Orientation in the Hydroboration of Tetrahydropyridines and Tropidines[1]

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The hydroboration of unsaturated amines 1-alkyl-1,2,3,6-tetrahydropyridine (**1**), tropidine (**8**), and 3-aryltropidines (**14**) provided a synthetic route to cyclic amino alcohols and indicated both steric and electronic factors in orientation of the reaction. The tetrahydropyridines showed no steric bias in the reaction, but the electron attraction of the nitrogen led to 75% 3-piperidinols. The amine borane of the tropidines caused hydroboration to occur from the α face of the double bond and, along with the steric effect of the ethano bridge, partially overcame the electronic effect of the nitrogen in the orientation. With the 3-aryltropidine, an additional electronic effect, that of the aryl group, can be demonstrated, which leads to small but significant yields of 3-aryltropines (**15**) as well as the expected 3-aryl-2α-tropanols (**16**).

A study of the syntheses of hydroxypiperidines by the hydroboration of unsaturated amines followed by oxidation of the borane provided information concerning the parameters governing the orientation of the addition. The direction of the addition of diborane to alkenes has been shown to be affected by the substitution pattern of the alkene (with boron becoming attached to the less hindered carbon),[4] by large inductive effects of substituents near the π system (with the boron bonding to the carbon nearer the electronegative group),[5] and/or by stabilization of the amine borane by five- or six-membered cyclic complexes.[6] The unsaturated heterocycles investigated in this hydroboration study provided an opportunity to evaluate the relative importance of these effects. The reaction also proved to be an effective synthetic route to the medicinally important, hydroxy-nitrogen heterocycles from available unsaturated heterocycles.

The hydroboration–oxidation reaction was studied with a series of 1-substituted 1,2,3,6-tetrahydropyridines **1** prepared by the sodium borohydride reduction of the corresponding pyridinium salts.[7] With an excess of diborane a mixture of hydroxypiperidines was obtained in moderate yields as shown in Table I. Approximately 75% of the mixture was the 3-hydroxypiperidine **2** and 25% was the 4-hydroxypiperidine **3**, regardless of the 1 substituent. Separation of the mixture could be accomplished by gas–liquid chromatography or by recrystallization of the salts of the amines.

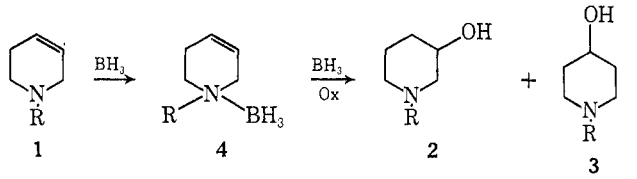

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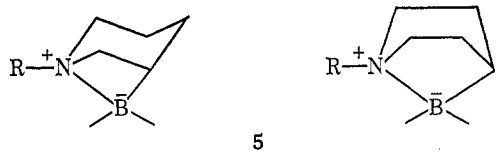
TABLE I
HYDROBORATION OF 1-ALKYL-1,2,3,6-TETRAHYDROPYRIDINES

1,	R =	Total yield,[a] %	Relative yield, % 3-ol 2[b]	Relative yield, % 4-ol 3[b]
a	CH_3	84[c]	71	29[d]
b	$CH_3(CH_2)_2$–	34[e]	79	21
c	$PhCH_2$	42–70[f]	76	24
d	$PhCH_2CH_2$–	58–65[g]	74	26

[a] Yields are based on the product mixture after distillation. [b] The relative yields are based on gas chromatographic analysis of the mixture. These percentages represent the average of at least two separate injections. [c] Boiling point 96–98° at 45 mm from five experiments. [d] At 25° the ratio was 75:25. [e] Yield from only a single experiment. [f] Yields from five experiments. [g] Yields from three experiments.

Treatment of **1** with one molar equivalent of borane gave only the unsaturated amine borane **4**. Heating compound **4** and oxidation of the resulting borane gave a low yield of a 50:50 mixture of **2** and **3**. The initial formation of **4** showed that the nonbonded electrons of the nitrogen underwent reaction more rapidly than the π electrons, and indicated that the hydroboration of **1** with an excess of diborane occurred by the amine borane **4**. A cyclic amine borane such as **5** is not important in the hydroboration reaction, and no steric difference biases the reaction for preferred attachment of the boron at the 3 position.



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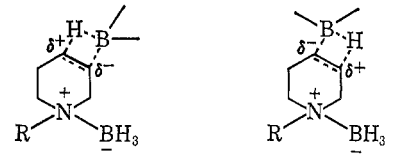
The use of the sterically large hydroborating agent diisopinocampheylborane with 1-methyl-1,2,3,6-tetrahydropyridine did not change the ratio of 3- to 4-piperidinol formation, showing that steric factors were not important in determining the position of reaction. The nitrogen in the amine borane bears a formal positive charge, and thus the transition state leading to the 3-borane **6** is favored over that leading to the 4 deriva-



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(3) (a) University of New Hampshire Fellow, 1964–1968; (b) Public Health Service Fellow of the General Medical Institute of the National Institutes of Health, GM-18,974.

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tive **7**.[5c-g] This effect is predominant in leading to an excess of **2**.

The steric influence of the amine borane salt was evident from the results of the hydroboration–oxidation of tropidine derivatives. The product mixture from the reaction with 2-tropidine (**8**) contained four tropanols **10–13** in the amounts indicated in Table II.

TABLE II
HYDROBORATION OF TROPIDINE DERIVATIVES

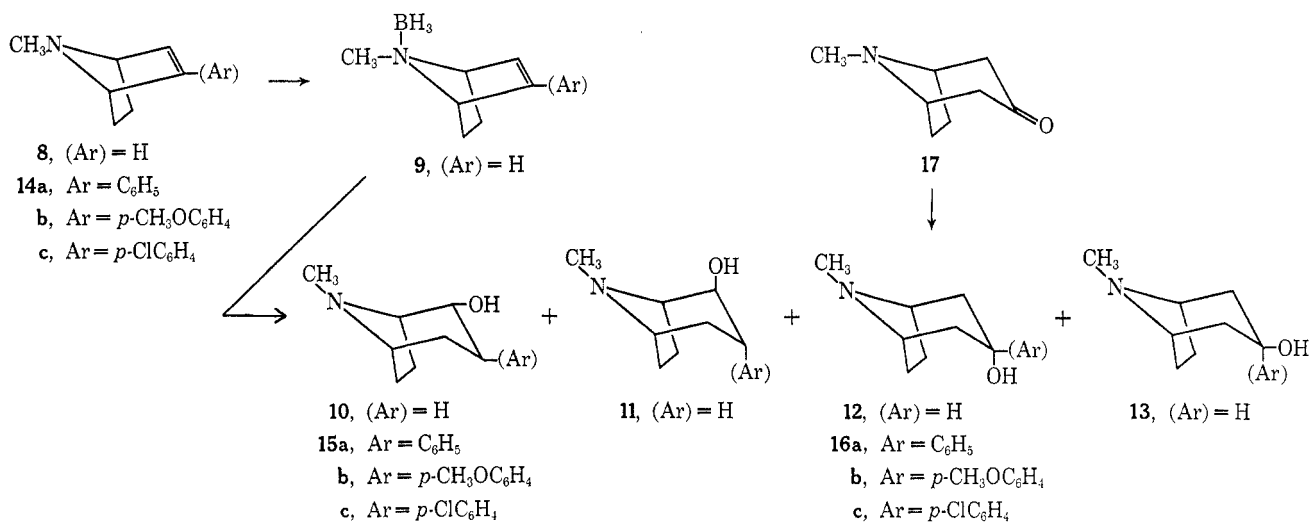
Ar =	Yield of tropanols, %	Relative yield, % 2α **10, 15**	2β **11**	3α **12, 16**	3β **13**
H (**8**)	68	43 ± 3	3	50 ± 3	3
p-ClC_6H_4 (**14c**)	64	70		30	
C_6H_5 (**14a**)	73	75		25	
p-$CH_3OC_6H_4$ (**14b**)	75	80		20	

The identity of the tropanols was based on a comparison of properties with authentic samples before and after epimerization. The overwhelming predominance (~90%) of α alcohols **10** and **12** was unexpected, for reactions at the 3-position usually occur by attachment of the reacting species from the β side. Again it could be easily demonstrated that the reaction of diborane with 2-tropidine (**8**) gave a rapid formation of the amine borane **9**. The sp^3 hybridization of the nitrogen requires that either the methyl or BH_3 group shield the β side of the double bond from reaction. The *syn* interaction of the CH_3 or BH_3 attached to nitrogen would destabilize the π complex and transition state which would lead to the β-tropanols. A similar effect has been noted with the addition to 3-tropanones and their quaternary salts. This picture of the steric interactions in the developing transition states also provides a rationalization for the decreased electronic influence of the salt of the heteroatom on the orientation during hydroboration. Reaction to form the 2β-tropanol (**11**) would require the borane to bond to carbon *via* a transition state with a *syn* axial interaction, and to form the 2α-tropanol (**10**) the transition state to the borane is destabilized by interactions with the *cis*-vicinal ethano bridge. Because the six-membered ring is flattened, the transition state leading to the 3α-tropanol (**12**) would have less repulsive interaction with the ethano bridge.

The hydroboration of 2-tropidine (**8**) with the bulky reagents diisopinocampheylborane and triisopinocampheyl diborane gave low yields (25–30%) of a mixture of tropanols considerably richer in β-tropanols, 63% **11** and 30% **13**. This isomer distribution may indicate that in the amine borane both the α and β faces of the double bond are too protected to give reaction with the substituted boranes. Thus reaction can occur slowly only with any dissociated amine present in the medium, and the reaction of the free amine with borane should lead to β alcohols.

The formation of *trans*-1-methyl-4-phenyl-3-piperidinol by the hydroboration–oxidation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine suggested the convenient synthesis of 3-aryl-2-tropanols **15** by the hydroboration–oxidation of 3-aryl-2-tropidines **14**.[8a] The starting material for **14** was 3-tropanone **17** which was converted to 3-aryltropines **16** by reaction with aryllithium reagents. It is interesting to note that the conversion of **17** into **16** was always accompanied by recovered 3-tropanone **17**, suggesting that significant enolization of **17** accompanied the desired addition of the lithium reagent. The 3-aryltropines **16** were dehydrated to the 3-aryltropidines **14** by hydrobromic acid.[8b]

In the hydroboration of the series of 3-aryltropidines **14** there was a significant amount of the 3-aryltropine **16** detected in the product mixture. The amounts of the tropines resulting from bond formation between boron and the tertiary carbon varied slightly with the substituent on the 3-aryl group and were in the order Cl > H > CH_3O (see Table II), which is in agreement with the previously described electronic effect in the orientation of hydroboration reaction with styrenes.[9] By comparison, however, no 1-methyl-4-phenyl-4-piperidinol was detected in the synthesis of *trans*-1-methyl-4-phenyl-3-piperidonol on hydroboration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.[8a]



The major product in the hydroboration of all of the 3-aryltropidines **14** was the 3-aryl-2α-tropanol **15**. The stereochemistry of **15** was shown to have the substituents 2α–3β, for the hydroxyl group was clearly α since no hydrogen bonding of the hydroxyl with nitrogen

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was observed in the infrared spectrum. The resonance signal for the carbinol proton was a doublet of doublets with coupling constants of $J_{2,3} = 10$ and $J_{1,2} = 3$ Hz. These values require the proton at position 2 to be axial. Again the reactivity by addition from the α side of the double bond was evident. It is clear that no intramolecular cycle involving the amine borane governed the course of the reaction, but the amine borane formation provided steric interference to reaction from the β side of the double bond.

These results show that both steric and electronic effects must be considered in anticipating the products of hydroboration. With unsaturated amines the amine borane is the intermediate and may play an important role in determining the availability of diastereotopic faces of a double bond to reaction with borane. The stereochemistry of the products of hydroboration of the tropidines illustrate this point. Finally, the yields from the hydroboration of the 3-aryltropidines show the dominent effect of an aryl group to stabilize the developing boron–carbon bond during hydroboration.

Experimental Section

General.—The infrared spectra were determined using Perkin-Elmer 137B and 337 spectrophotometers. Liquids were sampled as liquid films and solids as mulls in Halocarbon[10] (4000–1300 cm^{-1}) and Nujol (1300–650 cm^{-1}). Ultraviolet spectra were determined using a Cary Model 15 spectrophotometer, and nuclear magnetic resonance spectra were determined with a Varian Model A-60 spectrometer in the solvents indicated. The chemical shifts are reported in parts per million shift downfield from tetramethylsilane as an internal standard. The coupling constants J are reported in hertz. The gas–liquid chromatographic analyses were made with a Perkin-Elmer Model 154C vapor fractometer or an Aerograph Autoprep A-700. The conditions are indicated below.

Hydroboration of 1-Alkyl-1,2,3,6-tetrahydropyridines (1).—Into a dry 500-ml three-necked flask under nitrogen, fitted with a mercury-sealed, mechanical stirrer, dropping funnel, and reflux condenser, were introduced solutions of 0.025 mol of 1-alkyl-1,2,5,6-tetrahydropyridine (1) in 10 ml of diglyme and 30 ml of a 1 M solution of sodium borohydride in diglyme. A solution of 7.5 g (0.052 mol) of boron trifluoride etherate in 10 ml of diglyme was added to the mixture. The reaction was stirred at 25° for 2 hr, cooled, and treated with 40 ml of 6 N sodium hydroxide, and 5 ml of 30% hydrogen peroxide. The resulting mixture was heated on a steam bath for 2 hr, cooled, and acidified with concentrated hydrochloric acid. The diglyme layer was removed by decantation, and a minimum of water was added to the aqueous layer. Steam distillation removed most of the residual diglyme and diethylene glycol monomethyl ether. Anhydrous potassium carbonate was added, the resulting mixture was extracted three times with ether, and the ether extracts were dried and concentrated. The yellow residue was distilled under reduced pressure. The analyses of the crude distillate are given in Table I. Gas chromatographic analyses were made using a 2-m Carbowax 1500 column on 60–100 mesh "Embacel" Kieselguhr, 150°.

Similar reactions run in tetrahydrofuran with externally generated borane gave similar results. Heating the reaction mixture at higher temperatures changed the ratio of piperidinols **2** and **3** only slightly.

1-Methyl-1,2,3,6-tetrahydropyridine Amine Borane (4).—The reaction of 3.88 g (0.04 mol) of 1-methyl-1,2,3,6-tetrahydropyridine (1) in 50 ml of THF, with (0.02 mol) of diborane generated externally from sodium borohydride and boron trifluoride, gave **4** as a yellow oil after evaporation of the solvent. A sample of the amine borane gave the calculated volume of hydrogen on acid hydrolysis. The infrared (neat) (B–H stretching bands at 2350 and 2270 cm^{-1} and B–N vibration at 1177 and 1166)[11] and nmr ($CDCl_3$) (C-6 methylene, t, 2.90, C-2 methylene, m, 3.30, C-1 methyl, s, 2.50 ppm) spectra confirmed the structure. The downfield shift of the signals for the protons of **4** given above, compared with the analogous protons of **1**, requires that the nitrogen of **4** have a formal positive charge.

Thermal Reaction of 1-Methyl-1,2,6,6-tetrahydropyridine Amine Borane (4).—A 1.2-g sample of the amine borane **4** was added to 20 ml of diglyme, and this mixture was heated at 150° with stirring for 10 hr. The mixture was cooled, 5 ml of 6 N sodium hydroxide was added, and the basic mixture was oxidized with 5 ml of 30% hydrogen peroxide. The solution was extracted with ether and the ether extracts were concentrated and analyzed by gas chromatography. The chromatogram showed the 3- and 4-piperidinols **2** and **3** to be present in the relative amounts of 43 ± 4% and 57 ± 4%, respectively. There was no 1-methyltetrahydropyridine (1) present.

Hydroboration–Oxidation of 2-Tropidine (8).—A dry 200-ml three-necked flask, equipped with magnetic stirrer, condenser, and pressure-equalizing dropping funnel, was flushed with dry nitrogen which was exited in an acetone trap. Using a reaction flask as above, solutions of 1.49 g (0.0394 mol) of sodium borohydride in 40 ml of diglyme and 3.08 g of 2-tropidine (**8**) (0.025 mol) in 10 ml of diglyme were mixed and stirred at 0°. A solution of 6.7 ml (*ca.* 0.0425 mol) of boron trifluoride etherate in 10 ml of diglyme was added dropwise over a period of 1.5 hr, and the mixture was stirred for an additional 1.5 hr at room temperature. This mixture was made basic with 15 ml of 6 N sodium hydroxide and oxidized at 50–64° with 5 ml of 30% hydrogen peroxide, and acidified with 20 ml of concentrated hydrochloric acid. After concentrating the reaction mixture, the residue was taken up in a small amount of water, solid potassium carbonate was added, and the basified mixture was extracted with several portions of ether. The combined extracts were dried over potassium carbonate and concentrated by evaporation to leave 2.41 g (68%) of a light yellow oil as residue. This oil was analyzed in detail by gas chromatography (2 m 5% Quadrol on 60–80 mesh KOH-washed Chromosorb W, 157°, 11 psi). The four predicted tropanol isomers were present in the relative amounts of 3% 2β-tropanol (**11**), 50 ± 3% tropine (**12**), 43 ± 3% 2α-tropanol (**10**), and 4% pseudotropine (**13**). The gas chromatographic retention times of these compounds were 4.20, 11.2, 12.5, and 16.0 min, respectively, and were exactly the same as those of a synthetic mixture containing authentic L-2α-tropanol, tropine, L-2β-tropanol, and pesudotropine. A sample of tropine, mp 60–64° (lit.[12] mp 63–64°), was isolated from the reaction mixture by preparative gas chromatography (20 ft × 1/8 in. aluminum column packed with 20% Carbowax 20M on DMCS-treated, acid-washed Chromosorb W).

A sample containing 1% 2β-tropanol (**11**), *ca.* 52% tropine (**12**), *ca.* 41% 2α-tropanol (**10**), and 6% pseudotropine (**13**) was epimerized by the sodium 3-pentoxide–fluorenone equilibration procedure of Bell and Archer.[13] The product contained the four epimeric tropanols in the relative amounts of 32% 2β-tropanol (**11**), *ca.* 7% tropine (**12**), *ca.* 10% 2α-tropanol (**10**), and 51% pseudotropine (**13**), and pseudotropine (**13**), mp 99–108.5°, could be isolated. One recrystallization from benzene–ligroin (30–60°) gave a pure sample of pseudotropine (**13**), mp 104–108° (lit.[12] mp 109–110°).

Tropidine Amine Borane (9).—A 1 M solution (8 ml) of borane (BH_3) in tetrahydrofuran was added to a solution of 1.00 g (0.00813 mol) of tropidine (**8**) in 10 ml of n-hexane. Evaporation of the solvent gave 1.12 g of a white solid residue which was recrystallized once from water to give 71%, 0.78 g, tropidine amine borane (**9**), mp 118–122°. Purification by vacuum sublimation gave an analytical sample, mp 117–119° dec (softens at 97°). This compound was characterized by a distinctive odor similar to that of camphor.

Anal. Calcd for $C_8H_{16}BN$: C, 70.12; H, 11.77; N, 10.22. Found: C, 69.93; H, 11.55; N, 10.43.

Preparation of 3-Aryltropidines 14a–c and 3-Aryltropines 16a–c.—The reaction of phenyllithium with 3-tropone (**17**) following the procedure of Cope and D'Addieco[14] gave a maximum of 76% 3-phenyltropine (**16a**), mp 161–162°, after recrystallization from hexane.

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(11) (a) R. C. Baumgarten and M. C. Henry, *J. Org. Chem.*, **29**, 3400 (1964). (b) Reference 4a, pp 179–181.

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(13) M. R. Bell and S. Archer, *J. Amer. Chem. Soc.*, **82**, 4642 (1960).

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Anal. Calcd for $C_{14}H_{19}NO$: C, 77.36; H, 8.82; N, 6.45. Found: C, 77.07; H, 8.69; N, 6.19.

The metal–halogen exchange of 7.48 g (0.04 m) of *p*-bromoanisole with 25 ml of 1.6 *M* *n*-butyllithium in hexane[15] gave an organolithium reagent, which, on reaction with 5.08 g (0.036 m) of **17**, produced 9.54 g of a mixture of **3-*p*-anisyltropine (16b)** and **3-(2-methoxy-5-*p*-bromophenyl)tropine**. The crude mixture was boiled with 100 ml of hexane and cooled to give 4.81 g (53.4%) of **16b**, mp 156.5–159°, as residue. The aromatic protons gave an A_2B_2 pattern centered at 7.16 ppm in the nmr spectrum in $DCCl_3$.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.57; N, 5.66. Found: C, 72.30; H, 8.50; N, 5.71.

The hexane wash on partial evaporation deposited 0.85 g of **3-(2-methoxy-5-bromophenyl)tropine**, mp 162–164°. The nmr spectrum showed the resonance signals for the aromatic hydrogens as a one-proton doublet ($J_{2,4}$ = 2.5 Hz) at 7.49 ppm, a one-proton doublet of doublets ($J_{4,2}$ = 2.5 and $J_{4,5}$ = 8.5 Hz) at 7.29 ppm, and a one-proton doublet ($J_{5,4}$ = 8.5 Hz) at 6.73 ppm.

Anal. Calcd for $C_{15}H_{20}BrNO_2$: C, 55.21; H, 6.19; N, 4.29. Found: C, 55.26; H, 6.07; N, 4.35.

The *p*-chlorophenyllithium reagent, prepared from 30.66 g (0.15 mol) of *p*-bromochlorobenzene and 140 ml of 1.6 *M* solution of *n*-butyllithium,[15] was treated with 20.67 g (0.15 mol) of 3-tropanone (**17**) in anhydrous ether. Decomposition of the reaction with water gave 33.40 g (89%) of **3-*p*-chlorophenyltropine (16c)**, mp 192–195°. Recrystallization of the solid from benzene gave an analytical sample, mp 194–195.5°.

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.78; H, 7.22; N, 5.56. Found: C, 67.20; H, 7.42; N, 5.69.

Dehydration of the 3-Aryltropines 16.—A solution of 22.5 g of 3-phenyltropine (**16a**) in 90 ml of 40% hydrobromic acid was prepared by heating the mixture until the solid dissolved. On cooling and standing for 10 hr a solid precipitated and was collected by filtration to give 29.2 g (quantitative) of **3-phenyltropidine hydrobromide**, mp 179–181°, after recrystallization from isopropyl or ethyl alcohol.[8b]

Anal. Calcd for $C_{14}H_{18}BrN$: C, 60.00; H, 6.49; N, 5.00. Found: C, 60.01; H, 6.31; N, 5.03.

Uv spectrum: λ_{max}^{EtOH} (log ϵ) 216.2 (4.01), 247.9 (4.11), 290.3 (2.39).

The reaction of 1.44 g of 3-*p*-anisyltropine (**16b**) in 6 ml of 40% hydrobromic acid on neutralization with potassium carbonate gave 1.20 g (90%) of 3-*p*-anisyltropidine (**14b**), mp 77.5–81.0°. Recrystallization of the solid from hexane raised the melting point to 85–87°.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.55; H, 8.37; N, 6.11. Found: C, 78.45; H, 8.40; N, 6.18.

The dehydration of 2.05 g of 3-*p*-chlorophenyltropine (**16c**) with 10 ml of 40% hydrobromic acid gave 1.65 g (88%) of **3-*p*-chlorophenyltropidine (14c)**, mp 95–97°, on neutralization. Recrystallization from heptane raised the melting point to 98–100°.

Anal. Calcd for $C_{14}H_{16}ClN$: C, 71.93; H, 6.91; N, 5.99. Found: C, 71.94; H, 6.86; N, 6.06.

Hydroboration–Oxidation of 3-Aryltropidines.—The following general procedure was employed for the hydroboration of 3-phenyltropidine (**14a**), 3-*p*-chlorophenyltropidine (**14c**), and 3-*p*-anisyltropidine (**14b**). A solution of 1.0 *M* BH_3 (in excess of two equiv) in tetrahydrofuran was added to a solution of the 3-aryltropidine in anhydrous tetrahydrofuran in a three-necked flask. The solutions were stirred at room temperature for 4 hr and then were heated under reflux for an additional 4 hr. Water was added cautiously and the reaction solution was made basic with 6 *N* sodium hydroxide, and 30% hydrogen peroxide was added slowly. After heating under reflux for 2 hr, concentrated hydrochloric acid was added. The reaction mixture was concentrated, the residue was dissolved in water, and potassium carbonate was added. The alkaline solution was extracted with several portions of ether, and the combined ether extracts were dried over anhydrous potassium carbonate. Removal of the ether produced white solids that were immediately recrystallized from ethanol–water. Table II gives the quantitative data on the three 3-aryltropidines that were treated in this manner.

The composition of the product was estimated from the nmr analysis. The percentage of the 3-aryl-2α-tropanol (**15**) in the product mixture was considered to be (the integral of the two-proton signal of **15**/25% of the integral for the aromatic protons) × 100. The percentage of the minor component was obtained by difference, since no convenient resonance band for **16** was evident. Thin layer chromatography on Eastman silica gel plates using chloroform–ethanol (50/50, v/v) as the solvent showed that there were two compounds. These components were identified from the hydroboration–oxidation of 3-phenyltropidine (**14a**).

The major component of the reaction of 3-phenyltropidene (**14a**) was **3-phenyl-2α-tropanol (15a)**, which was identified by nmr analysis of the mixture or purified sample. The minor constituent was found to be 3-phenyltropine (**16a**), which was isolated by chromatography on a Florisil column using 95% ethanol–chloroform (50/50, v/v) as the eluent. The early fractions were a mixture, but the later fractions contained only 3-phenyltropine (**16a**), which was identified by comparison of the infrared spectrum with that of an authentic sample, thin layer chromatography, and mixture melting point.

Analytical and spectral data for the three hydroboration–oxidation products are given below.

(a) **3-Phenyl-2α-tropanol** and **3-phenyltropine**: uv λ_{max}^{EtOH} (log ϵ) 237.2 (1.82), 242.4 (1.97), 247.3 (2.12), 251.9 (2.24), 257.7 (2.32), 260.4, sh (2.24), 263.7 (2.20), and 267.4 nm (2.08); nmr (TMS, $DCCl_3$) 7.00–7.51 (m, Ar), 4.84 (s, –OH), 3.80 (dd, J = 10, J = 5 Hz, –CH–OH), 2.99 (m), and 2.00 ppm (s, –N–CH_3).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.36; H, 8.82; N, 6.45. Found: C, 77.55; H, 9.00; N, 6.30.

(b) **3-*p*-Anisyl-2α-tropanol** and **3-*p*-anisyltropine**: nmr (TMS, $DCCl_3$) 6.67–7.33 (m, –Ar), 3.72 (s, –O–CH_3), 3.63 (s, –OH), 3.06 (m), and 2.15 ppm (s, –N–CH_3).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.57; N, 5.66. Found: C, 72.81; H, 8.52; N, 5.57.

(c) **3-*p*-Chlorophenyl-2α-tropanol** and **3-*p*-chlorophenyltropine**: nmr (TMS, $DCCl_3$) 7.13–7.58 (m, –Ar), 3.96 (s, –OH), 3.79 (dd, J = 10, J = 4 Hz, –CH–OH), 3.06 (m), and 2.13 ppm (s, –N–CH_3).

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.78; H, 7.22; N, 5.56. Found: C, 66.92; H, 7.17; N, 5.58.

Registry No.—**4**, 22932-17-8; **8**, 529-18-0; **9**, 22932-19-0; **14a** HBr, 22979-20-0; **14b**, 22932-20-3; **14c**, 22932-21-4; **15a**, 22932-22-5; **15b**, 22932-23-6; **15c**, 22932-24-7; **16a**, 22932-25-8; **16b**, 22932-26-9; **16c**, 22932-27-0; 3-(2-methoxy-5-bromophenyl)tropine, 22932-28-1.

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