Hydro-1,3-ethanoindeno[2,1-*c*]pyridines

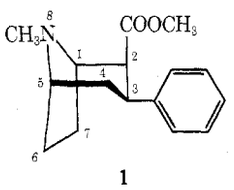
Sol J. Daum, Anthony J. Gambino, and Robert L. Clarke*

Sterling-Winthrop Research Institute, Rensselaer, New York 12144

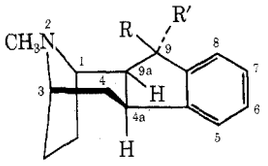
Received March 22, 1974

Methyl 3β-phenyl-1α*H*,5α*H*-tropane-2β-carboxylate (1) has been cyclized by polyphosphoric acid to form 1,2,3,4,4a,9a-hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridin-9-one (**2a**). Conversions of this 9-one to the corresponding 9-ols, 9-CH_2, and some unsaturated products are described. Absolute configurations are assigned to all products.

In the course of our studies on the biological properties of rigid phenylalkylamines we prepared a series of tropanes carrying an aromatic ring at C-3 and a carboalkoxyl group at C-2.[1] These compounds are exemplified by structure **1**. Reactions of such compounds with polyphosphoric acid (PPA) gives rise to an even more restricted ring system typified by structure **2a.** The chemistry of these 1,3-ethanoindeno[2,1-*c*]pyridines is the subject of this paper.



1



2a, RR′ = O

b, RR′ = 

c, R = R′ = H

d, R = OH; R′ = H

e, R = OAc; R′ = H

f, R = H; R′ = OH

Treatment of tropane ester **1** (cocaine configuration) or its C-2 equatorial epimer[2] with PPA at 150° for 5 hr produced ketone **2a** (76%). Formation of a bisulfite addition complex facilitated separation of the product from 8% of unchanged starting material.

The thermodynamically more stable form of **2a** is that in which the cyclopentanone ring is fused to the tropane moiety in a cis manner. Nmr coupling constants for **2a** substantiated that the compound at hand had this structure.[3] The 4a hydrogen of **2a** originated as a nonepimerizable, α-oriented hydrogen in the starting material **1** and thus controlled which cis isomer was obtained.

It has been observed[1,4] that axial substituents at C-2 in a tropane ring system prevent or significantly inhibit quaternization of the nitrogen atom. In accord with predictions in the present system, the axial carbonyl group at C-9a prevented quaternization with EtI at room temperature (1 hr).

The carboxylic acid corresponding to structure **1**[1] also could be cyclized with PPA to give **2a** (75%). Its 2α epimer[1] gave **2a** in 57% yield. However, ring closure utilizing HF, H_2SO_4 (dioxane), PPA (dioxane), or PPA in hexamethylphosphoramide was not successful.

Since the absolute configuration of tropane ester **1** was known,[1] the configuration of **2a** could be assigned. Chemical and spectral data below then allowed absolute configurational assignments to the other products described here.

Conversion of ketone **2a** to thioketal **2b** followed by desulfurization with Raney nickel afforded the 9-methylene derivative **2c.** Failure of the product to quaternize with EtI indicated that the C-9 methylene was still in an axial configuration with respect to the tropane moiety.

Reduction of ketone **2a** with $NaBH_4$ produced an epimeric mixture of alcohols. The 9β-ol **2d** was readily recognized in that its ir spectrum demonstrated intramolecular hydrogen bonding (3200 cm^{-1}). This value is rather low but is close to that found (3231 cm^{-1}) for a similar case of intramolecular N···H–O bonding in 3β-phenyl-1α*H*,5α*H*-tropane-2β-methanol.[1] Incidentally, the acetate ester **2e** of alcohol **2d** was prepared.

The ir spectrum of a 0.001 *M* solution of 9α-ol **2f** in CCl_4 showed hydroxyl stretching bands at 3644 (nonbonded) and 3604 cm^{-1} (H π bonded). Benzyl alcohol shows similar ir bands at 3632 and 3615 cm^{-1}.[5]

Reduction of ketone **2a** by adding it to borane in THF resulted in formation of the 9-methylene derivative **2c** in 40% yield along with 9β-ol **2d** (54%) and 9α-ol **2f** (3%). Inverse addition in this reaction raised the yield of 9-methylene compound to 73% and lowered the yield of 9β-ol **2d** to 23%. No 9α-ol was isolated.

There was indication that a mixture of 9α- and 9β-ols was initially formed and that the 9α-ol was transformed to 9-CH_2 more rapidly than was the 9β-ol. Thus, treatment of a mixture of equal parts of 9α- and 9β-ols with borane gave two parts of 9-CH_2 product and one part of 9β-ol with no 9α-ol remaining.

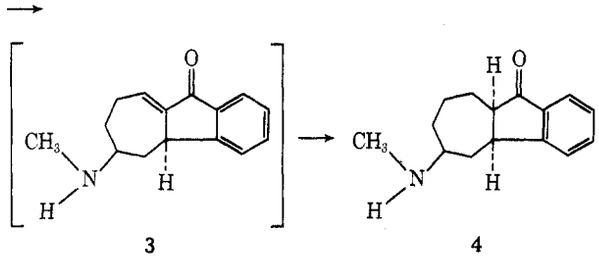
These observations afford a plausible explanation for the formation of considerably more 9-CH_2 compound **2c** by the *inverse* addition described above. In the initial experiment where the amino ketone was added to the borane, the high relative concentration of the latter produced complexing with the nitrogen[6] and effective blocking of the β face of the ketone. Considerable α-attack then occurred to give 9β-ol **2d,** the epimer which was reduced further only slowly. In the inverse addition, the borane added found less amino ketone in complexed form and was able to attack from the β face to form more 9α-ol **2f,** the epimer which was easily reduced further.

A methoxyl group on either C-6 or C-8 of ketone **2a** dramatically affected the reduction reaction with borane. It considerably activated the benzylic position with the result that the hydroxyl groups of both intermediates were completely cleaved and only the 9-methylene product was isolated. The details of these reactions are reported in a related, biologically oriented paper.[7]

Reduction of aromatic ketones such as xanthone and thioxanthone to the corresponding methylene derivatives has been accomplished by BH_3-THF at 0°.[8] In the present work with mixed aliphatic–aromatic ketones a reflux temperature was necessary for good yields of the methylene derivatives. The mechanism of the reaction was not determined.

Hitherto, all reductions discussed have been chemical in nature. Reduction with Adams catalyst in EtOH afforded a simple mixture (two tlc spots) of 9β-ol **2d** (25%) and 9α-ol **2f** (49%).[9] Although the 9β-ol is a benzylic alcohol, it was not hydrogenolyzed by either Pt or Pd in EtOH in the presence of $HClO_4$. This reaction was not checked with the 9α-ol.

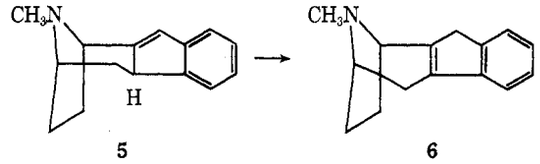
Reduction of ketone **2a** in the form of the free base or its HCl salt with 10% Pd/C in EtOH gave a surprising result. Apparently β-elimination of the amino group occurred followed by hydrogenation of the resulting unsaturated ketone as shown. Ketone **4** (44%) was the only product isolat-



3 4

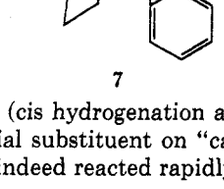
ed but some more-polar products observed by tlc indicated that further reduction occurred.

Dehydration of alcohol **2d** (9β-ol) with $POCl_3$ apparently produced only $\Delta^{9(9a)}$ olefin **5** because immediate hydrogenation of the crude product with Pd/C furnished essentially only the cis–syn compound **2c** (aromatic ring on the same side as the nitrogen). A model shows that the 9–9a double bond is directed toward the β face and that hydrogenation should be expected from the α side. Attempted isolation of this $\Delta^{9(9a)}$ olefin (exposure to NH_4OH) resulted in partial isomerization to $\Delta^{4a(9a)}$ olefin **6** (~7:3 ratio of **5**:**6**). This ratio was little affected by tosyl acid in refluxing



5 6

ethanol, but $NaOCH_3$ in CH_3OH caused complete isomerization to **6**.[10] Hydrogenation of this olefin with Pd/C produced cis–anti indenopyridine **7**, resulting from β-side at-



7

tack by hydrogen (cis hydrogenation assumed). This compound had no axial substituent on "carbon-2" of the tropane moiety and indeed reacted rapidly with EtI to form a quaternary salt.

Chemical reduction (Na–NH_3) of the 70:30 mixture of isomers **5** and **6** produced only the two cis compounds **2c** (38%) and **7** (32%) with no evidence of any trans product; 3% of unreduced material was recovered. Pure olefin **6** was reduced by the same reagent to form only the cis–anti product **7**.

The effect of the double bonds in olefins **5** and **6** on the nmr peak positions of the NCH_3 is worthy of note. The NCH_3 peak in compound **2c** with no styrenic double bond appears at 2.2 ppm. A $\Delta^{4a(9a)}$ double bond (**6**) deshields the methyl group (δ 2.4 ppm). A $\Delta^{9(9a)}$ bond (**5**) has a slight shielding effect (δ 2.1 ppm).

The enantiomers of tropane ester **1** and its 2α epimer were available from earlier work.[1] They were transformed by PPA into the enantiomer of ketone **2a** according to the procedure used for **2a.** Borane (24 hr) reduced this ketone in the expected manner to give the enantiomers of 9β-ol **2d** and 9-methylene compound **2c.** When the reflux time with borane was reduced to 3 hr, some of the enantiomer of 9α-ol **2f** was isolated. Enantiomeric 9-methylene compound **2c** was also formed *via* the thioketal route used for **2c.** As mentioned earlier in this paper, enantiomeric ketone **2a** was reduced by PtO_2–H_2 to form a mixture of 9α- and 9β-ols.

Some final comments are related to other than reductive reactions of ketone **2a.** A tendency toward β-elimination in this β-amino ketone was evidenced in the formation of **4.** Yet this ketone was stable to $NaOCH_3$ in boiling THF for 20 min.

An attempted Wittig reaction failed using trimethyl phosphonoacetate and $NaOCH_3$ in DMF and again in DMSO. Starting ketone was recovered. This ketone also failed to react with trimethylsulfoxonium ylide and did not form an enamine with morpholine.

Ketone **2a** reacted with N_2H_4 to form a complex mixture with at least seven components, probably involving β-elimination. Acrylonitrile also produced a complex mixture and acetic anhydride gave other than a simple enol acetate.

The biological activity of the compounds described here together with a considerable number of analogs is being reported in the *Journal of Medicinal Chemistry.*[7]

Experimental Section[11]

(1*R*,3*S*,4a*S*,9a*S*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridin-9-one (2a). A 1:3 mixture of methyl (1*R*,2*S*,3*S*,5*S*)-3β-phenyl-1α*H*,5α*H*-tropane-2β-carboxylate (**1**) and its 2α epimer, methyl (1*R*,2*R*,3*S*,5*S*)-3β-phenyl-1α*H*,5α*H*-tropane-2α-carboxylate[1] (370 g, 1.42 mol) was warmed to 100° and added all at once to 3.7 kg (11 mol) of PPA at 100° with stirring. This mixture was stirred at 150° for 5 hr and poured onto a large volume of crushed ice. Concentrated NH_4OH (5.4 kg) was added with cooling and the alkaline mixture was extracted with CH_2Cl_2. Concentration of the dried (Na_2SO_4) extracts gave an oily residue which was extracted multiply with a total of 8 l. of pentane. Partial concentration precipitated 136 g of **2a,** mp 75–78°. The mother liquor residue in 500 ml of MeOH was added to a solution of 440 g of $Na_2S_2O_5$ in 2.2 l. of H_2O. Extraction of this solution with 6 × 500 ml of CH_2Cl_2 separated 31 g (8%) of starting material. The aqueous solution together with some bisulfite adduct which had precipitated was treated with 560 g of solid $NaHCO_3$. Water (200 ml) and CH_2Cl_2 (1.1 l.) were added and the mixture was heated under reflux for 5 hr. The CH_2Cl_2 layer yielded a solid residue which was recrystallized from pentane, giving 85.2 g more of **2a,** mp 75–78° (76% based on 1 consumed). The analytical sample melted at 78–79° (pentane): $[\alpha]^{25}D$ +13.4°; ir 1712 cm^{-1}; uv max 245 nm (ϵ 11,600) and 288 (2900); nmr δ 1.30–2.40 (m, 6, CH_2), 2.20 (s, NCH_3), 2.45 (q, C_9 H, $J_{1,9a}$ = 1.8 Hz, $J_{4a,9a}$ = 7.5 Hz), 3.15 (m, C_3 H), 3.52 (q, C_{4a} H), 3.90 (d, C_1 H), 7.20–7.80 ppm (m, 4, aromatic H).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.1; H, 7.6; N, 6.2.

The HCl salt of 2a from CH_3CN showed polymorphism: mp 222–224 and 259° dec (evacuated capillary); $[\alpha]^{25}D$ +39.8°.

Anal. Calcd for $C_{15}H_{17}NO$·HCl: C, 68.30; H, 6.88; Cl, 13.44. Found: C, 68.2; H, 6.9; Cl, 13.6.

Ketone 2a from Tropanecarboxylic acids. Treatment of 3β-phenyltropane-2β-carboxylic acid hydrochloride[1] with PPA at 150° for 5 hr with work-up as above gave a 73% yield of **2a** using preparative tlc (3:97 *i*-$PrNH_2$–Et_2O) for purification. In the same manner the 2α-carboxylic acid[1] gave **2a** in 57% yield.

Nonreaction of Ketone 2a with EtI. A solution of 5 g of **2a** in 150 ml of Et_2O was treated with 3.44 g of EtI at room temperature. After 1 hr there was no evidence of precipitate formation and concentration of the solution *in vacuo* gave only recovered starting material.

(1*R*,3*S*,4a*S*,9a*S*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridine Hydrochloride (2c). A solution of 9.35 g (0.040 mol) of ketone **2a** in 250 ml of HOAc was treated with 20 ml of ethanedithiol and 20 ml of boron trifluoride etherate. The next day the precipitate was separated, Et_2O was added to the filtrate, and more solid was collected. The solid residues were washed with fresh Et_2O and then dissolved in H_2O. Dilute NaOH (2 *N*) was added and the free base was separated with Et_2O. Crystallization from pentane gave 6.7 g (55%) of **(1*R*,3*S*,4a*S*,9a*S*)-9,9-ethylenedithio-1,2,3,4,4a,9a-hexahydro-2-methyl-9*H*-1,3-ethano-**

indeno[2,1-*c*]pyridine (2b): mp 102–103°; uv max 262 nm (ε 3400), 271 (3100), and 280 (2800).

Without further purification this product was dissolved in 350 ml of 95% EtOH and refluxed for 12 hr in the presence of 12 tsp of Raney Ni. Removal of catalyst and solvent gave 3.4 g of crude **2c.** A portion (0.5 g) was chromatographed on silica preparative plates (Et_2O–pentane–*i*-$PrNH_2$, 50:47:3) to give pure, oily **2c:** *m/e* 213; nmr δ 1.0–2.7 (m, 6, CH_2), 2.2 (s, NCH_3), 2.7–3.6 (m, 5, NCH, benzylic H), and 7.0–7.3 ppm (m, 4, Ar); R_f 0.55 (SiO_2, 97:3 Et_2O–*i*-$PrNH_2$).

The remainder of the crude **2c** was converted to the **HCl salt:** 2.4 g; mp 301° dec (from acetone); $[\alpha]^{25}D$ +93.5°; total yield 51% from thioketal.

Anal. Calcd for $C_{15}H_{19}N$·HCl: C, 72.13; H, 8.07; N, 5.61. Found: C, 72.3; H, 8.2; N, 5.9.

$NaBH_4$ Reduction of (1*R*,3*S*,4a*S*,9a*S*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridin-9-one (2a). A solution of 3.13 g (13 mmol) of **2a** in 50 ml of EtOH was treated with 1.5 g (40 mmol) of $NaBH_4$ in 5 ml of H_2O. After 72 hr at room temperature the cooled solution was treated with acetone. More H_2O and Et_2O were added. The Et_2O layer was dried (Na_2SO_4) and concentrated to afford a crude mixture of alcohols **2d** and **2f.** Plate chromatography (3:97 *i*-$PrNH_2$–Et_2O, 11 plates, two solvent passes) gave 1.8 g of a more polar alcohol (**2f**), 57%, mp 98–100°, ir (CCl_4, 0.05–0.001 *M*) 3644 and 3604 cm^{-1}, and 0.25 g of a less polar alcohol (**2d**), 8%, mp 140–142°, ir (CCl_4, 0.05–0.001 *M*) 3200 cm^{-1}.

The HCl salt of 2f (acetonitrile) melted at 285–287° dec, $[\alpha]^{25}D$ + 62.9°.

Anal. Calcd for $C_{15}H_{19}NO$·HCl: C, 67.79; H, 7.59; Cl, 13.34. Found: C, 68.0; H, 7.7; Cl, 13.3.

The HCl salt of 2d melted at 230–231° dec (acetone), $[\alpha]^{25}D$ +74.1°.

Anal. Calcd for $C_{15}H_{19}NO$·HCl: C, 67.79; H, 7.59; Cl, 13.34. Found: C, 67.5; H, 7.6; Cl, 13.6.

(1*R*,3*S*,4a*S*,9*R*,9a*S*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridin-9-ol Acetate (2e). Alcohol **2d** (10 g, 41 mmol) was treated with 50 ml of pyridine and 40 ml of Ac_2O for 24 hr at room temperature and the product was isolated in the usual manner. Its crude methanesulfonate salt (9.48 g, 89%) melted at 202–205°. Recrystallization from acetone gave mp 214–215°; $[\alpha]^{25}D$ +197°; ir (KBr) 1740 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}NO_2$·CH_3SO_3H: C, 58.84; H, 6.86; S, 8.73. Found: C, 58.8; H, 6.9; S, 8.5.

Borane Reduction of 2a. A solution of 80 g (0.38 mol) of **2a** in 1.0 l. of THF was added in 1.5 hr to 1.8 l. of 1 *M* BH_3 in THF with stirring under N_2 and cooling by ice. The solution was heated under reflux for 24 hr. After standing at room temperature for 66 hr, 160 ml of H_2O was added dropwise followed by 800 ml of 2 *N* NaOH. Most of the THF was boiled away over a 2.5-hr period. Et_2O was added and the layers were separated. The Et_2O solution was dried (Na_2SO_4) and concentrated to afford 89.4 g of an oily residue that partially crystallized from pentane. The solid was digested with Et_2O to afford 37.3 g of 9β-ol **2d,** mp 138–140°. The combined mother liquors were distilled at 1 mm. The fraction boiling at 116–126° (29.9 g, 40%) was almost pure **2c,** $n^{28}D$ 1.5562. The pot residue crystallized and afforded another 2.4 g of **2d,** mp 139–142° (54% yield). The mother liquor obtained from this solid (5.1 g) appeared to be a 1:1 mixture of α-alcohol **2f** (3% yield) and β-alcohol **2d** by tlc analysis.

Borane Reduction of 2a by Inverse Addition. A solution of 1850 ml of 1 *M* BH_3 in THF was added over 0.5 hr to 80 g (0.38 mol) of **2a** in 940 ml of THF with stirring under N_2 at room temperature. The solution was then heated under reflux for 24 hr. After standing at room temperature for another 66 hr, it was worked up as in the preceding experiment, affording 93.1 g of oily residue. Distillation at 0.7 mm and collection of the fraction that boiled at 110–123° gave 54.9 g (73%) of almost pure **2c.** A fraction that boiled at 123–140° solidified, giving 11.7 g of **2d,** mp 140–142°. The pot residue afforded another 6.9 g of **2d** (from Et_2O), mp 138–140° (23%).

Borane Reduction of a Mixture of α-Alcohol 2f and β-Alcohol 2d. A solution of 9.6 g of mother liquor from an experiment like the above containing an equal mixture of **2d** and **2f** in 160 ml of THF was added to 250 ml of 1 *M* BH_3 in THF at ice-bath temperature. After 18-hr reflux and work-up as above the crude product showed only two components (**2c** and **2d**) by tlc. Distillation gave 3.6 g of **2c,** bp 115–130° (0.7 mm). The pot residue crystallized and afforded 1.8 g of β-alcohol **2d,** mp 138–140°.

(4b*R*,6*S*,9a*R*)-5,6,7,8,9,9a-Hexahydro-6-(methylamino)-benz[*a*]azulen-10(4b*H*)-one (4). A solution of 3.35 g (0.013 mol) of **2a** HCl salt in 300 ml of 95% EtOH was hydrogenated at 3.5 kg/cm^2 in the presence of 0.3 g of 10% Pd/C. Absorption of 1 mol of H_2 required 2 hr. Removal of the catalyst and solvent afforded 3.4 g of a mixture of HCl salts. Liberation of the free bases with 2 *N* NaOH and extraction with Et_2O gave 3.0 g of a mixture which was chromatographed on 12 preparative plates using 3:97 *i*-$PrNH_2$–Et_2O and six solvent passes. A less polar band afforded 1.3 g (44%) of **4.** A mixture of more polar compounds (0.63 g) was poorly resolved and was not investigated further. Amino ketone **4** formed massive prisms: mp 76–78° (Et_2O–acetone); ir (CCl_4) 3423 cm^{-1}; ir (KBr) 1700 cm^{-1}; nmr δ 1.0–2.4 (m, 9 H, CH_2 and NH), 2.4–3.0 (d, 3 H, NCH_3; m, 1 H, CHN; m, 1 H, ArC**H**), 4.6 (m, 1 H, >CHC=O), and 7.0–8.0 ppm (m, 4 H, aromatic); *m/e* 229.

The HCl salt of 4 melted at 262–264° dec (CH_3CN), $[\alpha]^{25}D$ −22.1°.

Anal. Calcd for $C_{15}H_{19}NO$·HCl: C, 67.79; H, 7.59; Cl, 13.34. Found: C, 67.8; H, 7.7; Cl, 13.5.

Similar results were obtained when the free base was reduced with 10% palladium on carbon in EtOH.

Catalytic Hydrogenation of the Kinetic Dehydration Product of 2d. A solution of 9.7 g (0.042 mol) of 9β-hydroxy compound **2d** in 60 ml of $POCl_3$ was heated under reflux for 3 hr. The excess reagent was removed by warming *in vacuo.* The residue was dissolved in 300 ml of EtOH and hydrogenated at 3.5 kg/cm^2 in the presence of 0.5 g of 10% Pd/C. When the theoretical amount of H_2 had been absorbed the catalyst and solvent were removed and the residue was treated with NH_4OH and Et_2O. Concentration of the Et_2O layer afforded 8.9 g of crude cis–syn amine **2c** which appeared almost entirely as a single tlc spot of R_f 0.55 (silica, 3:97 *i*-$PrNH_2$–Et_2O). Conversion to the HCl salt and recrystallization from acetone afforded 7.5 g (72%) of **2c,** mp 295–297° dec. Glpc of the base from the mother liquors showed 45% of **2c** (retention time 63 min) and six minor peaks, none of which corresponded to the cis–anti amine **7.**

Dehydration of 9β-ol 2d with $POCl_3$ and Rearrangement of the Product to (1*R*,3*S*)-1,2,3,4-Tetrahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridine (6). β-Hydroxy compound **2d** (26.4 g, 0.12 mol) and 150 ml of $POCl_3$ were refluxed for 3 hr. The excess reagent was removed by heating *in vacuo.* A small aliquot was treated with dilute NH_4OH. Et_2O extraction gave an oil: uv max 260 nm (ε 10,500), 225 (8000), and 217 (11,900); *m/e* 211; tlc on silica gel (97:3 Et_2O–*i*-$PrNH_2$) a more intense band at R_f 0.45 and a less intense band at R_f 0.40 (uv indicator and Dragendorff spray); nmr δ 6.47 (s, 0.7 H, vinyl) and 6.98–7.50 ppm (m, 4 H, aromatic). When this mixture was refluxed with *p*-toluenesulfonic acid in EtOH for 24 hr, tlc indicated no change in composition. The bulk of the oily residue was dissolved in MeOH and treated with 2.5 g of NaOMe. The mixture was heated under reflux for 1.5 hr and filtered free of NaCl. The filtrate was diluted with Et_2O, washed with saturated NaCl, dried ($NaSO_4$), and concentrated to give 20.0 g of almost pure **6** (84%). Distillation at 112–116° (0.5–0.6 mm) yielded 18.0 g of **6** (74%): *m/e* 221; nmr δ 6.80–7.60 (m, 4 H, aromatic), 3.45 (m, 1 H, CHN), 3.62 (m, 1 H CHN), 3.25 (s, 2 H, CH_2 aromatic), 2.95 (m, 1 H, allylic), 2.80 (m, 1 H, allylic), 2.38 (s, 3 H, CH_3N), and 1.00–2.60 ppm (m, 4 H, CH_2); uv max 260 nm (ε 11,700), 225 (8900), and 217 (13,300); tlc (silica, 97:3 Et_2O–*i*-$PrNH_2$) R_f 0.40.

The HCl salt of 6 melted at 268–270° (from acetone), $[\alpha]^{25}D$ +80.7°.

Anal. Calcd for $C_{15}H_{17}N$·HCl: C, 72,71; H, 7.32; Cl, 14.31. Found: C, 72.6; H, 7.4; Cl, 14.2.

Catalytic Hydrogenation of 6 to Form (1*R*,3*S*,4a*R*,9a*R*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]-pyridine Hydrochloride (7). A solution of 5.0 g (0.02 mol) of the HCl salt of **6** in 300 ml of 95% EtOH was hydrogenated at 3.5 kg/cm^2 in the presence of 0.5 g of 10% Pd/C. When 1 mol of H_2 was absorbed, the catalyst and solvent were removed. The crystalline residue (5.0 g) was recrystallized from acetone to give 4.0 g (80%) of **7:** mp 306° dec; $[\alpha]^{25}D$ −27.9°; glpc retention time 68 min; tlc (silica, 97:3 Et_2O–*i*-$PrNH_2$) R_f 0.25; nmr compatible with the assigned structure but without sufficient separation of the 4a and 9a hydrogens.

Anal. Calcd for $C_{15}H_{19}N$·HCl: C, 72.13; H, 8.07; N, 5.61. Found: C, 72.0; H, 8.1; N, 5.6.

Reaction of 7 with EtI. A solution of 100 mg of **7** in 1 ml of acetone was treated with 0.2 ml of EtI. There was almost immediate precipitation of a crystalline solid. After 2 hr, Et_2O was added and a quantitative yield of the ethiodide of **7** was collected. The nmr was consistant with this quaternary salt.

Anal. Calcd for $C_{17}H_{24}NI$: C, 55.29; H, 6.55; I, 34.36. Found: C, 55.1; H, 6.6; I, 34.3.

Attempted Reaction of 2c with EtI. A solution of 100 mg of **2c** in 1 ml of acetone was treated with 0.2 ml of EtI. After 2 hr, Et_2O was added. There was no precipitation. Evaporation of the solvent afforded **2c** (tlc confirmation).

Na–NH_3 Reduction of the Dehydration Product from 2d. A solution of 10 g (0.044 mol) of 9β-ol **2d** in 60 ml of $POCl_3$ was heated under reflux for 3 hr. The excess reagent was removed by warming *in vacuo*. Ice–water and dilute NH_4OH were added and the mixture was extracted with Et_2O. The Et_2O was washed (saturated NaCl), dried (Na_2SO_4), and concentrated to afford 9.2 g of dehydrated product. Tlc indicated an approximately 70:30 mixture of kinetic (**5**) to thermodynamic (**6**) product.

This product in 125 ml of THF was added to 1 l. of NH_3 containing 2.3 g (0.1 g-atom) of Na. After the reaction mixture was stirred for 20 min, 7.5 g of NH_4Cl was added. The NH_3 was evaporated and Et_2O and H_2O were added. The Et_2O layer afforded 9.2 g of crude product which was chromatographed on 500 g of silica gel pretreated with 100 ml of *i*-$PrNH_2$ and air dried. A least polar band, eluted with 3:1 pentane–Et_2O, yielded 3.6 g (38%) of cis–syn compound **2c,** which was identical with **2c** described above by glpc, tlc, ir, and nmr. Its HCl salt melted at 298° dec.

A mid band (0.3 g), eluted with 1:1 Et_2O–pentane, was indicated to be starting material by tlc.

A more polar band, eluted by 99:1 Et_2O–*i*-$PrNH_2$, afforded the cis–anti compound **7** (3.0 g, 32%). Its HCl salt melted at 301° dec and a sample of liberated base was identical with **7** described above (glpc, tlc, ir, and nmr).

Na–NH_3 Reduction of 6. Compound **6** (1.8 g, 8.5 mmol) in 25 ml of THF was added to 0.46 g (0.02 g-atom) of Na in 100 ml of liquid NH_3 and the reaction was worked up in the conventional manner. The HCl salt of the crude product was recrystallized from acetone to give 1.2 g of **7** HCl, mp 303° dec, $[\alpha]^{25}D$ – 27.1°. A sample of liberated base was identical with **7** described above (glpc, tlc, ir, and nmr). Tlc analysis of the reaction mother liquor indicated a 1:1 content of **7** and starting material **6** (estimated total yield of **7** was 80%).

(1*S*,3*R*,4a*R*,9a*R*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno-[2,1-*c*]pyridin-9-one (2a enantiomer) was prepared from a 1:3 mixture of the enantiomer of **1** and its 2α epimer[1] in the same manner used to prepare **2a.** The analytical sample melted at 78–80° (*n*-pentane), $[\alpha]^{25}D$ –13.6°.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.2; H, 7.5; N, 6.3.

The HCl salt of 2a enantiomer from acetonitrile exhibited polymorphism, melting at 218–220 and 261° dec (evacuated tube), $[\alpha]^{25}D$ –39.4°.

Anal. Calcd for $C_{15}H_{17}NO$·HCl: C, 68.30; H, 6.88; Cl, 13.44. Found: C, 68.3; H, 6.9; Cl, 13.5.

(1*S*,3*R*,4a*R*,9a*R*)-1,2,3,4,4a,9a-Hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-*c*]pyridine hydrochloride (2c enantiomer) was prepared from **2a** enantiomer *via* the thioketal method used for conversion **2a** → **2b** → **2c.**

The analytical sample from acetone melted at 298° dec, $[\alpha]^{25}D$ –95.8°.

Anal. Calcd for $C_{15}H_{19}N$·HCl: C, 72.13; H, 8.07; N, 5.61. Found: C, 72.2; H, 8.1; N, 5.6.

Borane reduction of ketone 2a enantiomer in the manner described for **2a** (ketone added to the borane) afforded **2c enantiomer,** bp 120–134° (1–1.5 mm), $n^{27}D$ 1.5552. Its **HCl salt** melted at 298° dec, $[\alpha]^{25}D$ – 93.0°.

Also obtained was **2d enantiomer,** mp 138–140°. The **HCl salt** melted at 220° dec, $[\alpha]^{25}D$ –74.7°.

Anal. Calcd for $C_{15}H_{19}NO$·HCl: C, 67.79; H, 7.58; Cl, 13.34. Found: C, 67.5; H, 7.7; Cl, 13.0.

In a similar experiment that was heated under reflux for only 3 hr, **2f enantiomer** was also obtained after chromatography.

The **HCl salt** melted at 282° dec, $[\alpha]^{24}D$ – 62.6°.

Anal. Calcd for $C_{15}H_{19}NO$·HCl: C, 67.79; H, 7.58; Cl, 13.34. Found: C, 67.6; H, 7.6; Cl, 13.4.

Platinum Oxide Catalyzed Hydrogenation of 2a Enantiomer. A solution of 0.59 g (2.6 mmol) of **2a** enantiomer in 300 ml of 95% EtOH containing 0.25 g of Pt_2O was hydrogenated at 3.5 kg/cm^2. Removal of the catalyst and solvent gave 0.59 g of an epimeric mixture of alcohols which was separated by plate chromatography (97:3 Et_2O–*i*-$PrNH_2$). The less polar band afforded 150 mg (25%) of somewhat impure **2d** enantiomer, mp 128–135°. The more polar band gave 290 mg (49%) of **2f** enantiomer, mp 99–100°. Ir and tlc comparison of these alcohols with their enantiomers confirmed their identity.

Acknowledgment. We thank Dr. R. K. Kullnig, Miss Catherine M. Martini, and their associates for the spectral data presently reported. Also we thank the Analytical Division of this Institute for the measurement of optical rotations.

Registry No.—**1,** 50372-80-0; **1** enantiomer, 50583-05-6; **1** 2α epimer, 50370-54-2; **2a,** 51805-79-9; **2a** enantiomer, 51868-65-6; **2a** HCl, 51868-66-7; **2a** enantiomer HCl, 51897-49-5; **2b,** 51805-80-2; **2c,** 51805-81-3; **2c** HCl, 51829-78-8; **2c** enantiomer HCl, 51829-77-7; **2d,** 51805-82-4; **2d** enantiomer, 51829-79-9; **2d** HCl, 51868-72-5; **2d** enantiomer HCl, 51868-67-8; **2e** methanesulfonate salt, 51805-84-6; **2f,** 51829-80-2; **2f** HCl, 51868-68-9; **2f** enantiomer HCl, 51829-81-3; **4,** 51868-73-6; **4** HCl, 51805-85-7; **6,** 51868-74-7; **6** HCl, 51805-86-8; **7** HCl, 51829-82-4; **7** ethiodide, 51805-87-9; 3β-phenyltropane-2β-carboxylic acid hydrochloride, 50373-05-2; 3β-phenyltropane-2α-carboxylic acid hydrochloride, 51829-83-5.

References and Notes

(1) R. L. Clarke, S. J. Daum, A. J. Gambino, M. D. Aceto, J. Pearl, M. Levitt, W. R. Cumiskey, and E. F. Bogado, *J. Med. Chem.*, **16,** 1260 (1973).
(2) The mixture of these C-2 epimers formed in their preparation[1] can be used directly in this cyclization process.
(3) Spin decoupling of the C-9a H from the C-1 H of **2a** resulted in a doublet with a coupling constant $J_{9a,4a}$ = 7.5 Hz. This corresponds roughly to a dihedral angle of 30°, an angle close to that found in a Dreiding model of **2a.** The trans isomer cannot be formed without damage to the models.
(4) I. Weisz, P. Agocs, M. Halmos, and K. Kovacs, *Acta Chir. (Budapest)*, **56** (2), 195 (1968).
(5) P. v. R. Schleyer, D. S. Trifan, and R. Bacskai, *J. Amer. Chem. Soc.*, **80,** 6691 (1958).
(6) R. E. Lyle, K. R. Carle, C. R. Ellefson, and C. K. Spicer, *J. Org. Chem.*, **35,** 802 (1970).
(7) R. L. Clarke, A. J. Gambino, and S. J. Daum, *J. Med. Chem.*, in press.
(8) W. J. Wechter, *J. Org. Chem.*, **28,** 2935 (1963).
(9) This experiment was done on the *enantiomer* of ketone **2a,** which will be described below.
(10) A. Ebnother and J. Bastian, U. S. Patent 3,573,316 (March 1971).
(11) All melting points were determined in capillary tubes and are not corrected. EtOH (95%) was used for uv spectra, $CHCl_3$ for ir spectra, and $CDCl_3$ for nmr spectra. Optical rotation of bases were measured in $CHCl_3$; those of salts were measured in H_2O. Nmr spectra were recorded on a Varian HA-100 pmr spectrometer with an internal TMS standard, spin-decoupling experiments were done with the same instrument using a Hewlett Packard Audio Oscillator-4204A, uv spectra were recorded on a Cary Model 15 spectrometer, ir spectra were recorded on a Perkin-Elmer Model 21 spectrometer, and hydrogen-bonding studies were done using a Beckman IR-7 instrument. The mass spectra were measured with a Joelco JMS-1-OCS mass spectrograph. Preparative plate chromatography was accomplished using 1-mm thick coatings of Brinkmann P_{254} silica gel on 20 × 40 cm glass plates. Glpc data were obtained from a 6-ft 10% Carbowax column at 210°.