

Intermolecular Hydride Transfer in Acid Induced Disproportionation of

1,2-Dihydro-3-hydroxy-3*H*-pyrido[3,2,1-*kl*]phenothiazines

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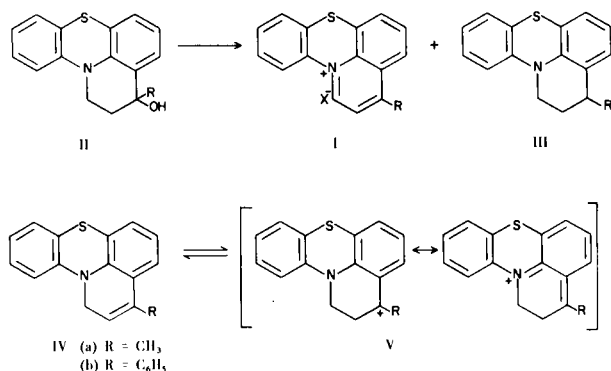
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Received December 9, 1977

1,2-Dihydro-3-hydroxy-3*H*-pyrido[3,2,1-*kl*]phenothiazines and 1*H*-pyrido[3,2,1-*kl*]phenothiazines undergo acid catalyzed disproportionation with intermolecular hydride transfer to form pyrido[3,2,1-*kl*]phenothiazinium salts and 1,2-dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazines. Sodium borohydride reduction of 3-alkyl- or 3-arylpyrido[3,2,1-*kl*]phenothiazinium salts gives 3-alkyl- or 3-aryl-1*H*-pyrido[3,2,1-*kl*]phenothiazines. In the presence of a proton source, borohydride reduction of pyrido[3,2,1-*kl*]phenothiazinium fluoroborate or 3-chloropyrido[3,2,1-*kl*]phenothiazinium perchlorate gives 1,2-dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazine, while 1*H*-pyrido[3,2,1-*kl*]phenothiazine is formed in aprotic solvents with pyridine present.

J. Heterocyclic Chem., 15, 1331 (1978)

Sunagawa and Ichii (3) reported the isolation and identification of 3-substituted pyrido[3,2,1-*kl*]phenothiazinium salts (I) following the treatment of 3-methyl- or 3-phenyl-1,2-dihydro-3-hydroxy-3*H*-pyrido[3,2,1-*kl*]phenothiazines (II) with concentrated hydrochloric acid in acetic acid. Although it is apparent that this conversion represents not only a dehydration of II, but dehydrogenation (oxidation) as well, no reduction products were reported isolated. Repetition of the reaction using concentrated hydrochloric acid or perchloric acid, followed by careful workup, revealed the formation of two principal reaction products: the benzene insoluble salts I and the benzene soluble 3-methyl- or 3-phenyl-1,2-dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazines (III).

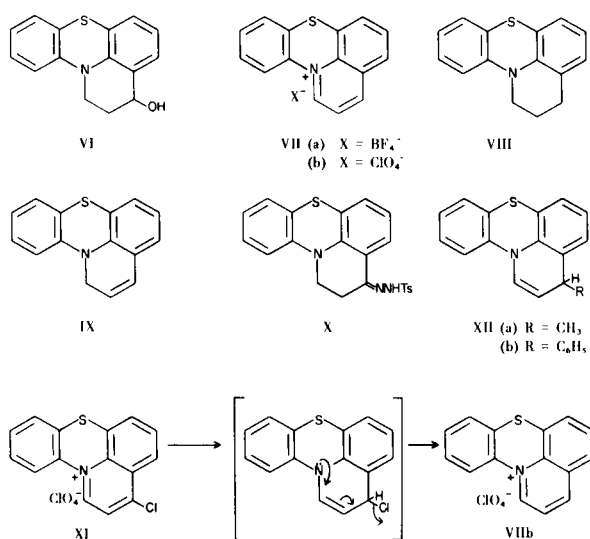


When 3-methyl- or 3-phenyl-1*H*-pyrido[3,2,1-*kl*]phenothiazines, IVa or IVb, (prepared by sodium borohydride reduction of Ia or Ib) were reacted with strong mineral acids (hydrochloric acid or perchloric acid), I and III were again isolated. This result suggests that the reaction reported by Sunagawa and Ichii proceeds, in part, through the intermediacy of the carbonium ion V, which abstracts hydride from the olefin IV to yield I and III. Similar intermolecular hydride transfers have been observed in acid catalyzed disproportionations of 3,4-dihydroquino-

linolines (4), 1,2-dihydroisoquinolines (5), 3,4-dihydrochromenes (6), 3,4-dihydrothiachromenes (7), and 1,2-dihydronaphthalenes (8) and in abstractions of hydride from these types of compounds by triphenylmethyl cation (4a) and other electrophilic species (9). Treatment of IVa and IVb, respectively, with triphenylmethyl perchlorate (10) gave quantitative yields of the corresponding perchlorates, Ia and Ib, and triphenylmethane. In the case of the reaction of either II or IV with mineral acids, however, the stoichiometry of the products was not 1:1, but ranged from around 2-4:1 depending on the acid employed. These results suggest that considerable direct oxidation of the olefin, either by oxidants in the mineral acid (perchlorate, chlorine, hypochlorous) or by dissolved oxygen, also occurs.

Somewhat surprisingly, treatment of 1,2-dihydro-3-hydroxy-3*H*-pyrido[3,2,1-*kl*]phenothiazine (VI) with hydrochloric acid or perchloric acid failed to yield characteristic products, i.e., VII and VIII. The insoluble purple solid obtained from these reactions was assumed to be polymeric since it failed to form IX (or VIII) when reacted with sodium borohydride. Similar acid catalyzed dimerization and trimerization reactions of 1,2-dihydroisoquinolines have been reported (11). When IX, prepared by reduction of the tosylhydrazone X with methyllithium (12), was reacted with triphenylmethylfluoroborate an excellent yield of VIIa was obtained. Sodium borohydride reduction of VII in an aprotic solvent (tetrahydrofuran or acetonitrile) gave the very unstable IX (identified by pmr). However, when the reduction was carried out in 95% ethanol (or in tetrahydrofuran with ethanol or methanol used to decompose the excess borohydride and borane in the workup) the tetrahydro derivative VIII was formed. The latter reaction is similar to the reductions of pyridinium (13) and isoquinolinium (14) salts with sodium borohydride, the second stage of which is acid catalyzed (15). Sodium borohydride reduction of 3-

chloropyrido[3,2,1-*kl*]phenothiazinium perchlorate (16) (XI) also gave IX in acetonitrile and VIII if ethanol was employed. Since XI is reported to react with nucleophiles exclusively at the 3-position, we assume that borohydride initially attacks the 3-position to form the 3H-intermediate XII, which immediately eliminates hydrogen chloride to give the salt VIIb. Further reduction of VIIb gives IX or VIII. It was found convenient to use an equivalent of pyridine in the reductions of VII and XI, respectively, to VIII (to complex any borane formed in the reduction) and then to convert IX to the stable salt VIIa.



As in the case of the alcohol VI, treatment of IX with mineral acids (hydrochloric acid, perchloric acid or fluoroboric acid) gave only uncharacterized purple solids which did not react with sodium borohydride to give either VIII or IX. In fact, we were unable to purify IX for elemental analysis: it was characterized by its nmr spectrum and its conversion to the stable salt VII. Attempts to chromatograph IX on silica gel, or neutral or alkaline alumina gave apparently the same highly colored material.

The structures of the 1H-pyrido[3,2,1-*kl*]phenothiazines IVa, IVb and IX were established from their nmr spectra (Table I), confirming that hydride attack had occurred at C₁ and not at C₃. Thus, the NCH₂ protons of IVa, IVb and IX appeared in the same range (δ 4.48, 4.68 and 4.38 ppm, respectively). A doublet for this resonance in IVa and a triplet for the H₂ resonance (after the long-range coupling from the CH₃ was removed by irradiation of the CH₃ resonance) is consistent with the $\Delta^{2,3}$ -structure and not the $\Delta^{1,2}$ -structure XIIa. Similarly, the simple nmr spectrum of the pyrido-ring protons of IVb consisting of a doublet for the NCH₂ protons and a triplet for the H₂ proton supports only the $\Delta^{2,3}$ -structure. Three distinctly different protons with a more complex coupling pattern would be anticipated for the $\Delta^{1,2}$ -structure XIIb. Finally, the ring CH₂ chemical shift of IX appears at a lower field than would be anticipated for a benzylic CH₂ and the olefinic proton assigned to H₃ appears at a higher field than anticipated for an olefinic proton adjacent to a nitrogen atom in XIIc.

EXPERIMENTAL

All melting points below 230° were determined on a Thomas Hoover capillary melting point apparatus and are corrected; those above 230° were determined on a Fisher Johns block and were uncorrected. The ir spectra were obtained on a Beckman Model Ir-33 double beam spectrophotometer. The nmr spectra were obtained on a Varian Model T60 spectrometer. Chemical shifts were given in δ values with TMS as an internal standard.

Disproportionation of 1,2-Dihydro-3-hydroxy-3-methyl-3H-pyrido[3,2,1-*kl*]phenothiazine (IIa).

To a stirred solution of 4.2 g. (15.6 mmoles) of IIa in 75 ml. of ethyl acetate was added 1.5 ml. of 60% perchloric acid in 15 ml. of glacial acetic acid. The addition of the first drop of acid changed the color of the solution from yellow to red. During the addition, which required 20 minutes, a dark red precipitate formed. The mixture was stirred an additional hour then cooled to 0° and filtered. The filtrate was condensed *in vacuo* (aspirator) and the residue triturated with benzene and again filtered. The combined solid residue was washed with cold ethyl acetate, dried and recrystallized from ethyl acetate to give 3.1 g. (55.7%) of the perchlorate salt of Ia as maroon needles, m.p. 242°; ir ν max

Table I

Nmr Data for 1H-Pyrido[3,2,1-*kl*]phenothiazine Pyrido-Ring Protons (in deuteriochloroform)

Compound	R ₃ (δ)	H ₁ (δ)	H ₂ (δ)	J _{1,2}
IVa	CH ₃ 1.97 (m)	4.48 (m) (a)	5.69 (m) (b)	4.1
IVb	C ₆ H ₅ 7.33 (s)	4.68 (d)	5.89 (t)	4.8
IX	H 6.15 (m)	4.38 (q)	5.7 (m)	(c)

(a) Irradiation of CH₃ collapsed the H₁ protons to a doublet. (b) Irradiation of CH₃ collapsed the H₂ protons to a triplet. (c) Not determined.

1644 cm^{-1} ($\text{C}=\text{N} +$).

The benzene soluble material was chromatographed on a neutral alumina (Woelm activity grade 1) column (benzene/hexane) to give 720 mg. (18.3%) of IIIa as white rhombic crystals from 95% ethanol, m.p. 88-89°; nmr (deuteriochloroform): δ 6.60-7.22 (7H, m, aryl), 3.38-3.78 (2H, m, NCH_2), 2.55-3.15 (1H, m, benzylic CH), 1.5-2.4 (2H, m, alicyclic CH_2) 1.23 (3H, t, $J = 6.6$ Hz, CH_3).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{NS}$: C, 75.85; H, 5.97; N, 5.53; S, 12.65. Found: C, 75.62; H, 5.97; N, 5.41; S, 12.71.

Repetition of the procedure of Sunagawa and Ichii (2) on 2.7 g. (1 mole) of IIa gave 1.67 g. (46%) of the iodide salt of Ia, m.p. 286-288° dec. (lit.(1) 288 dec.) and 410 mg. (16.2%) of IIIa.

Disproportionation of 3-Methyl-1H-pyrido[3,2,1-kl]phenothiazine (IVa).

Treatment of 1.25 g. (5 mmoles) of IVa with 60% perchloric acid (as above) gave 1.07 g. (61.1%) of the perchlorate salt of Ia and 240 mg. (19%) of IIIa.

Disproportionation of 1,2-Dihydro-3-hydroxy-3-phenyl-3H-pyrido[3,2,1-kl]phenothiazine (IIb).

The disproportionation of IIb was carried out by the identical procedure used for IIa. Thus, 1.82 g. (5.5 mmoles) of IIb treated with 60% perchloric acid gave 1.3 g. (57.5%) of the perchlorate salt of Ib as maroon needles, m.p. 230° dec. from acetonitrile; ir: ν max (potassium bromide): 1662 cm^{-1} ($\text{C}=\text{N}^+$) and 300 mg. (17.3%) of IIIb, m.p. 162° from 95% ethanol (lit. (1) 162°); nmr (deuteriochloroform): δ 6.58-8.65 (3H, m, aromatic), 4.09 (1H, t, $J = 5.4$ Hz, benzylic CH), 3.51 (2H, t, $J = 5.9$ Hz, NCH_2), 2.1-2.3 (2H, m, alicyclic CH_2).

Repetition of the procedure of Sunagawa and Ichii (2) on 2.37 g. (6 mmoles) of IIb gave 1.1 g. (53%) of the chloride salt of Ib and 340 mg. (19.3%) of IIIb.

Disproportionation of 3-Phenyl-1H-pyrido[3,2,1-kl]phenothiazine (IVb).

Treatment of 1.8 g. (5.8 mmoles) of IVb with 60% perchloric acid (as above) gave 1.54 g. (64.8%) of the perchlorate salt of Ib and 330 mg. (18%) of IIIb.

3-Methyl-1H-pyrido[3,2,1-kl]phenothiazine (IVa).

To 340 mg. (9 mmoles) of sodium borohydride was added 2.5 g. (7.15 mmoles) of Ia as the perchlorate salt in portions with stirring. As the salt reduced the color of the suspension changed from deep red to yellow. The mixture was stirred an additional 2 hours and a clear yellow solution resulted. The solvent was removed *in vacuo* (aspirator) leaving a pale yellow glass which was washed several times with distilled water and then dissolved in the minimum quantity of absolute ethanol (to which a few mg. of anhydrous potassium carbonate had been added) with gentle heating. Successive cooling and concentration of the ethanol solution gave several crops of IVa as rhombic yellow crystals totalling 1.2 g. (66.9%), m.p. 75°; nmr (deuteriochloroform): δ 6.63-7.21 (7H, m, aromatic), 5.69 (1H, m, vinyl), 4.48 (2H, m, NCH_2), 1.97 (3H, m, CH_3).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{NS}$: C, 76.49; H, 5.18; N, 5.69; S, 12.75. Found: C, 76.60; H, 5.25; N, 5.69; S, 12.93.

3-Phenyl-1H-pyrido[3,2,1-kl]phenothiazine (IVb).

To a stirred suspension of 380 mg. (10 mmoles) of sodium borohydride suspended in 100 ml. of freshly distilled tetrahydrofuran was added 3.5 g. (8.5 mmoles) of Ib as the perchlorate salt in small portions. The mixture was allowed to stir 2 hours at room temperature. Methanol (10 ml.) was cautiously added over

a period of 15 minutes and the resulting solution was concentrated *in vacuo* (aspirator). The oily residue was dissolved in the minimum of absolute ethanol (basified with a few mg. of potassium carbonate) with gentle heating and the solution cooled to give (in several crops) 1.9 g. (71.9%) of pale yellow rhombic crystals, m.p. 121-122°; nmr (deuteriochloroform): δ 7.33 (5H, s, phenyl) 6.85-7.15 (7H, m, other aromatic), 5.89 (1H, t, $J = 4.8$ Hz, vinyl), 4.68 (2H, d, $J = 4.8$ Hz, NCH_2).

Anal. Calcd. for $\text{C}_{21}\text{H}_{15}\text{NS}$: C, 80.25; H, 5.10; N, 4.45; S, 10.19. Found: C, 80.04; H, 4.94; N, 4.45; S, 10.38.

3-Phenylpyrido[3,2,1-kl]phenothiazinium Perchlorate (Ib).

To a stirred suspension of 2.1 g. (6.7 mmoles) of IVb dissolved in 10 ml. of the same solvent was added 2.3 g. (6.7 moles) of freshly prepared tritylperchlorate (10). A red precipitate immediately formed. The mixture was stirred for 4 hours, 50 ml. of anhydrous ether was added and the suspension filtered. The red solid was collected, dried and recrystallized from acetonitrile to give 2.3 g. (91.6%) of Ib. The filtrate was condensed *in vacuo* (aspirator) and the residue dissolved in hexane and chromatographed on neutral alumina (Woelm activity grade 1) to give 1.4 g. (94.6%) of triphenylmethane, m.p. 94° [authentic sample (Aldrich), m.p. 94°].

p-Toluenesulfonylhydrazone of 1,2-dihydro-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (X).

Concentrated hydrochloric acid (5 ml.) was added to a solution of 3.64 g. (14 mmoles) of 1,2-dihydro-3-keto-3H-pyrido[3,2,1-kl]phenothiazine and 2.7 g. (14.5 mmoles) of p-toluenesulfonylhydrazine (Aldrich). The reaction mixture was refluxed for 90 minutes and then cooled to 25° causing a yellow solid to precipitate which was collected on a filter, washed with 95% ethanol and dried to give 4.5 g. (76.3%) of the tosylhydrazone X. Recrystallization of X from absolute ethanol gave yellow needles, m.p. 203°. The ir spectrum indicated a mixture of tautomers: ν max (potassium bromide): cm^{-1} 1642, $\text{C}=\text{N}$; 1616, aromatic $\text{C}=\text{C}$; 1595, $\text{C}=\text{C}$.

Anal. Calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_2\text{S}_2$: C, 62.68; H, 4.54; N, 9.96; S, 15.21. Found: C, 62.78; H, 4.52; N, 10.06; S, 15.32.

1H-Pyrido[3,2,1-kl]phenothiazine (IX).

To a suspension of 2.1 g. (5 mmoles) of the tosylhydrazone (X) in 50 ml. of dry ether under a nitrogen atmosphere in the dark was added dropwise with stirring 8 ml. of methyllithium (1.77M) in ether. The mixture was stirred for 15 hours, quenched with 10 ml. of ice water and filtered. The solid material was washed with ether and discarded. The ethereal solution was dried over anhydrous sodium sulfate and evaporated (aspirator) to give the crude IX which was not isolated because of its instability; nmr (deuteriochloroform): δ 6.24-7.04 (7H, m, aromatic), 6.15 (1H, m, $\text{Ar}-\text{CH}=\text{C}$), ~ 5.7 (1H, m, $\text{C}-\text{CH}=\text{C}$), 4.38 (2H, q, NCH_2).

Pyrido[3,2,1-kl]phenothiazinium Fluoroborate (VIIa).

Tritylfluoroborate (10), 0.8 g. (2.4 mmoles) was added to a solution of the crude residue containing IX dissolved in dry dichloromethane. The reaction was stirred 10 hours at 25°. The purple solid which formed was collected on a filter. Concentration of the filtrate gave a gummy purple solid which was triturated with dry ether and collected on the filter. The solid was washed again with ether and dried to give 550 mg., m.p. 188-190° from acetonitrile; ir ν max (potassium bromide): 1644 cm^{-1} ($>\text{C}=\text{N}^+<$); nmr (perdeuterionitromethane): δ 9.63 (1H, AB quartet, $J = 6.4$ Hz, $>\text{N}=\text{CH}$), 9.11 (1H, AB quartet, $J = 7.6$ Hz, benzylic $>\text{C}=\text{CH}$), 7.35-8.31 (8H, m, aromatic and vinylic $\text{C}=\text{CH}-\text{CH}$).

Anal. Calcd. for $C_{15}H_{10}BF_4NS$: C, 55.74; H, 3.11; N, 4.33; S, 9.92. Found: C, 55.88; H, 3.24; N, 4.13; S, 10.08.

Sodium Borohydride Reductions of Pyrido[3,2,1-*kl*]phenothiazinium Fluoroborate (VIIIa).

A.

The fluoroborate salt (VIIa), 6.5 g. (20 mmoles) was added in small portions with stirring to a suspension of 840 mg. (22 mmoles) of sodium borohydride in 80 ml. of freshly distilled acetonitrile. As the salt reduced the color of the suspension changed from red to yellow. The mixture was stirred 2 hours and then 10 ml. of methanol was cautiously added with stirring. The solvents were removed *in vacuo* (aspirator) and the residue dissolved in benzene and chromatographed (benzene/hexane) on a neutral alumina (Woelm activity grade 1) column to give 4.1 g. (85.6%) of 1,2-dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazine (VIII), m.p. 55-56° [lit. (17) m.p. 56°]; nmr (deuteriochloroform): δ 6.7-7.1 (7*H*, m, aromatic), 3.59 (2*H*, t, J = 5.8 Hz, NCH_2), 2.71 (2*H*, t, J = 6.1 Hz, benzylic CH_2) 1.90-2.40 (2*H*, m, CCH_2C).

B.

To a suspension of 210 mg. (5.5 mmoles) of sodium borohydride in 50 ml. of freshly distilled acetonitrile was added 1.55 g. (4.8 mmoles) of VIIIa in portions (as above) followed by 0.5 ml. of pyridine and the mixture was stirred 2 hours. The solvent was then removed *in vacuo* and the residue taken up in benzene, extracted several times with distilled water, and dried over anhydrous sodium sulfate. After the nmr spectrum of the residue, demonstrated the principal product to be IX, it was taken up in acetonitrile and reacted with 1.48 g. (5 mmoles) of tritylfluoroborate to give 1.22 g. (78.8%) of VIIa.

Sodium Borohydride Reduction of 3-Chloropyrido[3,2,1-*kl*]-phenothiazinium Perchlorate (XI).

A.

Reduction of 1.85 g. (5 mmoles) of XI (16) using procedure A (above) gave 862 mg. (72.2%) of VIII.

B.

Procedure B (above) gave 740 mg. (58.2%) of VIIa (after treatment of the crude VIII with tritylfluoroborate) from 1.85 g. (5 mmoles) of XI.

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