and at 2.97 ppm for H_5 (doublet of doublets with large coupling to

***exo*-5-*F*-Octylnortricyclene-2,*endo*-3-dicarboxylic Acid (15b).** To a stirred solution of sodium hydroxide (1.70 g, 40.0 mmol) in ethanol (40 mL, 90%) at 60 °C was added **5a** (8.00 g, 9.52 mmol, 90%, in 10 mL of ethanol), and the mixture was kept at 50–60 °C for 3 h. Solid **15b** was precipitated in water (100 mL) and hydrochloric acid (0.10 mol), redissolved in base, extracted with ether, reprecipitated with acid, collected, washed, and air-dried to give 4.42 g (82%), mp 132–142 °C. Recrystallization from acetone (20 mL) and benzene (20 mL) gave **15b** (2.34 g), mp 157–158 °C, and subsequent fractions of lower and higher melting point. However, infrared spectra of these materials did not differ from those of pure **15b.** An NMR spectrum gave resonances at 1.76 (AB quartet for $H_{7a,s}$), 2.13 (AB quartet for H_1 and H_6), 2.50 (singlet for H_4), 2.80 (broadened singlet for H_3), 2.99 (doublet of doublets for H_5), and 12.38 (broad resonance for $(COOH)_2$) ppm.

Acknowledgment. Assistance by Dr. Robert Grulich and Dr. Ronald Rodebaugh in obtaining and interpreting the NMR spectra is gratefully acknowledged.

Registry No.—**1,** 129-64-6; **2**, 2746-19-2; **3a,** 39589-98-5; **3b,** 7288-32-6; **3c,** 4883-79-8; **4a,** 3014-58-2; **4b,** 26272-67-3; **4c,** 1200-88-0; **5a** ($R_F = (CF_3)_2CF$), 69653-62-9; **5a,** ($R_F = CF_3(CF_2)_3$), 69653-63-0; **5a** ($R_F = CF_3(CF_2)_5$), 69653-64-1; **5a** ($R_F = CF_3(CF_2)_7$), 69685-73-0; **5b** ($R_F = CF_3(CF_2)_7$), 69653-65-2; **5c** ($R_F = CF_3(CF_2)_5$), 69653-66-3; **5c** ($R_F = CF_3(CF_2)_7$), 69685-74-1; **5d** ($R_F = CF_3(CF_2)_5$), 69686-92-6; **6a** ($R_F = (CF_3)_2CF$), 69685-75-2; **6a** ($R_F = CF_3(CF_2)_3$), 69653-67-4; **6a** ($R_F = CF_3(CF_2)_5$), 69685-76-3; **6a** ($R_F = CF_3(CF_2)_7$), 69685-77-4; **6c** ($R_F = CF_3(CF_2)_7$), 69685-78-5; **6d** ($R_F = CF_3(CF_2)_7$), 69685-79-6; **7a** ($R_F = CF_3(CF_2)_5$), 69685-80-9; **7a** ($R_F = CF_3(CF_2)_7$), 69685-81-0; **7b** ($R_F = CF_3(CF_2)_7$), 69685-82-1; **7c** ($R_F = CF_3(CF_2)_7$), 69685-83-2; **8a** ($R_F = CF_3(CF_2)_5$), 69685-84-3; **8a** ($R_F = CF_3(CF_2)_7$), 69685-85-4; **8b** ($R_F = CF_3(CF_2)_7$), 69685-86-5; **8c** ($R_F = CF_3(CF_2)_7$), 69685-87-6; **9a,** 69686-95-9; **9b,** 69686-96-0; **9c,** 69653-68-5; **9d,** 69653-50-5; **9e,** 69653-51-6; **10d,** 69744-59-8; **10e,** 69685-71-8; **11a** ($R_F = CF_3(CF_2)_7$), 69653-52-7; **11b** ($R_F = CF_3(CF_2)_7$), 69653-53-8; **11c** ($R_F = CF_3(CF_2)_7$), 69653-54-9; **11e** ($R_F = CF_3(CF_2)_7$), 69653-55-0; **12b,** 69653-56-1; **12c,** 69686-97-1; **12e,** 69685-72-9; **13a** ($R_F = CF_3(CF_2)_7$), 69667-92-1; **13b** ($R_F = CF_3(CF_2)_7$), 69686-98-2; **13c** ($R_F = CF_3(CF_2)_5$), 69667-93-2; **14a** ($R_F = CF_3(CF_2)_5$), 69653-57-2; **14a** ($R_F = CF_3(CF_2)_7$), 69653-58-3; **14b** ($R_F = CF_3(CF_2)_7$), 69653-59-4; **15a** ($R_F = CF_3(CF_2)_7$), 69653-60-7; **15b** ($R_F = CF_3(CF_2)_7$), 69653-61-8; $CF_3(CF_2)_7I$, 507-63-1; $CF_3(CF_2)_5I$, 355-43-1; $CF_3(CF_2)_3I$, 423-39-2; $(CF_3)_2CFI$, 677-69-0.

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Influence of the Heteroatom in the Addition of BH_4^- to the Carbonyl Group in Amino and Thio 4-Ketones

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The nucleophilic addition reaction of BH_4^- has been studied in the case of heterocyclic ketones such as various substituted 4-piperidones (1-methyl, 1-ethyl, 1-*tert*-butyl, 2,6-diphenyl, 3-methyl-2,6-diphenyl, 3,5-dimethyl-2,6-diphenyl and the corresponding 1-methyl compounds, and 2,2,6,6-tetramethyl), 4-tetrahydrothiopyranone, and aliphatic compounds [(dimethylamino)acetone, 4-(dimethylamino)-2-butanone, and 4-(dimethylamino)-3-methyl-2-butanone]. The kinetic results show, for example, an acceleration of 6.2 and 11.2 by N and S in the 4 position compared to the reactivity of the cyclohexanone. On the other hand, throughout this series the replacement of NH by NCH_3 causes an increase of 1.6 in the ratio of rate constants.

The participation of heteroatoms in reactions which occur across a ring or further along a chain has been the subject of numerous studies.[1-13] As part of our continuing studies[13-16] of the mechanism of the nucleophilic addition at carbonyl carbons, we investigated cases in which heteroatom (N or S) participation in the nucleophilic addition reaction is possible. As models we chose substituted 4-piperidones, for which stereochemical analyses have been reported,[17-20] 4-tetrahydrothiopyranone, and aliphatic ketones which contain nitrogen in the chain.

Results and Discussion

The results are given in Tables I, II, and III.

Heteroatom Effect. We found that the presence of the heteroatom increases the reactivity of the 4-piperidones and of 4-tetrahydrothiopyranone relative to the corresponding cyclanones. It is assumed that all ketones react in the same conformation:[10-12] $k_7/k_1 = 11.2$, $k_3/k_1 = 6.2$, $k_6/k_2 = 5.5$, and $k_{10}/k_9 = 5.6$.

In the case of substrates **3**, **6**, **7** (preferential axial attack) and **10** (preferential equatorial attack), the difference in reactivity may be attributed to a transannular dipolar "through space effect" which destabilizes the ground state because of the interaction of partial positive charges, but which stabilizes the transition state where the reacting carbon goes from sp^2 to sp^3 and carries a partial negative charge[16] (Chart I).

This explanation is equally valid for the aliphatic compounds, but in this case the ratio of the rate constants is lower, $k_{18}/k_{16} = 3.2$, presumably because here only inductive effects are possible.

If we go from cyclic to aliphatic compounds, the ratio of the rate constants decreases dramatically, from 88.0 to 0.17 in cases **4** and **18** (Chart II). The effect of the heteroatom is much less pronounced in the aliphatic series because rotation of the

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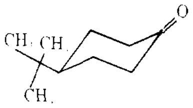
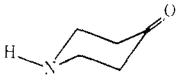
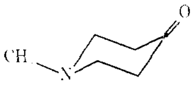
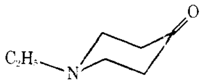
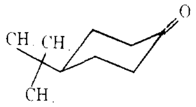
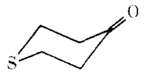
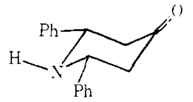
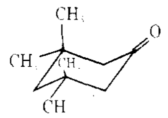
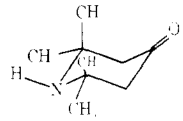
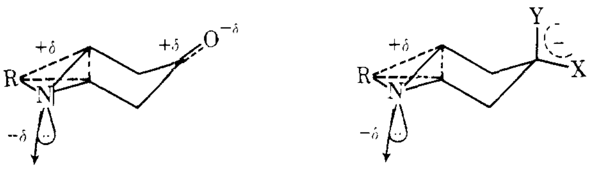
Table I. Rate Constants for BH_4^- Addition on Substituted 4-Heterocyclanones[a]

products	no.	k, L mol^{-1} min^{-1}	% axial attack
	1	8.9	
	2	9.0	80[b]
	3	55	
	4	88	>84[c,17,18]
	5	87	>84[c,17,18]
	6	49	>90[c,18,19]
	7	100	
	8	45	90[20] 91[b]
	9	0.9 × 10^{-2}	25[d]
	10	5 × 10^{-2}	

[a] In water–dioxane (50:50 by volume) at 25 °C, [>C=O] = 10^{-2} M, and [BH_4^-] = 5 × 10^{-3} M. [b] This work. [c] Methyl α to the C=O analogues. [d] Estimated.[28]

Chart I



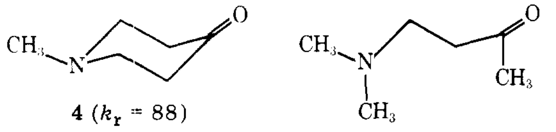
ground state

transition state

axial attack, X = O, Y = H
equatorial attack, X = H, Y = O

R = CH_3, C_2H_5, $C(CH_3)_3$

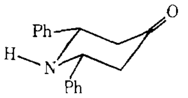
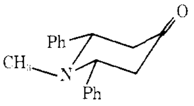
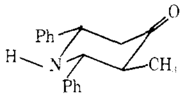
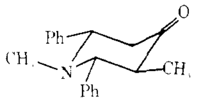
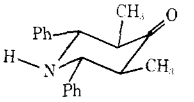
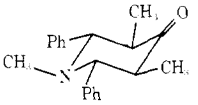
Chart II



4 (k_r = 88)

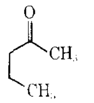
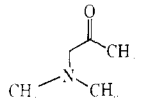
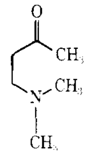
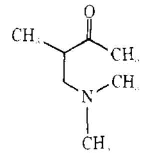
18 (k_r = 0.17)

Table II. Rate Constants for BH_4^- Addition on Substituted 4-Heterocyclanones[a]

products	no.	k, L mol^{-1} min^{-1}	% axial attack
	8	30	90[20] 91[b]
	11	55	92[20]
	12	6.5	86[20]
	13	10	86[20]
	14	0.35	56[20]
	15	0.52	55[20]

[a] In isopropyl alcohol, 0.1 M in NaOH at 25 °C, [BH_4^-] = 10^{-2}–10^{-3} M, and [>C=O] = 10^{-2}–10^{-3} M. [b] This work.

Table III. Rate Constants for BH_4^- Addition on Heterosubstituted Aliphatic Ketones[a]

products	no.	k, L mol^{-1} min^{-1}
	16	0.054
	17	0.14
	18	0.17
	19	0.12

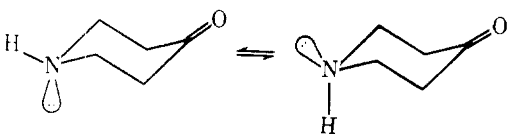
[a] In water–dioxane (50:50 by volume), 0.05 M in NaOH at 25 °C, [>C=O] = 10^{-2} M, and [BH_4^-] = 5 × 10^{-2} M.

chain minimizes these interactions.

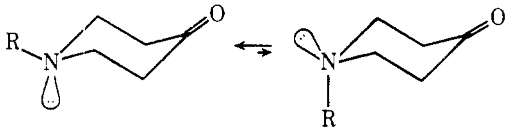
These conclusions agree with those made by Tarbell and Hazen in the solvolysis of the brosylates,[6] where, symetrically to the addition reaction, the hybridization of the reactive center changes from sp^3 to sp^2 and carries a positive charge.

N–R/N–H Effect. Throughout this series the replacement of N–H by N–CH_3 causes an increase in the ratio of reaction rate constants: $k_4/k_3 = 1.6$, $k_{11}/k_8 = 1.8$, $k_{13}/k_{12} = 1.6$, and $k_{15}/k_{14} = 1.5$. This result is difficult to rationalize only on the basis of the inductive effects of the methyl group. It is presumably due to conformational effects, i.e., a change in orientation of the nitrogen lone pair. In the secondary amine the

Scheme I



Scheme II



R = CH_3, C_2H_5, $C(CH_3)_3$

lone pair may be axial or equatorial,[21] and its orientation probably affects its transannular effect (Scheme I). In the tertiary amine the alkyl group is preferentially equatorial, and the partial negative charge is therefore preferentially axial[11] below the average plane of the cycle (Scheme II).

The reactivity of the *N*-ethyl derivative **5** is about the same as that of the *N*-methyl derivative 4, but the *N-tert*-butyl derivative **6** reacts only half as rapidly. This order of reactivity may be explained in the same way as in the nucleophilic addition reactions.[14-16] Thus, the *tert*-butyl group is a more efficient electron donor than the methyl or ethyl group and consequently decreases the partial positive charge on nitrogen. As a result, the interaction with the partial positive charge on the carbonyl carbon is less important; i.e., the ground state is less destabilized. On the other hand, in the transition state the partial positive charge distributed on the C atoms interacts with a developing negative charge on the reacting carbone; i.e., here the transition states of the *N*-methyl and *N*-ethyl derivatives are more stabilized (Chart I). These two effects make the *N*-methyl and *N*-ethyl derivatives more reactive than the *N-tert*-butyl derivative.

Ring Substituent Effect. Substitution at the 2 and 3 positions in the ring causes a decrease in reactivity. Introduction of phenyl groups in positions 2 and 6 decreases the reaction rate. This effect may be due to two factors. The phenyl groups are slightly electron withdrawing, and they are quasi-perpendicular to the plane of the molecule and hinder the approach of the reactant.[22]

Methyl substitution at positions 3 and 5 also slows down the reaction. Compared to the unsubstituted molecule, a methyl group at position 3 slows the reaction rate to 0.2 and one methyl group each at positions 3 and 5 slows the rate to 0.01: $k_{12}/k_8 = 0.22$, $k_{13}/k_{11} = 0.18$, $k_{14}/k_8 = 0.011$; $k_{15}/k_{11} = 0.010$.

This agrees with Wigfield's results[23] for the BH_4^- addition to α-substituted cyclanones and is presumably due to steric hindrance to approach of the reactant.

Experimental Section

Compounds **1-4, 7, 9, 16, 17,** and **19** were commercial products, which were purified by recrystallization, distillation, or chromatography. The remaining ketones were prepared according to published procedures: **5,**[24] **6,**[25] **8** and **11-15,**[20] **10,**[26] and **18.**[27]

Kinetic studies of the borohydride reduction were carried out under bimolecular conditions following the decrease in carbonyl absorption at 280 nm (25 °C) using a UV spectrometer as described in our earlier studies.[16] For reasons of solubility, two solvents have been used (water-dioxane or isopropyl alcohol). Under these conditions there was no decomposition of keto amines, and the curves obtained are completely compatible with an addition mechanism and with a second-order addition rate. We checked that the OD_∞ was zero with no appearance of secondary products. The rate constants were obtained by curve fitting based on the method of least squares. Error, expressed as the average deviation for at least three runs, was about 2%. Under our experimental conditions compounds **6, 8, 13,** and **15** gave >98% of the alcohol as previously determined,[18-20] and in the case of compound 8, 91% of the equatorial isomer was determined by LC analysis.

Registry No.—**1,** 108-94-1; **2,** 98-53-3; **3,** 41661-47-6; **4,** 1445-73-4; **5,** 3612-18-8; **6,** 1465-76-5; **7,** 1072-72-6; **8,** 5554-55-2; **9,** 14376-79-5; **10,** 826-36-8; **11,** 5554-56-3; **12,** 5554-57-4; **13,** 5554-58-5; **14,** 5707-11-9; **15,** 5554-59-6; **16,** 107-87-9; **17,** 15364-56-4; **18,** 2543-57-9; **19,** 22104-62-7; BH_4^-, 16971-29-2.

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