydrogen chloride in dioxane at room temperature followed by saponification of the ester [4]. The acid was cyclized and converted to the corresponding oxime acetate in a similar manner as the one shown in Figure I for **17**.

When refluxed with excess of the borane-tetrahydrofuran complex for 20 hours, **9** was reduced successfully to the corresponding amine (63% yield).

Under the same reaction conditions, a compound of related structure bearing oxidized sulfur, the 1,2-dihydro-3*H*-dibenzo[*c*,*jk*]pyrido[2,1-*c*]-1,4-thiazepine-3,12-dione 3-oxime acetate 7,7-dioxide (**12**) was reduced as well to the corresponding amine **13** (60% yield). Simultaneous reduction of the tertiary amide function to the corresponding amine took place [9].

Compound **12** was prepared by a known synthetic scheme [7,12] (Figure II). According to this scheme, thioxanthone (**18**) was first oxidized in the presence of hydrogen peroxide and subsequently transformed to the oxime **19** which underwent Beckmann rearrangement in the presence of polyphosphoric acid to yield the lactam **20**. The steps leading from **20** to **12** were essentially the same as those described above for the preparation of **9**.

We believe that the difference in behavior of the three oxime acetates, **6**, **9**, and **12**, towards the borane-tetrahydrofuran complex can be explained by the influence of the oxidation state of the sulfur to the resonance forms of the tetracyclic ring system.

Specifically, in the case of compound **6**, the existence of a charge separated resonance form **6a** may weaken the

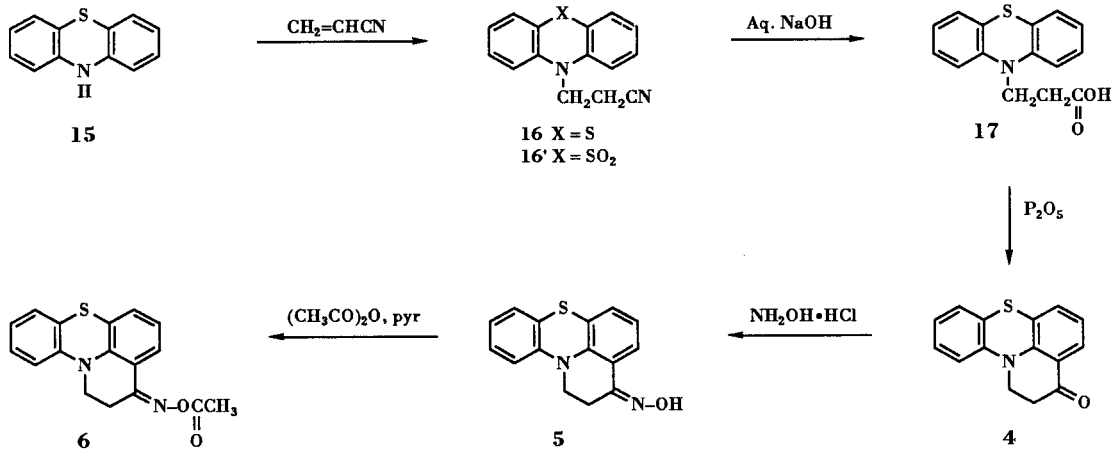


Figure I. Synthetic scheme to 2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one oxime acetate (6).

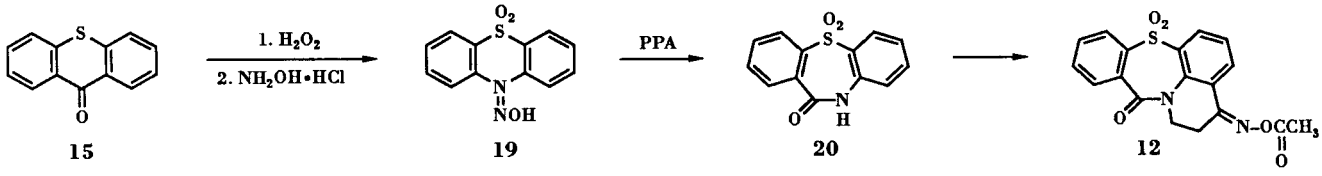


Figure II. Synthetic scheme to 1,2-dihydro-3*H*-dibenzo[*c*,*jk*]pyrido[2,1-*c*]-1,4-thiazepine-3,12-dione 3-oxime acetate 7,7-dioxide (12).

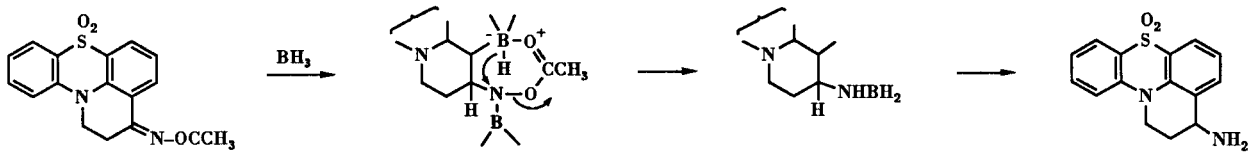


Figure III. Proposed mechanism for the reduction of oxime acetates by the borane-tetrahydrofuran complex.

double bond character of the C=N double bond and inhibit hydride transfer from borane to this function. Van Allan *et al.* have provided spectroscopic evidence for the existence of charge separated resonance forms **21**↔**21a** in ketones of analogous to **6** structures of benzologs of phenothiazine [13]. In our case, the presence of the isosteric to the ketone, oxime acetate function is expected to exert an even more powerful pull on the electrons and further promote the formation of charge-separated resonance forms.

When sulfur is present as a sulfone, its strong inductive effect pulls the electrons in a different direction and inhibits the formation of charge-separated resonance forms. The C=N bond retains its double bond character and reduction of the oxime acetate may proceed by the well established mechanism [6] given in Figure III.

According to this mechanism, borane coordinates with one of the acetate oxygens providing thus a good leaving group that facilitates internal transfer of a second hydride and generation of the amine.

Comparisons of the ir absorptions of the ketones **4, 7, 10** in spectra obtained in chloroform solution show a trend which is in agreement with the above arguments. Specifically, the keto-group of **4** appears at 1684 cm^{-1} while the keto-group of **7** and **10** appear at 1695 and 1700 cm^{-1} respectively, indicating increased double bond character for the keto-function of **7** and **10** as compared to **4** (the C=N ir absorptions of the oximes or the oxime acetates were not so well distinguished to allow for comparisons).

EXPERIMENTAL

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 298 spectrophotometer with polystyrene as reference peak. The nmr spectra were obtained in deuteriochloroform on a Varian FT-80A spectrophotometer with TMS as internal standard. The C, H, N elemental analyses were performed at the Laboratory of Organic Chemistry, University of Salonica, Greece.

2,3-Dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one (**4**).

Compound **4** was prepared by the existing literature procedure [10] with one differentiation: In our case, cyanoethylation of phenothiazine was effected by the dropwise addition of 10% methanolic potassium hydroxide instead of the reported 40% aqueous benzyltrimethylammonium hydroxide. The resulting precipitate was added to water and collected by filtration.

2,3-Dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one Oxime Acetate (**6**).

To a solution of 5 g of **4** in a mixture of pyridine (20 ml) and ethanol (20 ml) was added 7 g of hydroxylamine hydrochloride and the mixture was heated under reflux for 7 hours. It was subsequently cooled, diluted with water and extracted with chloroform (3 x 30 ml). The organic extracts were combined, dried over sodium sulfate and filtered. Evaporation of chloroform gave 5.5 g of the oxime **5** which was subsequently acetylated in excess of acetic anhydride and pyridine for 12 hours, mp 155-157° (chloroform/methanol); ir (potassium bromide): 1766, 1429, 1200, 940, 752 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.26 (s, 3H), 3.08 (t, 2H, J = 6.40 Hz), 3.88 (t, 2H, J = 6.40 Hz), 6.77-7.91 (m, 7H, Ar).

Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.81; H, 4.52; N, 9.05. Found: C, 65.70; H, 4.47; N, 9.15.

3-[10-(Phenothiazinyl)]propionic Acid 5,5-Dioxide (**17'**).

To a solution of 4 g of 10-cyanoethylphenothiazine (**16**) prepared according to published procedure [10] (see also preparation of **4**) in 100 ml of acetic acid was added 60 ml of hydrogen peroxide 30% and the mixture was refluxed for 15 hours. The mixture was subsequently poured into water and extracted with chloroform (3 x 30 ml). The organic extracts were combined, dried over magnesium sulfate, filtered and evaporated to yield 3.7 g of the corresponding 5,5-dioxide **16'**. It was recrystallized from methanol to yield purplish crystals, mp 176-177°; ir (potassium bromide): 2230, 1591, 1466, 1367, 1274, 1165, 1140, 1082, 881, 750 cm^{-1}.

To an ice-cold suspension of 3.5 g of the 10-cyanoethylphenothiazine 5,5-dioxide (**16'**) in a mixture of dry dioxane (75 ml) and methanol (140 ml) was bubbled dry hydrogen chloride until most of the material was dissolved (*ca.* 2 g). The mixture was stirred at room temperature for 70 hours and was subsequently poured into a water-ice mixture. The resulting precipitate of the corresponding methyl ester was collected by vacuum filtration (3.7 g), mp 168-169° (methanol); ir (potassium bromide): 1730, 1590, 1464, 1380, 1275, 1160, 750 cm^{-1}.

To a solution of 3.4 g of the methyl ester in 70 ml of methanol was added 1 g of potassium hydroxide in 35 ml of water. The mixture was stirred at room temperature for 2 hours and was subsequently poured in ice and acidified with hydrochloric acid. The resulting precipitate was collected by vacuum filtration and dried (3.0 g), mp 192-193° (methanol); ir (potassium bromide): 1705, 1590, 1465, 1283, 1165, 1140, 1085, 750 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_4S$: C, 59.40; H, 4.29; N, 4.62. Found: C, 59.31; H, 4.41; N, 4.52.

2,3-Dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one Oxime Acetate 5,5-Dioxide (**9**).

Acid **17'** was cyclized to the corresponding ketone **7** following the same procedure as for the preparation of **4**. Ketone **7** was subsequently transformed into the corresponding oxime acetate

9 following the same procedure as for **6**, mp 201-203° (ethyl acetate); ir (potassium bromide): 1760, 1586, 1450, 1289, 1216, 951, 760 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}N_2O_4S$: C, 59.65; H, 4.09; N, 8.19. Found: C, 59.55; H, 4.09; N, 8.23.

1,2-Dihydro-3*H*-dibenzo[*c,jk*]pyrido[2,1-*c*]-1,4-thiazepine-3,12-dione 3-Oxime Acetate 7,7-Dioxide (**12**).

Compound **12** was prepared from the corresponding ketone **10** as previously described for **6**, mp 292-295°; ir (potassium bromide): 1770, 1640, 1440, 1360, 1320, 1190, 930, 720.

Anal. Calcd. for $C_{18}H_{14}N_2O_5S$: C, 58.38; H, 3.78; N, 7.57. Found: C, 58.43; H, 3.75; N, 7.43.

Preparation of the ketone **10** has been previously described [7,12].

Reduction of Oxime Acetates **6**, **9**, **12** with the Borane-tetrahydrofuran Complex.

The procedure was common to all oxime acetates. Excess of the borane-tetrahydrofuran complex (1.0 *M*, Aldrich #17,619-2) was added to the oxime acetate with a hypodermic syringe (*ca.* 40 ml for 1 g of oxime acetate) and the solution was heated under reflux for 20 hours while protected from moisture. The reaction mixture was subsequently cooled in an ice-bath and aqueous potassium hydroxide solution (10%) was added dropwise under the hood until evolution of hydrogen ceased. Excess of aqueous potassium hydroxide was added and the basic solution stirred for 2 hours. It was extracted with chloroform and the combined organic layers were dried over sodium sulfate and evaporated. The residue was chromatographed on a column (silica gel, chloroform initially, followed by chloroform:methanol, 95:5) and the products isolated were:

2,3-Dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one Oxime (**5**).

This compound was obtained from **6**, mp 219-220° (yellow needles from chloroform); ir (potassium bromide): 3230 (broad), 1427, 962, 742 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.03 (t, J = 6.40 Hz, 2H), 3.90 (t, J = 6.4 Hz, 2H), 6.76-7.72 (m, Ar).

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.16; H, 4.48; N, 10.45. Found: C, 67.24; H, 4.63; N, 10.62.

3-Amino-2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazine 5,5-Dioxide (**2**).

This compound was obtained from **9** and characterized as the corresponding acetamide **3**, mp 222-223° (ethyl acetate); ir (potassium bromide): 3328 (sharp), 1668, 1587, 1470, 1448, 1432, 1270, 1128, 790, 657 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.19; H, 4.88; N, 8.53. Found: C, 62.11; H, 4.71; N, 8.41.

3-Amino-1,2-dihydro-3*H*-dibenzo[*c,jk*]pyrido[2,1-*c*]-1,4-thiazepine 7,7-Dioxide (**13**).

This compound was obtained from **12** and characterized as the corresponding acetamide **14**, mp 275-276° (chloroform/methanol); ir (potassium bromide): 3390 (sharp), 1680, 1590, 1530, 1488, 1440, 1270, 1145, 1100, 780, 770, 731, 710, 595 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.18; H, 5.26; N, 8.19. Found: C, 62.99; H, 5.31; N, 8.04.

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