TETRACYCLIC PHENOTHIAZINES. VIII.[1] METAL HYDRIDE REDUCTIONS OF SOME 1,2-DIHYDRO-3-KETO-3H-PYRIDO[3,2,1-kl]PHENOTHIAZINES

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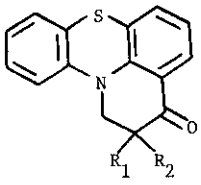
Abstract--Aluminum hydride (alane) in ether reduces 1,2-dihydro-3-keto-3H-pyrido[3,2,1-kl]phenothiazines bearing hydrogen, thioether or dimethylaminomethyl substituents at the 2-position to the respective hydrocarbons. In the corresponding 2-carbethoxy derivative (a β-ketoester), the ester group is reduced to a hydroxymethyl or methyl function depending on the amount of reagent and its mode of generation. Reductions with borane in tetrahydrofuran afford mixtures of the corresponding hydrocarbons, alcohols and occasionally alkenes in varying amounts depending on the nature of the 2-substituent.

In our projected study of conformationally restricted phenothiazine tranquilizers[2-4] the reduction of some tetracyclic ketone derivatives to the corresponding hydrocarbons was necessary. This report describes the results of some of these reductions. A variety of methods are available for conversion of ketones and aldehydes to hydrocarbons such as, Wolf-Kishner and Clemmensen reductions, or via sodium borohydride reduction of tosylate or mesylate of the respective alcohol.[5-7] However, these methods did not prove to be suitable for the phenothiazine derivatives in question, particularly those that are sensitive to acidic conditions. We, therefore, turned to the use of metal hydride reducing agents.

By analogy to the complete conversion of activated aromatic aldehydes and ketones to respective hydrocarbons observed with lithium aluminum hydride in ether,[8-10] one might expect a similar result with the similarly electron rich 1,2-dihydro-3-keto-3H-pyrido[3,2,1-kl]phenothiazine system (1). Contrary to this expectation, however, reduction of 1 stops at the alochol (3a) stage.[11,12] Borane in tetrahydrofuran[13] cleanly effects reductions of 1a to 2a and 1e to 2e. However, reduction of the 2,2-dithiophenyl ketone (1c)[14] with borane gave only partial reduction



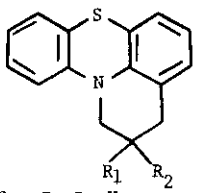
1a; $R_1=R_2=H$

b; $R_1=H$, $R_2=SC_6H_5$

c; $R_1=R_2=SC_6H_5$

d; $R_1=H$, $R_2=COOEt$

e; $R_1=H$, $R_2=CH_2N(CH_3)_2$



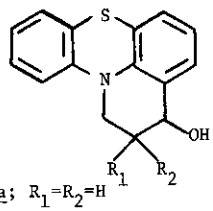
2a; $R_1=R_2=H$

b; $R_1=H$, $R_2=SC_6H_5$

c; $R_1=R_2=SC_6H_5$

d; $R_1=H$, $R_2=CH_2OH$

e; $R_1=H$, $R_2=CH_2N(CH_3)_2$



3a; $R_1=R_2=H$

b; $R_1=H$, $R_2=SC_6H_5$

c; $R_1=R_2=SC_6H_5$

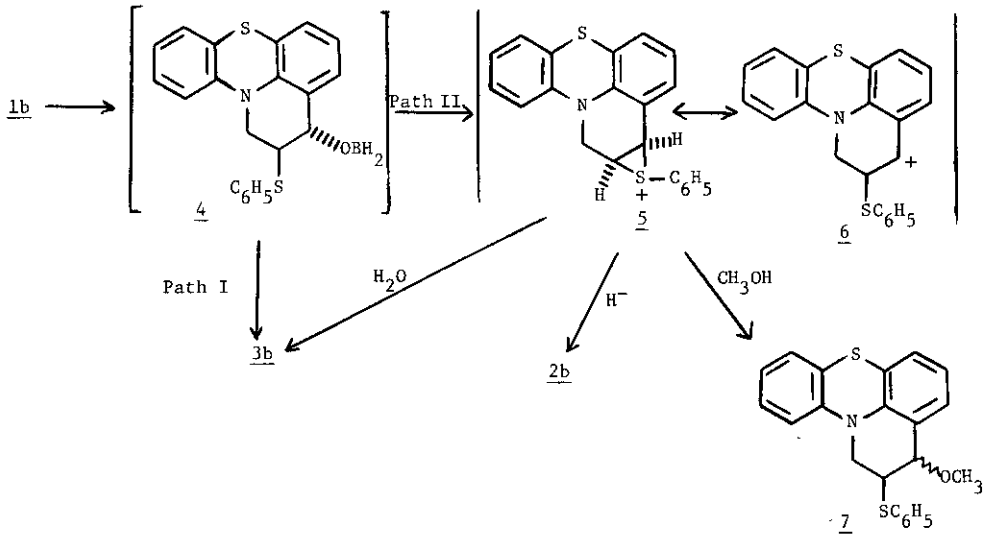
d; $R_1=H$, $R_2=CH_2OH$

e; $R_1=H$, $R_2=CH_2N(CH_3)_2$

to the corresponding alcohol 3c, with only trace amounts of hydrocarbon 2c and an alkene (detected in ir spectrum of the crude sample) being formed.

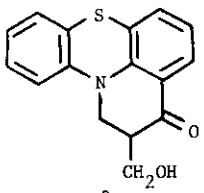
The reaction of 1,2-dihydro-2-thiophenyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (1b)[14] with borane in tetrahydrofuran gave 1,2-dihydro-2-thiophenyl-3-hydroxy-3H-pyrido[3,2,1-kl]phenothiazine (3b) as a major product and 1,2-dihydro-2-thiophenyl-3-methoxy-3H-pyrido[3,2,1-kl]phenothiazine (7) and 2b as the minor ones, after the borane complex (4) was decomposed with methanol during work up of the reaction.

Scheme 1



A likely mechanistic pathway, which accounts for the formation of products 2b, 3b and 7 is depicted in Scheme 1. Decomposition of the intermediate complex 4 along path II might be favored due to facile neighboring group participation of thiophenyl group leading to stabilized cationic species 5 or 6. Attack of the appropriate nucleophile (water, hydride ion or methanol) at the more electrophilic benzylic position of 5 (or 6) then forms 2b, 3b or 7. Additional support for the neighboring group participation mechanism in the reduction of 1b comes from the fact that side products analogous to 3b and 7 are not formed in the reduction of 1a. The methoxy derivative analogous to 7 from 1c was also formed in a very small amount (~1% by nmr), but was not isolated. Product 2b may also come from 4 due to hydride transfer to, and concurrent elimination of oxyborane moiety from, the benzylic position. The product 3b may also be generated along path I by an attack of methanol at the boron atom in the complex 4 followed by cleavage of O-B bond. The structure of 3b was confirmed by comparison of its spectral properties with those of the authentic specimen synthesized unambiguously by reduction of the ketone 1b with sodium borohydride.[14]

We proposed to obtain 1,2-dihydro-2-hydroxymethyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (8), an important intermediate in our further synthetic work, from its suitable precursor, 1,2-dihydro-2-carbethoxy-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (1d).[15] Thus, the reduction of 1d with ten fold excess of aluminum hydride (alane)[16] in ether at room temperature afforded a mixture of



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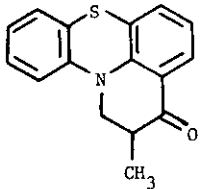

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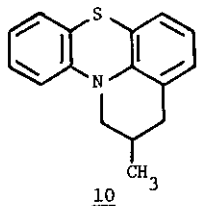

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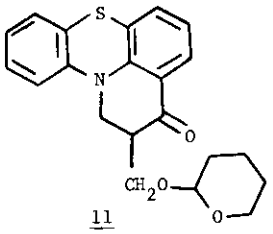
products 3d, 9 and 10, which were separated by preparative TLC. The spectral data for 3d, 9 and 10 are in conformity with the proposed structures. Under these conditions the desired product 8 was not formed at all, which apparently requires controlled reduction of the ketone 1d. This was achieved by treatment of the ketone 1d with stoichiometric amount of alane, prepared by reacting lithium aluminum hydride with 100% sulfuric acid,[17] which afforded the desired compound 8 in ~50% yield (nmr). Our results could be rationalized on the basis of those of Yoon and Brown[17] who reported similar results from the reduction of 2-carbethoxycyclopentanone with 30% excess alane[16] in tetrahydrofuran. The hydroxy ketone 8 was isolated as a diastereomeric mixture of tetrahydropyranyl ethers (11) because of its susceptibility to dehydration to 1,2-dihydro-2-methylenyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (12). The reduction of the β-ketoester (1d) with borane in tetrahydrofuran, as expected, gave a mixture of the products 2d, 3d, 13 and 14 which were characterized by their molecular ions present in the mass spectrum and strong OH,



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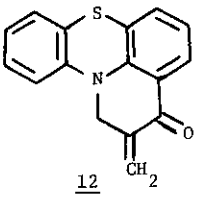

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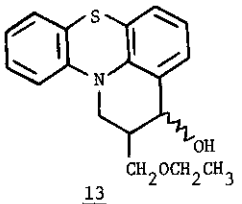

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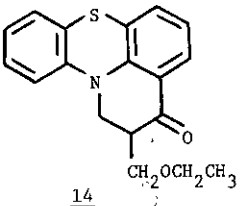

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ether linkage and C=O absorption bands in the ir spectrum of the crude sample. No attempt was made, however, to separate the individual components.

The reduction of 1,2-dihydro-2-dimethylaminomethyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (1e)[18] with alane in ether[16] gave a mixture of 2e (major product) and 3e (minor product). However, 2e was exclusively obtained[4] (85% yield) by reduction of 1e with borane in tetrahydrofuran.

Alane in ether[16] cleanly reduced the ketones 1a, 1b and 1c to the corresponding hydrocarbon products[19] 2a, 2b and 2c in 51-87% yields.

EXPERIMENTAL[20]

General procedure for reduction with diborane in tetrahydrofuran. 1,2-Dihydro-3H-pyrido[3,2,1-kl]phenothiazine (2a).

A 100 ml capacity three-necked round bottom flask fitted with rubber septa and a reflux condenser with gas outlet attached to a mineral oil bubbler was assembled in an oil bath on a magnetic stirrer. After purging the system with argon gas, the flask was charged with 0.11 g (0.003 mole) of sodium borohydride powder and 50 ml of freshly distilled dry tetrahydrofuran. Following the magnetic stirring, a solution of 0.42 g (0.37 ml, 0.003 mole) of borontrifluoride etherate in 10 ml of dry tetrahydrofuran was added slowly to the reaction mixture via syringe during a period of 5-10 min. About 15 min later a solution of 0.25 g (0.001 mole) of 1,2-dihydro-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (1a) was injected slowly via syringe. The time required for decolorization of yellow reaction mixture varied from 30 min to 6 h soon after the heating was started. After 16 h the reaction flask was cooled down to room temperature, placed in an ice-bath and excess diborane was decomposed with methanol. The solvent was removed on

rotary evaporator, the residue was extracted with methylene chloride (100 ml), washed with brine solution (2x100 ml), and dried (Na_2SO_4). The filtration and evaporation of solvent afforded 0.16 g (67%) of the product 2a as a light brown thick liquid which solidified on triturating with pentane. M.p. 55-56°C (lit.[21] m.p. 55-56°C). Mass spec. m/e (relative intensity)[1] 239 (M^+, 100), 238(49.5), 237(4.6), 236(10.7), 224(34), 223(25.5), 211(8.34), 210(33.3), 206(52.3), 205(19.4), 204(31.2), 167(11.7).

General procedure for reduction with alane in ether. 1,2-Dihydro-3H-pyrido[3,2,1-kl]phenothiazine (2a).

The procedure followed was essentially that of Nystrom and Berger.[16] A dry 250 ml capacity three-necked round bottom flask fitted with rubber septa and an efficient reflux condenser with gas outlet attached to a mineral oil bubbler was assembled on a magnetic stirrer. After purging the system with argon gas, the flask was charged with 0.84 g (0.022 mole) of lithium aluminum hydride and 50 ml of anhydrous ether. Following the magnetic stirring, a solution of 2.9 g (0.022 mole) of anhydrous granular aluminum chloride in 50 ml of anhydrous ether was added dropwise via syringe to the reaction mixture. A little grey material precipitated and supernatant ethereal solution become colorless. About 5-10 min later, a solution of 0.5 g (0.002 mole) of 1,2-dihydro-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (1a) in 30 ml of anhydrous ether was added via syringe at such a rate as to cause a gentle reflux. Almost instantly the yellow color of the ketone disappeared. About 3 h later, TLC (CH_2Cl_2:Pet ether, 1:1) showed a single homogeneous clean spot of the desired product (2a). The reaction flask was cooled in an ice-bath and excess reagent was decomposed by slow addition of 10 ml of ice-cold water followed by treatment with 12 ml of 6N H_2SO_4 solution. The pale yellow ethereal layer was separated. The aqueous gray muddy material was extracted with ether (2x30 ml). The combined ethereal solution was washed with brine solution (2x100 ml), dried (Na_2SO_4), filtered and ether was removed from the filtrate which afforded 0.41 g (87%) yield of light brown thick liquid of almost analytically pure product (2a). This material had identical properties with the one obtained by reduction with diborane and was much cleaner than obtained by the former process. For less soluble ketones the Soxhlet technique is preferred.

1,2-Dihydro-2-hydroxymethyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (8). The procedure followed was that of Yoon and Brown.[17] To a slurry of lithium aluminum hydride (0.362 g of 95% purity, 0.0091 mole) in 10 ml of dry tetrahydrofuran, 100% sulfuric acid (0.24 ml, 0.0045 mole) was added dropwise at 0°C. When the addition was complete, the reaction mixture was stirred for an additional 1 h and then allowed to stand overnight to settle the lithium sulfate precipitate. This solution was found to be 0.87 M. To this aluminum hydride slurry, a solution of β-keto-ester 1d (0.50 g, 0.00154 mole) in 5 ml of dry tetrahydrofuran was added dropwise at 0-5°C with

stirring under nitrogen. The stirring was continued for about 50 min, maintaining the bath temperature at 5°C. The excess aluminum hydride was decomposed by dropwise addition of tetrahydrofuran-water (1:1) and the reaction mixture was filtered. The inorganic precipitate was thoroughly washed with tetrahydrofuran and saturated sodium chloride solution was added to the filtrate. The tetrahydrofuran layer was separated and the solvent was evaporated to leave an oil which was chromatographed on silica gel with chloroform elution to give 0.20 g (48%) of slightly impure α-hydroxymethyl ketone (8) as yellow viscous material. IR (neat, cm^{-1}) 3600-3200 (broad and strong OH absorption), 3060, 2995, 2930, 2860, 1770 (C=O), 1595, 1545, 1480-1420 (multiplet), 1350, 1330, 1305, 1270, 1220, 1175, 1100, 1040, 940, 785, 735 and 655. Nmr (δ) 7.70-6.68 (m, 7H, aromatic), 4.45-2.80 (m, 5H, NCH_2, OCH_2 and one methine proton), 2.50 (broad hump, 1H, OH, exchangeable with D_2O).

1,2-Dihydro-2-(2-tetrahydropyranyloxy)methyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (11). To a solution of α-hydroxymethyl ketone 8 (0.150 g, 0.00053 mole) and dihydropyran (0.2 ml, 0.002 mole) in 10 ml of dry methylene chloride (distilled from phosphorus pentoxide) pyridinium p-toluene sulfonate (0.025 g, 0.00009 mole) was added and the contents were stirred under nitrogen for 8 h at room temperature. Half saturated sodium chloride solution (10 ml) was added, the methylene chloride layer was separated, dried over anhydrous sodium sulfate and the solvent was evaporated. The oily material obtained was chromatographed on silica gel, eluting with benzene-chloroform (9:1) to give 0.150 g (77%) of tetrahydropyranyl ether 11 which should be a mixture of diastereomers. Yellow viscous material. IR (neat, cm^{-1}) 3060, 3000, 2930, 2850, 1660, 1590, 1480-1420 (multiplet), 1375-1345 (multiplet), 1260, 1215, 1120, 1050, 1020, 955, 890, 855, 800, 780, 735 and 650. Nmr (δ) 7.68-6.53 (m, 7H, aromatic), 4.70-2.72 (m, 8H, NCH_2, $2XOCH_2$ and two methine protons), 1.48 (broad singlet, 6H, alicyclic methylene groups). Mass spec. m/e (relative intensity) 367 (M^+, 32), 265(45.9), 252(39), 251(6), 236(16.5), 225(2.9), 204(6), 196(11.8), 183(6), 167(8), 149(14.7), 85(100).

1,2-Dihydro-2-methylenyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (12). Orange-red viscous material. IR (cm^{-1}) 3060, 2920, 2850, 1668, 1615, 1585, 1545, 1475, 1420, 1345, 1270, 1215, 1090, 1060, 1040, 1010, 935 and 730. Nmr (δ) 8.00-6.80 (m, 7H, aromatic), 6.25 (br s, 2H, olefinic), 4.72 (s, 2H, NCH_2).

1,2-Dihydro-2-thiophenyl-3H-pyrido[3,2,1-kl]phenothiazine (2b). M.p. 158-159°C. Yield 7% with borane in tetrahydrofuran and 64% with alane in ether. IR (cm^{-1}) 3050, 2940, 2850, 1575, 1480, 1435, 1375, 1330, 1315, 1255, 1240, 1180, 1100, 1040, 730 and 670. Nmr (δ) 8.00-6.65 (m, 12H, aromatic), 4.20-3.30 (m, 3H, NCH_2 & SCH), 3.10-2.90 (m, 2H, benzylic CH_2). Mass spec m/e (relative intensity)[1] 347 (M^+, 52), 238(9), 237(8), 236(14), 224(100), 223(24), 204(12). Elemental analysis for $C_{21}H_{17}NS_2$: Calcd. C, 72.58; H, 4.93; N, 4.03. Found: C, 72.86; H, 4.92; N, 4.01.

1,2-Dihydro-2,2-dithiophenyl-3H-pyrido[3,2,1-kl]phenothiazine (2c). M.p. 184-185°C. Yield: 1.0% with borane in tetrahydrofuran and 74.6% with alane in ether. IR (cm^{-1}) 3050, 2860, 1592, 1568, 1478, 1432, 1418, 1378, 1300, 1250, 1235, 1202, 1180, 1135, 1090, 1060, 1035, 1010, 945, 910, 795, 760, 735 and 675. Nmr (δ) 8.20-6.00 (m, 17H, aromatic), 3.70 (s, 2H, NCH_2), 2.79 (s, 2H, benzylic CH_2). Mass spec. m/e (relative intensity)[1]: 455 (M^+, 46.6), 345(13.5), 237 (100), 236(79.5), 204(10.5). Elemental analysis for $C_{27}H_{21}NS_3$: Calcd. C, 71.17; H, 4.65; N, 3.08. Found: C, 71.11; H, 4.56; N, 3.37.

1,2-Dihydro-2-hydroxymethyl-3H-pyrido[3,2,1-kl]phenothiazine (2d). The product was present with other products 3d, 13 and 14 obtained by reduction of 1d with borane in tetrahydrofuran. M^+=269.

1,2-Dihydro-3-hydroxy-3H-pyrido[3,2,1-kl]phenothiazine (3a). M.p. 124-125°C. (lit[21] m.p. 124-125°C). Mass spec. m/e (relative intensity)[1]: 255(M^+, 100), 236(12), 227(5.5).

1,2-Dihydro-2-thiophenyl-3-hydroxy-3H-pyrido[3,2,1-kl]phenothiazine (3b). M.p. 100-130°C (mixture of threo- and erythro- diastereomers). Yield 68% isolated from the reduction of 1b with borane in tetrahydrofuran. Mass spec. m/e (relative intensity)[1]: 363(M^+, 50), 240(100), 236(29), 227(2), 224(13), 223(16), 212(28), 204(13), 162(18). Elemental analysis for $C_{21}H_{17}NOS_2$: Calcd. C, 69.39; H, 4.71; N, 3.85. Found: C, 69.17; H, 4.87; N, 3.86.

1,2-Dihydro-2,2-dithiophenyl-3-hydroxy-3H-pyrido[3,2,1-kl]phenothiazine (3c). M.p. 169-170°C. Yield: 62% with borane in tetrahydrofuran and 73% with alane in ether at 0°C. IR (cm^{-1}) 3540 (broad, OH) 3050, 2860, 1600, 1570, 1485, 1435, 1380, 1312, 1225, 1175, 1142, 1090, 1060, 1045, 1020, 915, 815, 770, 740, 730 and 685. Nmr (δ) 8.20-6.00 (m, 17H, aromatic), 4.65 (broad singlet which sharpens after D_2O exchange, 1H, benzylic methine), 3.70-2.90 (m, 3H, NCH_2 and OH, one proton exchangeable with D_2O). Mass spec. m/e (relative intensity)[1]: 471(M^+, 70), 345(11), 344(17), 253(100), 252(49.5), 236(47), 227(6), 225(18), 224(77), 223(26), 110(44.5), 109(27), 77(13), 66(16), 65(15.5). Elemental analysis for $C_{27}H_{21}NOS_3$: Calcd. C, 68.79; H, 4.49; N, 2.97. Found: C, 68.71; H, 4.66; N, 2.80.

1,2-Dihydro-2-hydroxymethyl-3-hydroxy-3H-pyrido[3,2,1-kl]phenothiazine (3d). Pale yellow amorphous solid, isolated from the reduction of 1d with alane in 33% yield. M.p. 152-153°C. Also detected in reduction mixture of 1d with borane in tetrahydrofuran. IR (cm^{-1}) 3600-3100 (broad and strong OH absorption), 3050, 2960-2820 (broad), 890 and 720. Nmr (δ) 7.35-6.40 (m, 7H, aromatic), 4.38 (m, 2H, NCH_2), 4.0-3,0 (m, 4H, one CH_2 and two methine), 2.15 (broad hump, 1H, OH, exchangeable with D_2O), 1.0 (broad hump, 1H, OH, exchangeable with D_2O). Mass spec. m/e (relative intensity)[1]: 285(M^+, 100), 236(70), 227(23.6), 204(16), 199(18), 198(12.7), 167(19.6).

1,2-Dihydro-2-dimethylaminomethyl-3-hydroxy-3H-pyrido[3,2,1-kl]phenothiazine (3e). Light brown viscous material. Mass spec. m/e (relative intensity): 312(M^+, 5), 266(10), 251(24), 236(45),

204(18), 58(100).

1,2-Dihydro-2-thiophenyl-3-methoxy-3H-pyrido[3,2,1-kl]phenothiazine (7). Brown gummy material. Yield: 1% from reduction of 1b with borane in tetrahydrofuran. IR (cm^{-1}) 3065, 2990, 2930, 2880, 2825, 1600, 1580, 1480, 1460, 1440, 1380, 1332, 1315, 1295, 1265, 1240, 1215, 1180, 1120, 1100, 1072, 960, 870, 810, 780, 735 and 685. Nmr (δ) 7.68-6.50 (m, 12H, aromatic), 4.35 (m, 1H, methine), 3.80 (m, 1H, methine), 3.40-3.45 (5H, NCH_2 and OCH_3 appear as two singlets). Mass spec. m/e (relative intensity)[1]: 377 (M^+, 100), 254(23.7).

1,2-Dihydro-2-methyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (9). Dark yellow viscous material isolated from reduction of 1d with alane in 6% yield. IR (cm^{-1}) 3060, 2960, 2920, 2840, 1680, 1590, 1475, 1450, 1440, 1425, 1380, 1265, 1245, 1215, 1130, and 730. Nmr (δ) 7.88-6.52 (m, 7H, aromatic) 4.75-2.50 (m, 3H, NCH_2 and one methine), 1.35 (d, J=6.6 Hz, 3H, CH_3). Mass spec. m/e (relative intensity)[1]: 267(M^+, 100), 225(12.6), 211(10.9), 197(36), 69(28).

1,2-Dihydro-2-methyl-3H-pyrido[3,2,1-kl]phenothiazine (10). Light brown viscous liquid isolated from the reduction of 1d with alane in 8% yield. IR (cm^{-1}) 3050, 2950, 2920, 2840, 1570, 1555, 1435, 1320, 1295, 1255, 1230, and 730. Nmr (δ) 7.40-6.50 (m, 7H, aromatic), 3.52 (m, 2H, NCH_2), 3.32 (m, 1H, methine), 2.90 (m, 2H, benzylic methylene), 1.23 (distorted d, J-6.5 Hz, 3H, CH_3). Mass spec. m/e (relative intensity)[1]: 253(M^+, 75.8), 252(27), 251(100), 250(56), 236(15.9), 223(14), 218(21.7), 217(10.8), 211(14.7), 204(10), 118(13.6).

1,2-Dihydro-2-ethoxymethyl-3-hydroxy-3H-pyrido[3,2,1-kl]phenothiazine (13). This was present in the sample with other products 2d, 3d and 14 in reduction of 1d with borane in tetrahydrofuran. M^+=313.

1,2-Dihydro-2-ethoxymethyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (14). This was present with other products 2d, 3d, and 13 in the crude sample obtained from the reduction of 1d with borane in tetrahydrofuran. M^+=311. IR 1685 cm^{-1}.

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12. Under these conditions, we isolated 1,2-dihydro-3-hydroxy-3H-pyrido[3,2,1-kl]phenothiazine (3a) in 90% yield. We also obtained 3a in quantitative yield by reduction of the ketone (1a) with excess sodium borohydride in tetrahydrofuran and methanol (3:1) mixture at 0°C.

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19. Reduction of 1,2-dihydro- 2,2-dithiophenyl-3-keto-3H-pyrido[3,2,1-kl]phenothiazine (1c) with alane in ether at 0°C afforded 73% yield of the alcohol product 3c. Only trace amount of the hydrocarbon product 2c was formed. In a separate experiment, alane in ether or tetrahydrofuran could convert 3c to 2c to the extent of ~50% even at reflux temperature.

20. Melting points were taken on Electrothermal apparatus and are uncorrected. The ir spectra were recorded on Beckman IR-33 instrument in potassium bromide pellets unless otherwise specified. The nmr spectra were recorded in deuteriochloroform on a Varian EM-360 instrument using tetramethylsilane as the internal standard. The elemental analyses were performed by the Analytical Center, Chemistry Department, University of Arizona, Tucson, Arizona, U.S.A. The mass spectra were recorded on Varian MAT 311 mass spectrometer at 70 eV. The products were separated on silica gel column by gradient elution technique or on preparative TLC plates by developing with a mixture of petroleum ether (30-60°C) and methylene chloride in appropriate ratio.

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ACKNOWLEDGEMENTS

We thank the National Institute of Mental Health for Support in the form of Research Grant MH31184. We are also grateful to Mr. Peter F. Baker for recording the mass spectra.

Received, 22nd January, 1982