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MECHANISTIC ASPECTS OF THE REACTION OF OXIME TOSYLATES WITH GRIGNARD REAGENTS

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BY

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INTRODUCTION

The reaction of oximes with Grignard reagents has been reported to lead to aziridines, α-amino alcohols, and amines.[1] The formation of aziridines from the reaction of alkyl aryl oximes with Grignard reagents was first reported by Hoch.[2] Subsequently, Campbell[3-6] prepared a series of aziridine derivatives and established that alkyl aryl oximes underwent reaction with Grignard reagents to give aziridines when the intermediate Grignard complexes were decomposed in non-acidic media, while decomposition in acidic media gave the corresponding α-amino alcohols. If the reaction sequence suggested by Campbell (Fig. 1) were operating, then the same product would be expected from the reaction of acetophenone oxime (1) with ethylmagnesium bromide as from the reaction of propiophenone oxime (4) with methylmagnesium bromide, since the same intermediate complex (2) would be formed from these two reactions (Fig. 2). Henze and Compton[7], however, reported that the former reaction gave 2-ethyl-2-phenylaziridine (3), while the latter gave 2,3-dimethyl-2-phenylaziridine (5). From these results, it is apparent that the α-carbon atom of the alkyl group in the oxime became incorporated in the aziridine ring. Henze and Compton suggested that the direction of ring closure was determined by the configuration of the oxime and the proximity of the OMgBr group to the hydrogen of the alkyl group. It is difficult to explain this selective cyclization, since the carbon-nitrogen single bond in the intermediate complex 2 cannot be fixed, and free rotation about this bond would allow the hydrogens of the two alkyl groups to become more or less equivalent.

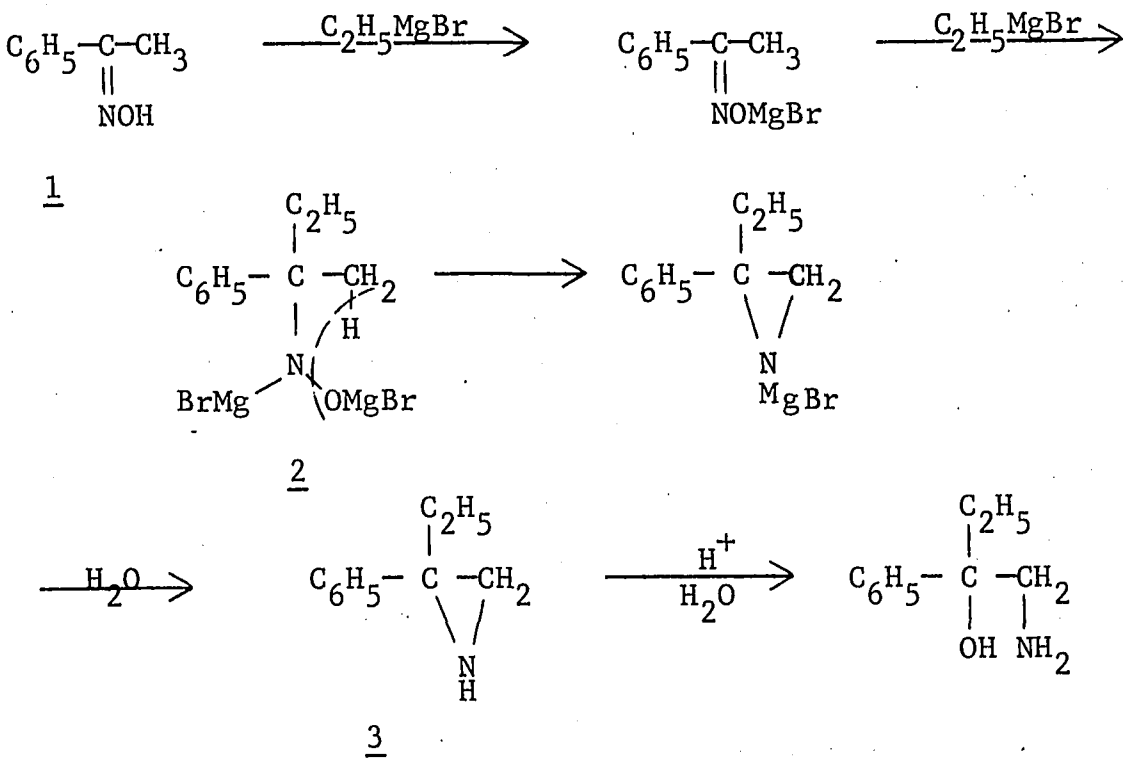


Fig. 1 Mechanism Proposed by Campbell et al.

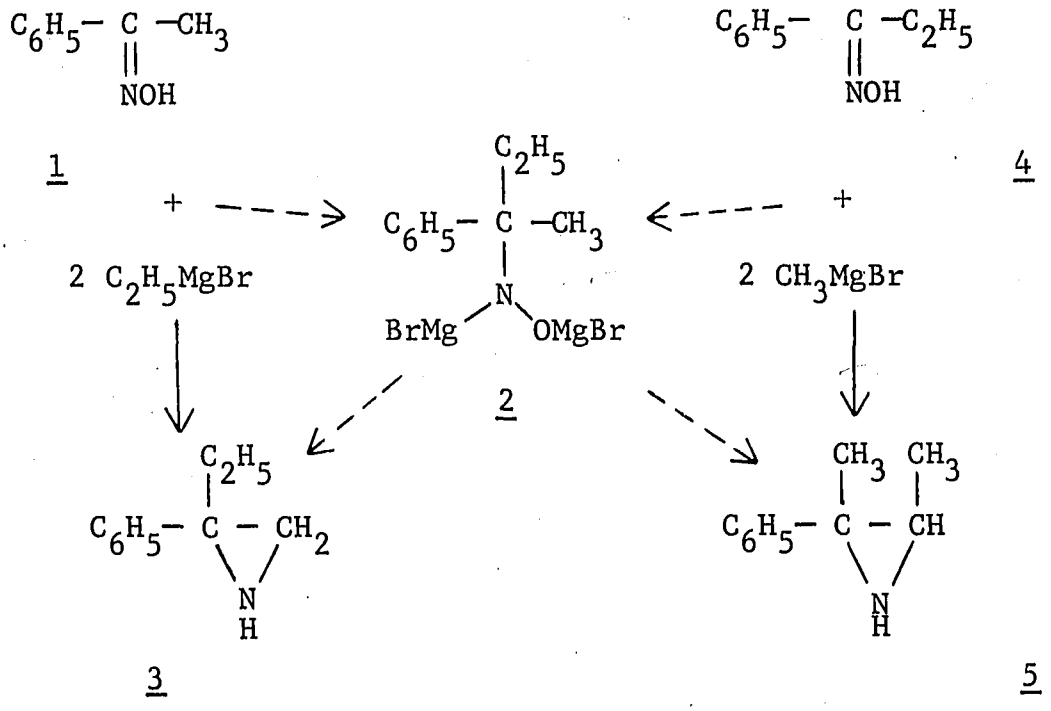
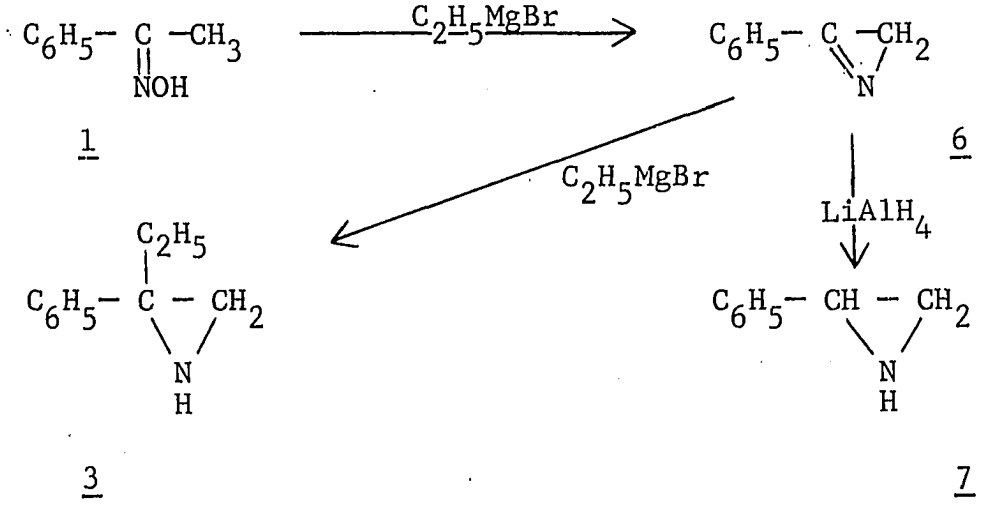


Fig. 2 Reactions of Oximes with Grignard Reagents.

During the development of this Thesis, Eguchi and Ishii[8] reported the confirmation of the work of Henze and Compton and suggested a more plausible reaction sequence in which the acidic hydrogen of the alkyl group is first



abstracted by the Grignard reagent, followed by cyclization to an azirine. Reaction of the Grignard reagent with this azirine intermediate then affords the substituted aziridine. The reaction of acetophenone oxime (1) with lithium aluminum hydride-ethylmagnesium bromide mixture gave a mixture of 64% of 2-ethyl-2-phenylaziridine (3), 1% of 2-phenylaziridine (7), and 35% of α-phenylethylamine. The formation of 2-phenylaziridine (7) suggested that 3-phenyl-2H-azirine (6) was indeed an intermediate. It was also shown that the reaction of 3-phenyl-2H-azirine (6) with ethylmagnesium bromide afforded 2-ethyl-2-phenylaziridine (3). The Neber rearrangement[9] of an oxime tosylate with strong base is probably similar to this cyclization reaction, and the mechanism[10,11] has been shown to involve an azirine intermediate.

Henze and Compton[7] also reported that dialkyl oximes underwent reaction with Grignard reagents to give aziridines.

The reaction of diaryl oximes with Grignard reagents could not afford aziridines, since they possess no α-carbon atom bearing a hydrogen atom. Hoch[12] reported that the reaction of benzophenone oxime with phenylmagnesium bromide gave o-phenylbenzhydrylaniline, and Campbell[3] later confirmed his findings.

The reactions of oximes with Grignard reagents do not take place readily except as active hydrogen replacement reactions. All other reactions reported have been carried out under "forced" conditions (with concentrated solutions of Grignard reagents or with high boiling solvents) and generally proceed in relatively poor yields. In the case of dialkyl oximes, Henze and Compton[7] reported the formation of an insoluble intermediate, probably $R_2C{=}NOMgBr$, in considerable amounts. The fact that oximes are relatively unreactive may be attributed to the formation of a negative charge on the oxygen atom on removal of the proton by an initial reaction with the Grignard reagent. While carboxylic acids are unreactive towards Grignard reagents (except as active hydrogen replacement reactions), their corresponding esters readily undergo an addition-elimination reaction. It seemed desirable, therefore, to replace the oximino hydrogen by a substituent unreactive to the Grignard reagent. The O-alkyl and O-tosyl derivatives of oximes offered such a type of compound, and their reactions with Grignard reagents are described in this Thesis.

DISCUSSION AND RESULTS

Reactions of Oximes with Phenylmagnesium Bromide

The selective stereochemical requirements imposed by the rigid steroidal nucleus and the possible formation of amino and azasteroids prompted the selection of 5α-cholestan-3-one oxime (8) as a model compound for this investigation. The starting material, cholesterol (9), was hydrogenated over platinum oxide as catalyst to give 5α-cholestan-3β-ol (10), and chromic acid oxidation of 10 afforded 5α-cholestan-3-one (11). Oximation of 11 with hydroxylamine hydrochloride gave 5α-cholestan-3-one oxime (8), and the O-methyl (12), O-benzoyl (13), and O-acetyl (14) derivatives of oxime 8 were prepared. All attempts to prepare the O-tosyl (15) derivative of oxime 8 failed resulting in the isolation of unreacted oxime and/or 3-aza-A-homo-5α-cholestan-4-one (16) which was identical with the lactam obtained from the Beckmann rearrangement of oxime 8.

The reaction of 5α-cholestan-3-one oxime (8) with phenylmagnesium bromide according to the procedure described by Campbell[3] did not give the expected steroidal aziridine. A basic material, however, was isolated as the hydrochloride (17) (6% yield) and was identified as aniline (18). Unreacted oxime 8 (58%) was also recovered. An unidentified material (19) separated at the ether-water interface during the work-up. The elemental carbon analysis of this solid was 16% lower than that calculated for the expected steroidal aziridine. The infrared spectrum of compound 19 contained strong bands at 3350-3314 cm^{-1}, indicative of the nitrogen-hydrogen or oxygen-hydrogen stretching vibration of an amine or hydroxyl group, and at 757 and 697 cm^{-1}, indicative of the

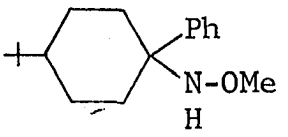
carbon-hydrogen out of plane bending of a mono-substituted phenyl group. No further work was done to determine the structure of this material.

When the reaction of 8 with phenylmagnesium bromide was carried out using tetrahydrofuran as the solvent, a greater yield (24%) of aniline hydrochloride was obtained. Similarly, the reaction of 4-t-butylcyclohexanone oxime (22) with phenylmagnesium bromide gave aniline hydrochloride (6%) along with the recovery of unreacted oxime 22 (59% yield). The isolation of aniline from these reactions suggested a reaction pathway involving a novel molecular rearrangement.

Reactions of 4-t-Butylcyclohexanone Oxime, Methyl Ether with Organometallic Reagents

It is apparent that the reactions of oximes with Grignard reagents are difficult, probably due to the formation of a negative charge on the oxygen atom on removal of the proton by an initial reaction with the Grignard reagent. It seemed desirable, therefore, to replace the oximino hydrogen with a substitutent unreactive to the Grignard reagent. The O-methyl derivative of an oxime offered such a substituent. Therefore, 4-t-butylcyclohexanone oxime, methyl ether (24) was prepared from 4-t-butylcyclohexanone (21) and methoxyamine hydrochloride. Treatment of 24 with phenylmagnesium bromide according to the procedure described by Campbell[3] gave an oil which was tentatively identified as N-methoxy-4-t-butyl-1-phenylcyclohexylamine (25). Gas chromatographic analysis showed 25 to be contaminated with aniline and biphenyl. The infrared spectrum contained a medium band at 3290 cm^{-1}, indicative of the nitrogen-hydrogen stretching vibration of an amine, medium bands at 1053 and 1022 cm^{-1}, indicative of the carbon-oxygen stretching vibration of an ether, and strong bands at 757 and 695 cm^{-1}, indicative of the carbon-hydrogen

out of plane bending of a phenyl group.



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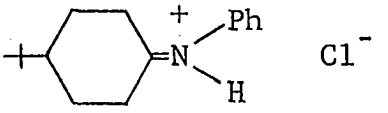

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When an ethereal solution of 25 was treated with hydrogen chloride, the solution became red but no solid was deposited. With excess hydrogen chloride a white solid was deposited which was identified as the hydrochloride (26) of 25. This peculiar hydrochloride formation suggested that a reaction could have occurred to give a rearranged hydrochloride such as 27 whose chlorine analysis (13.34%) was in agreement with the experimental analysis (12.99%). The infrared spectrum of the base generated from 26, however, was nearly identical to the infrared spectrum of 25, thereby indicating that no rearrangement had occurred. Since 25 is a substituted hydroxylamine, it should be a weak base, and it is, therefore, reasonable that an excess of hydrogen chloride was required for hydrochloride formation.

The reaction of 4-t-butylcyclohexanone oxime, methyl ether (24) with phenyllithium at the temperature of refluxing ether gave aniline hydrochloride (6% yield) which was the only product isolated which contained nitrogen. Treatment of the non-basic material with 2,4-dinitrophenylhydrazine reagent gave 4-t-butylcyclohexanone 2,4-dinitrophenylhydrazone (29) which was identical with an authentic sample. It should be noted that large amounts of resinous material were obtained from this reaction and the reaction of 24 with phenylmagnesium bromide.

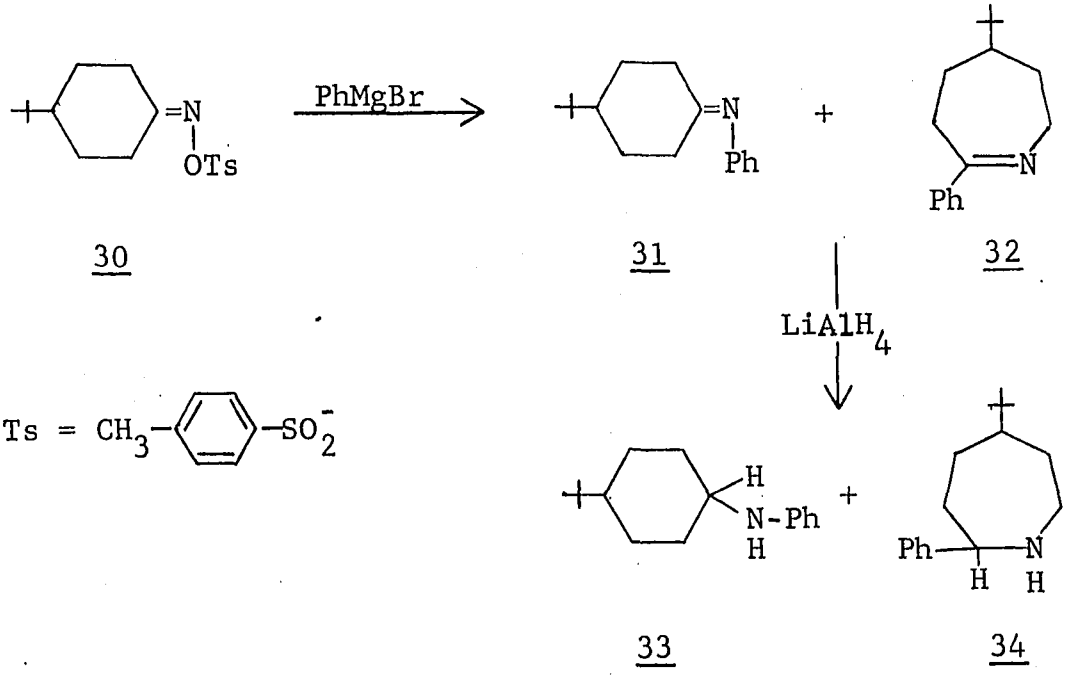
After this investigation was completed, Marxer and Horvath[13] reported that the reaction of n-butyllithium with cyclohexanone oxime, butyl ether at 0° occurred with addition

to the carbon-nitrogen double bond to give N-butoxy-1-butylcyclohexylamine (28). The structural assignment of 25 is, therefore, in agreement with the findings of Marxer and Horvath. Since the reactions investigated in this Laboratory were carried out under more drastic conditions, it was not surprising that large amounts of resinous material were obtained. It is apparent that the O-alkyl derivatives of oximes were much more reactive toward organometallic reagents than were the oximes.

Reaction of 4-t-Butylcyclohexanone Oxime Tosylate with Phenylmagnesium Bromide

A more interesting series of reactions was observed with O-tosyl derivatives of oximes. Since the tosylate ion is a good leaving group, reactions resulting from an electron-deficient nitrogen were anticipated. A detailed investigation was made of the reaction of 4-t-butylcyclohexanone oxime tosylate (30) with phenylmagnesium bromide, and the product was found to be a mixture of 4-t-butylcyclohexanone anil (31) and 4-t-butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32) in a 55-58% yield based on oxime 22. Gas chromatographic analysis of this mixture indicated the composition of 21% of 31 and 79% of 32. The infrared spectrum of the Schiff's base mixture (31 and 32) contained strong bands at 1665 and 1635 cm^{-1}, indicative of the carbon-nitrogen double bond stretching vibration, and at 774 and 693 cm^{-1}, indicative of the carbon-hydrogen out of plane bending of a phenyl group. Reduction of the Schiff's base mixture (31 and 32) by lithium aluminum hydride gave a mixture of 1-anilino-4-t-butylcyclohexane (33) and 5-t-butyl-2-phenylhexamethylenimine (34). The infrared spectrum of the reduction mixture (33 and 34) contained a weak

band at 3350 cm^{-1}, indicative of the nitrogen-hydrogen stretching vibration of an amine, and no bands between 1700-1600 cm^{-1}, indicating reduction of the carbon-nitrogen double bond.

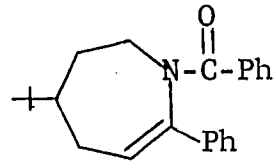


It was established that 4-t-butylhexamethylenimine (45) was not one of the products obtained from the lithium aluminum hydride reduction of the Schiff's base mixture (31 and 32). Lithium aluminum hydride reduction of 5-t-butyl-hexahydro-2H-azepin-2-one (41) which was prepared by the Beckmann rearrangement of 4-t-butylcyclohexanone oxime tosylate (30) gave 4-t-butylhexamethylenimine (45). This compound (45) was not identical with 33 or 34.

Since the Schiff's base mixture (31 and 32) could not be separated by physical methods, the use of chemical methods was investigated. When the mixture of 31 and 32 was treated with dilute hydrochloric acid, 31 underwent hydrolysis to 4-t-butylcyclohexanone (21) and aniline while 32 was recovered unchanged. Thus the structure of 31 was confirmed

by hydrolysis to 21 and aniline. A study of the chemical reactions of 32 was, therefore, undertaken to confirm the structural assignment.

The reaction of 32, which was contaminated with aniline from the hydrolysis of 31, with benzoyl chloride and sodium hydroxide produced a benzoyl derivative of 32 to which structure 35 was assigned on the basis of the following spectroscopic data. The infrared spectrum of 1-benzoyl-4-t-butyl-2,3,4,5-tetrahydro-7-phenyl-1H-azepine (35) contained strong bands at 1665 cm^{-1}, indicative of the carbonyl stretching vibration of an amide, and at 1640 cm^{-1}, indicative of the carbon-carbon double bond stretching vibration of an enamine. The ultraviolet absorption spectrum showed a maximum at 251 mμ (ε 17,100). The proton magnetic resonance spectrum showed a multiplet at 7.00 p.p.m. due to ten aromatic hydrogens, a triplet at 5.83 p.p.m. due to one vinyl hydrogen, and a singlet at 0.97 p.p.m. due to the nine t-butyl hydrogens.



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Compound 32, from the acid hydrolysis of the Schiff's base mixture (31 and 32) and contaminated with aniline, was reduced by lithium aluminum hydride to give 5-t-butyl-2-phenylhexamethylenimine (34). The reaction of 34 with benzenesulfonyl chloride and sodium hydroxide produced an insoluble benzenesulfonamide which was indicative of a secondary amine. The ultraviolet absorption spectrum of 34 showed

maxima at 263 (157), 257 (213), and 252 mμ (ε 198) which are characteristic of an isolated phenyl chromophore. This evidence suggested structure 34 to be the product of reduction by lithium aluminum hydride and, therefore, structure 32 to be Schiff's base formed during the Grignard reaction by a ring enlargement.

It was desirable, therefore, to show that the nitrogen atom was in the ring through application of the Hofmann degradation[14] (Fig. 3). 5-t-Butyl-2-phenylhexamethylenimine (34) was methylated with formic acid and formaldehyde to give 5-t-butyl-1-methyl-2-phenylhexamethylenimine (37). The infrared spectrum of 37 contained a medium band at 2800 cm^{-1}, indicative of the carbon-hydrogen stretching vibration of the N-methyl group. The proton magnetic resonance spectrum 37 contained a singlet at 2.13 p.p.m., indicative of the N-methyl hydrogens. Compound 37 was treated with methyl iodide to give the corresponding methiodide 38. Pyrolysis of the quaternary hydroxide of 38 gave (3-t-butyl-6-phenyl-5-hexenyl)-dimethylamine (40) which showed an ultraviolet absorption spectrum characteristic of a β-alkyl styrene, λ_{max} 292 (831) and 284 mμ (ε 16,800). Infrared data indicated that the single product (40) from the Hofmann elimination contained both the styryl and dimethylamino functions. The proton magnetic resonance spectrum of 40 showed a singlet at 0.93 p.p.m. due to the nine t-butyl hydrogens, a singlet at 2.10 p.p.m. due to the six N-methyl hydrogens, a doublet at 6.30 p.p.m. due to one vinyl hydrogen, and a multiplet at 7.22 p.p.m. due to six hydrogens (five aromatic hydrogens and one vinyl hydrogen). Thus the spectroscopic data clearly supports the assignment of structure 40 as the product of the Hofmann elimination reaction.

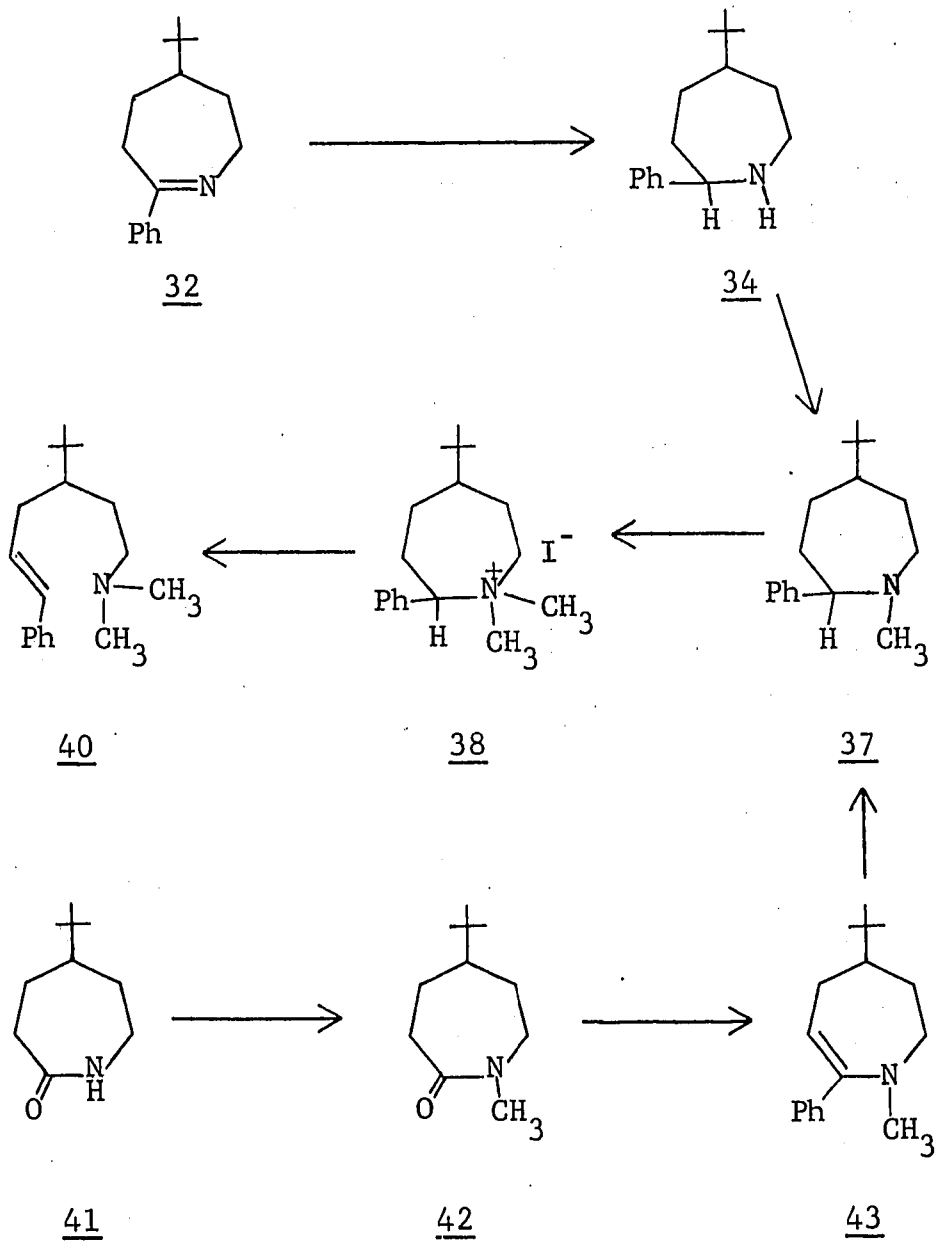


Fig. 3 Hofmann Degradation and Alternate Synthesis of 5-t-Butyl-1-methyl-2-phenylhexamethylenimine (37).

Unequivocal evidence for the assignment of structure 32 was obtained by an alternate synthesis of 37 employing 5-t-butylhexahydro-2H-azepin-2-one[15] (41) as starting material (Fig. 3). Compound 41 gave no reaction with phenylmagnesium bromide (or phenyllithium) under the reaction conditions (even in refluxing ether) employed in the reaction of 4-t-butylcyclohexanone oxime tosylate (30) with phenylmagnesium bromide, for 41 was recovered unreacted. Since it had been shown that N-alkyl-2-piperidones[16] underwent reaction with Grignard reagents, compound 41 was methylated with sodium hydride and dimethylsulfate in benzene to give 5-t-butylhexahydro-1-methyl-2H-azepin-2-one (42). Reaction of 42 with phenylmagnesium bromide (1:1 molar ratio) gave the expected enamine, 4-t-butyl-2,3,4,5-tetrahydro-1-methyl-7-phenyl-1H-azepine (43) whose infrared spectrum contained a strong band at 1625 cm^{-1}, indicative of the carbon-carbon double bond stretching vibration of the enamine. Treatment of an ethereal solution of 43 with a mixture (1:1 by volume) of perchloric acid[17] and ethanol gave 4-t-butyl-3,4,5,6-tetrahydro-1-methyl-7-phenyl-2H-azepinium perchlorate (44) whose infrared spectrum contained strong bands at 1115-1070 cm^{-1}, indicative of the perchlorate anion[18], and at 1651 cm^{-1}, indicative of the carbon-nitrogen double bond stretching vibration of the enamine salt. Inspection of the infrared spectra of 43 and 44 revealed that the characteristic band of the enamine in the carbon-carbon double bond stretching region had undergone a shift of 26 cm^{-1} to higher frequency on conversion of 43 to 44. This shift toward higher frequency in the infrared absorption on salt formation has been used in the identification of enamines.[19]

Reduction of the enamine 43 with sodium borohydride and acetic acid[20] in tetrahydrofuran gave 5-t-butyl-1-methyl-

2-phenylhexamethylenimine (37) which was identical in every respect with that prepared from 34. The infrared spectra of the two solids (37) were identical, and a mixture melting point showed no depression. The infrared spectra of the respective methiodides (38) were also identical, and a mixture melting point of the two solids showed no depression.

The formation of 32 could not occur from the lactam 41, for 41 was shown to be completely resistant to reaction with phenylmagnesium bromide or phenyllithium. Because of the formation of both 31 and 32, the most probable mechanism for the reaction of 30 with phenylmagnesium bromide seemed to be addition of the Grignard reagent to the carbon-nitrogen double bond with subsequent loss of tosylate ion with simultaneous rearrangement of a phenyl group or the ring methylene. It was also possible that the rearrangement could proceed through a "nitrene"[11,21] intermediate resulting from the initial loss of tosylate ion and subsequent migration of a phenyl group or the ring methylene (Fig. 4).

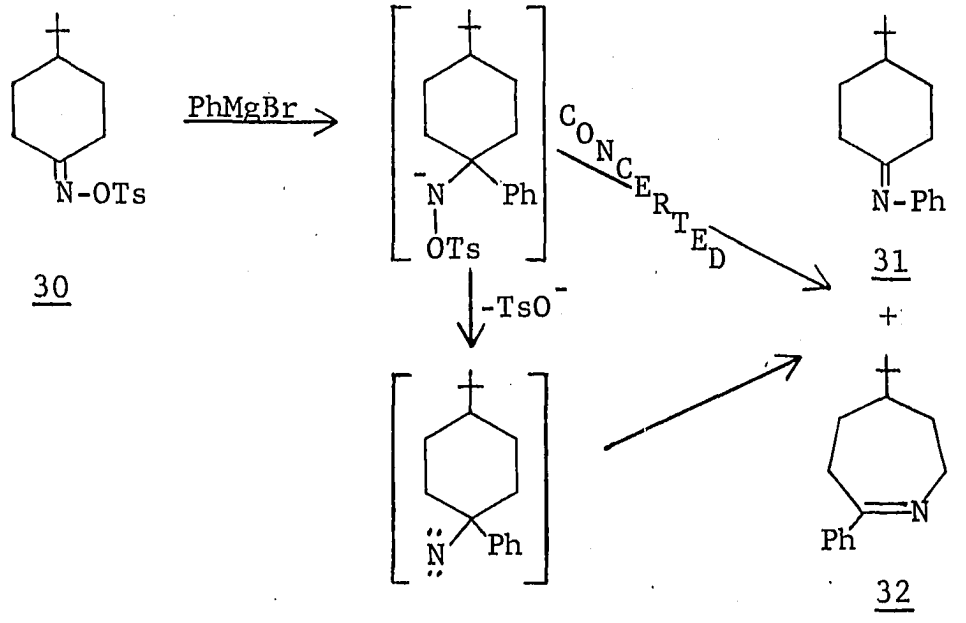


Fig. 4 Mechanism A of the Reaction of 4-t-Butylcyclohexanone Oxime Tosylate with Phenylmagnesium Bromide.

Reaction of Methyl Ethyl Ketoxime Tosylate with Phenylmagnesium Bromide

Further evidence that the reaction sequence involved a molecular rearrangement was obtained from the reaction of methyl ethyl ketoxime tosylate (54) with phenylmagnesium bromide which gave a mixture of aniline (48%), acetophenone (42%) and propiophenone (10%) (Fig. 5 and Table II). The reaction mixture was decomposed with dilute hydrochloric acid to insure complete hydrolysis of the Schiff's bases to their respective amine and ketone fragments, and the product mixture was analyzed by gas chromatography. The relative yields were calculated for the higher boiling component (either amine or ketone) and represent the area under the respective peak in the gas chromatogram (Fig. 9).

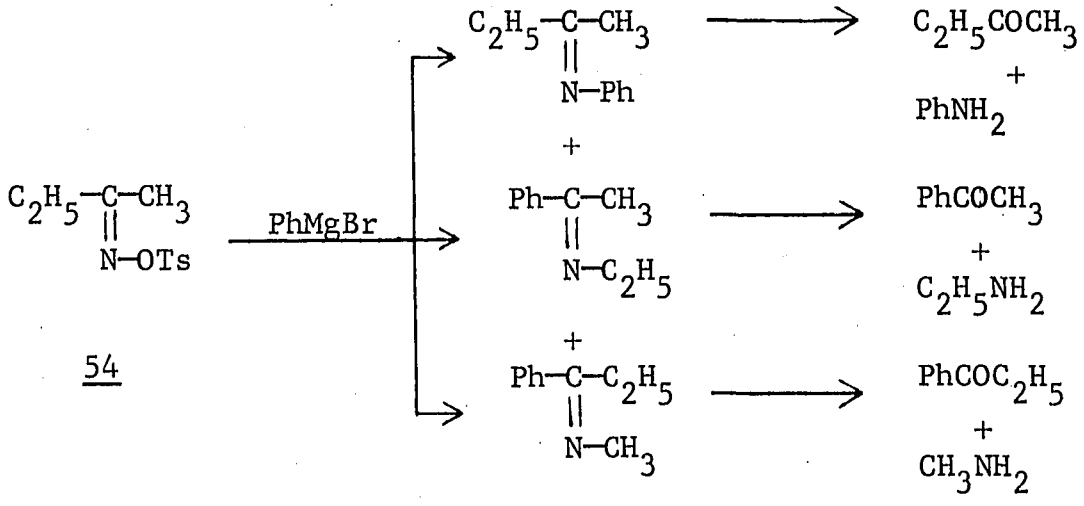


Fig. 5 Reaction of Methyl Ethyl Ketoxime Tosylate with Phenylmagnesium Bromide.

Reactions of Benzophenone Oxime Tosylate with Grignard Reagents

In an effort to determine the possibility of the rearrangement proceeding through a "nitrene", experiments were designed to determine the substituent effect of substituted phenyls on the ease of rearrangement. A concerted mechanism occurring with loss of tosylate ion and simultaneous rearrangement of the migrating group would be influenced by the nature of the migrating group (migratory aptitude) and, therefore, would be expected to show a substituent effect. On the other hand, a "nitrene" would be expected to be a highly reactive intermediate indiscriminate in character and show no substituent effect.

Benzophenone oxime tosylate (48) underwent reaction readily with phenylmagnesium bromide to give benzophenone anil (49) which on hydrolysis gave benzophenone and aniline. When benzophenone oxime tosylate (48) was treated with a series of p-substituted phenylmagnesium bromides ($-OCH_3$, $-CH_3$, $-Cl$, $-CF_3$), the only product which contained nitrogen was aniline. The reaction of p-tolylmagnesium bromide with 48 gave aniline and phenyl p-tolyl ketone. These results required that a rearrangement of the tosylate had occurred before reaction with the Grignard reagent. The intermediate which was produced must not be the amide which was shown to be resistant to reaction with the Grignard reagent. Thus the reaction sequence shown in Fig. 6 was considered.

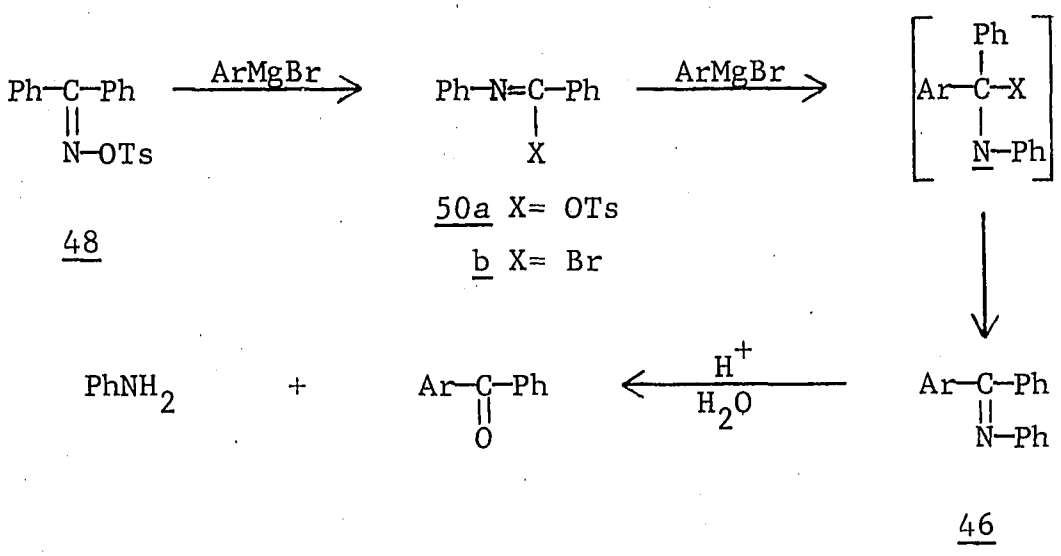


Fig. 6 Mechanism of the Reaction of Benzophenone Oxime Tosylate with Grignard Reagents.

Effect of Magnesium Bromide on Tosylates

In view of these results a study of the ultraviolet absorption of benzophenone oxime tosylate (48) solutions was undertaken to determine the nature of the rearrangement of the tosylate which occurred prior to reaction with the Grignard reagent. The absorption spectra of ethereal solutions of benzophenone oxime tosylate (48) after treatment with water and drying over magnesium sulfate or potassium carbonate were nearly identical (λ_{max} 249 mμ) with the spectrum of benzophenone oxime (47) (λ_{max} 250 mμ) showing that no rearrangement had occurred. An ethereal solution of benzophenone oxime tosylate (48) [λ_{max} 249 mμ (ε 16,100)] after treatment with anhydrous magnesium bromide showed a striking change in absorption in the ultraviolet spectrum now exhibiting maxima at 315 (2680) and 245 mμ (ε 19,300) indicative of structure 50 (Fig. 7). Compound 50 (X=$PhSO_3$) has been reported previously[22]; however, insufficient information was given to allow a comparison. This type of intermediate (50)

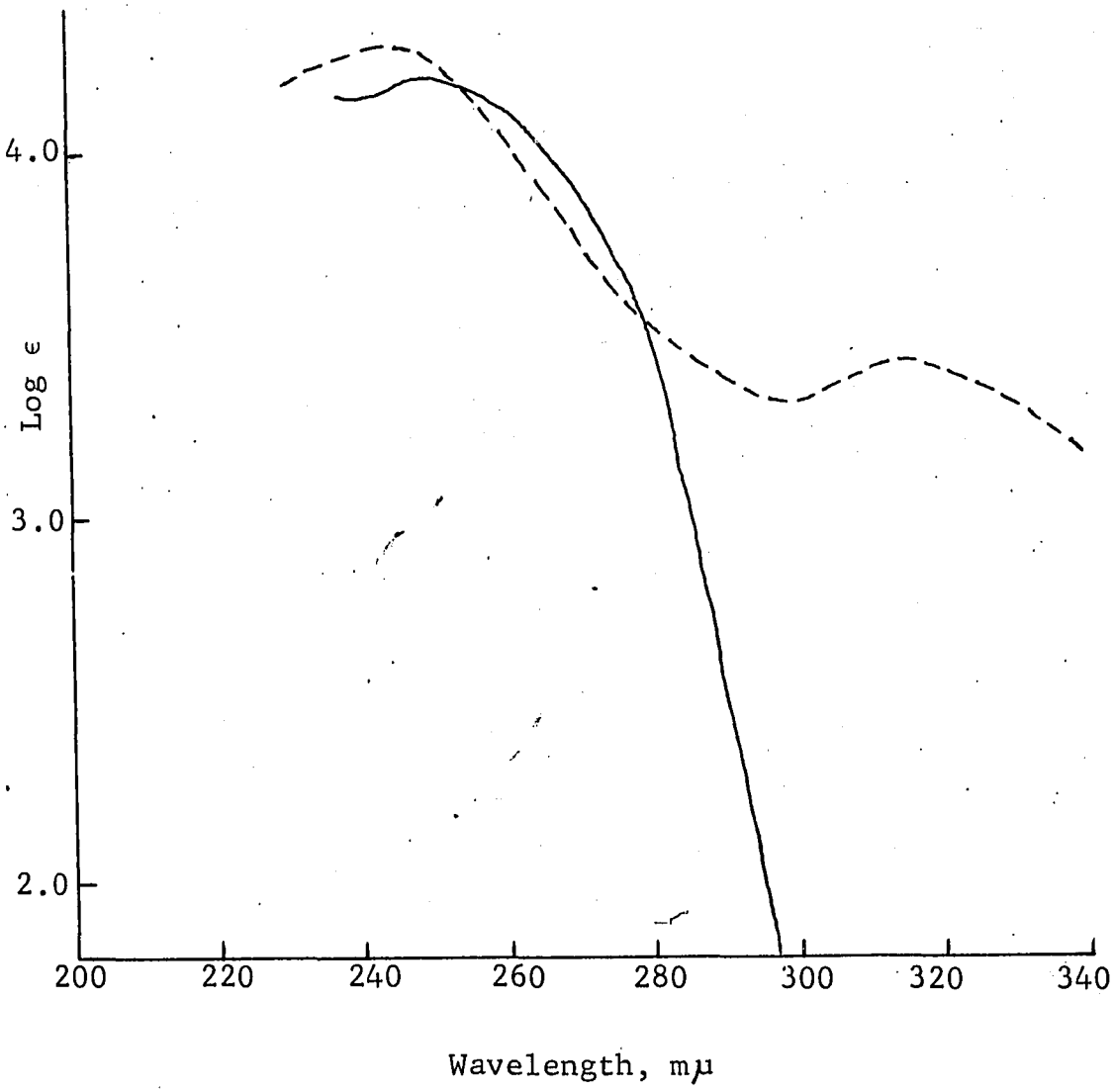
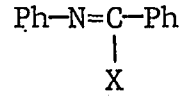


Fig. 7 Ultraviolet Absorption Spectra of Benzophenone Oxime Tosylate Before (—) and After Treatment with Magnesium Bromide (---).

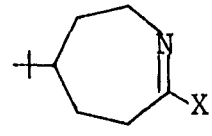
has been proposed and confirmed for Beckmann rearrangements of a number of O-substituted oxime derivatives.[23]



50a X= OTs

b X= Br

To distinguish between an imidyl tosylate and an imidyl bromide as the intermediate (50), a similar study of the ultraviolet absorption spectra of 4-t-butylcyclohexanone oxime tosylate (30) was made under varying conditions. The absorption spectrum of an ethereal solution of 30 showed maxima at 272 (415), 265 (582), 262 (593) and 256 mμ (ε 470). An ethereal solution of 30 after treatment with anhydrous magnesium bromide showed a striking change in absorption in the ultraviolet spectrum exhibiting now only one maximum at 271 mμ (ε 2260) indicative of structure 51a rather than 51b (Fig. 8).



51a X= OTs

b X= Br

The ultraviolet absorption spectrum of an ethereal solution of p-toluenesulfonyl chloride after treatment with anhydrous magnesium bromide was nearly identical with the spectrum of p-toluenesulfonyl chloride showing maxima at 278sh(700), 270sh(1350) and 242 mμ (ε 9,700). This indicated

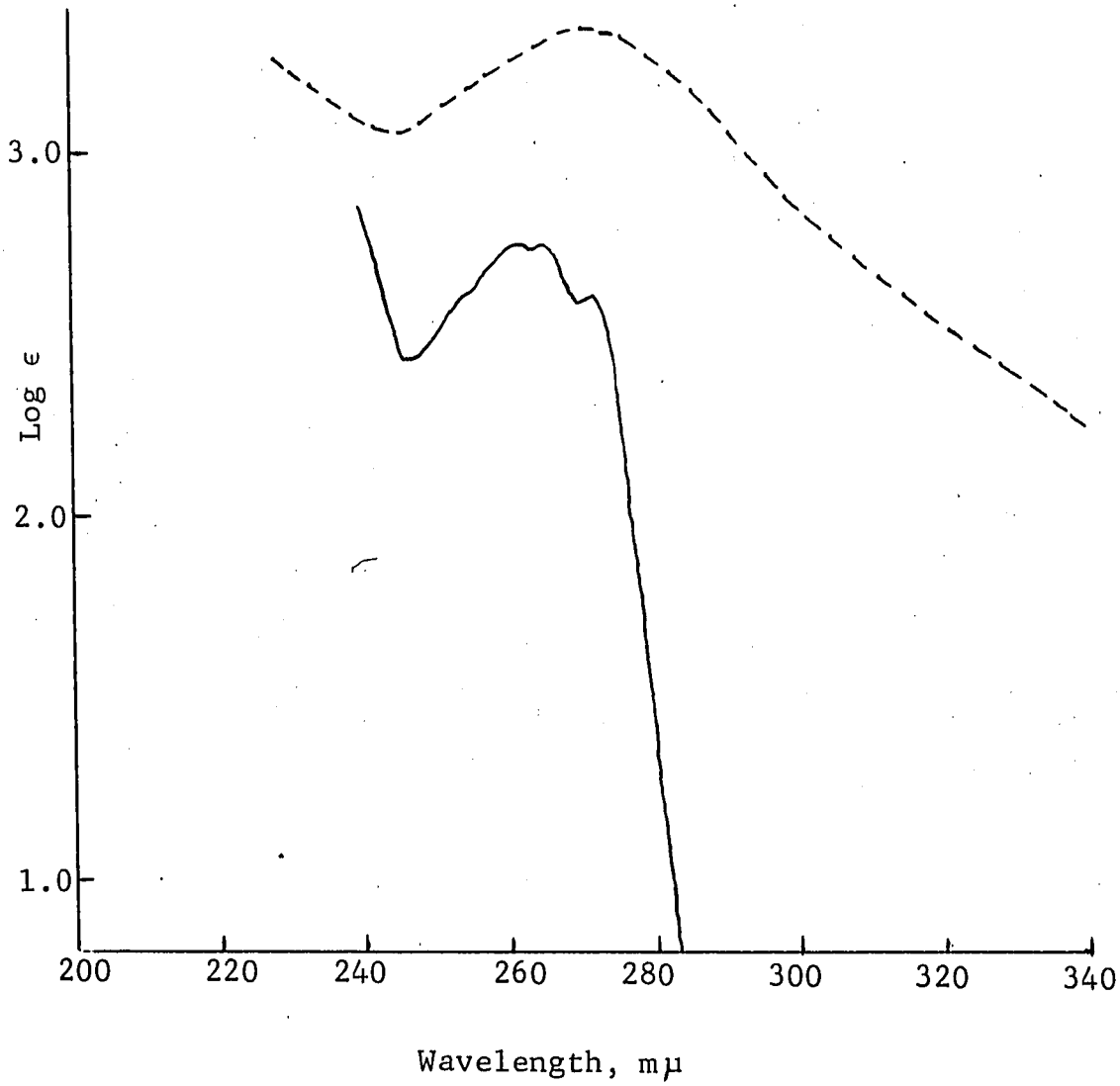


Fig. 8 Ultraviolet Absorption Spectra of 4-t-Butylcyclohexanone Oxime Tosylate Before (—) and After Treatment with Magnesium Bromide (---).

that the differences in the absorption spectra of tosylates 48 and 30 after treatment with anhydrous magnesium bromide were due to structural changes in the tosylates and not in p-toluenesulfonyl chloride which could have been present as an impurity.

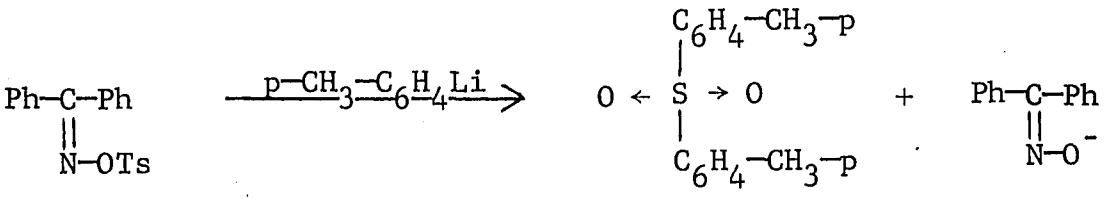
Reactions of Tosylates with Magnesium Bromide and Phenylmagnesium Bromide

Evidence for rearrangement of the tosylate prior to reaction with the Grignard reagent was obtained with 4-t-butylcyclohexanone oxime tosylate (30) and methyl ethyl ketoxime tosylate (54). These tosylates when pretreated with anhydrous magnesium bromide and then phenylmagnesium bromide gave only the products expected from a Beckmann-like rearrangement prior to reaction with the Grignard reagent. Thus 30 gave only 4-t-butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32) with no evidence for the formation of 4-t-butylcyclohexanone (21) or aniline (Table I). The reaction of methyl ethyl ketoxime tosylate (54) under similar reaction conditions gave only acetophenone (82%) and propiophenone (18%) (Fig. 9 and Table II). Since no aniline was obtained, complete rearrangement of the tosylate must have occurred prior to introduction of the phenylmagnesium bromide.

Reaction of Benzophenone Oxime Tosylate with p-Tolyllithium

To avoid the presence of magnesium bromide in the solution of the organometallic reagent, the reaction of benzophenone oxime tosylate (48) with p-tolyllithium was investigated. Unfortunately, the reaction proceeded with attack of p-tolyllithium on the sulfur atom rather than the carbon-nitrogen double bond to give p,p'-ditolylsulfone (57). Forma-

tion of sulfones has been reported to occur in the reaction of organonitrosohydroxylamine tosylates with phenyllithium.[24] On consideration of other reactions of tosylate esters this is not an unexpected reaction.[25-27]



48 57

Reactions of Tosylates with Diorganomagnesium Reagents

Schlenk and Schlenk[28] demonstrated that virtually all the halogen and part of the magnesium can be precipitated from an ethereal solution of a Grignard reagent by the addition of dioxane. This dioxane precipitation procedure of Schlenk has been shown to be an excellent method for the preparation of diorganomagnesium compounds.[29-32]

To avoid the presence of magnesium bromide in the solution of the organometallic reagent, the reaction of tosylates with dialkyl- and diarylmagnesium reagents (containing little or no magnesium bromide) was investigated. The reaction of 4-t-butylcyclohexanone oxime tosylate (30) with diphenylmagnesium gave aniline as the only product which contained nitrogen (Table I). Similarly, the reaction of methyl ethyl ketoxime tosylate (54) with diphenylmagnesium gave aniline (99%) and acetophenone (1%) (Fig. 9 and Table II). Hence, without magnesium bromide, no rearrangement of the tosylate occurred prior to reaction with the organometallic reagent.

Table I

Reactions of 4-t-Butylcyclohexanone Oxime Tosylate with Organometallic Reagents

Organometallic Reagent	Relative % Yields of 31	32
Ph_2Mg	100	--
PhMgBr	21	79
$MgBr_2$, PhMgBr	--	100

Table II

Reactions of Methyl Ethyl Ketoxime Tosylate with Organometallic Reagents

Organometallic Reagent	Relative % Yields of $PhNH_2$	$PhCOCH_3$	$PhCOC_2H_5$
Ph_2Mg	99	1	--
PhMgBr	48	42	10
$MgBr_2$, PhMgBr	--	82	18

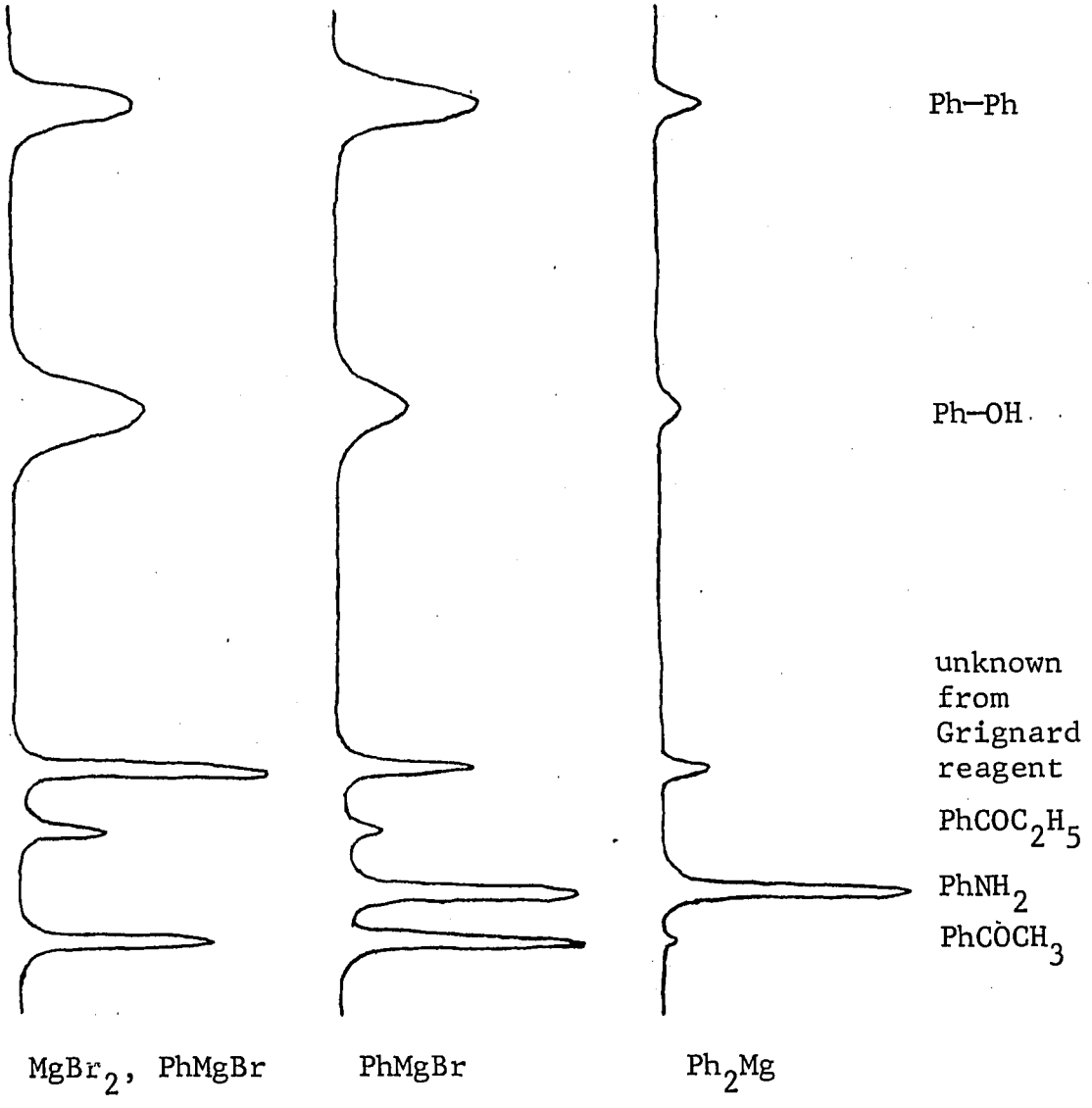


Fig. 9 Gas Chromatograms of the Product Mixtures from the Reactions of Methyl Ethyl Ketoxime Tosylate with Organometallic Reagents.

This additional information then required the following modification of the original mechanism proposed for the reaction of 4-t-butylcyclohexanone oxime tosylate (30) with phenylmagnesium bromide (Fig. 4). It was shown previously that the oxime tosylate of a phenyl ketone underwent rearrangement readily in an anhydrous medium in the presence of a Lewis acid to give the O-tosyl derivative of the amide 50a (Fig. 6). The O-tosyl derivative 50a then underwent rapid reaction with the Grignard reagent, most likely by an addition-elimination mechanism, to give the Schiff's base 46 which on hydrolysis gave aniline. A similar series of reactions most likely occurred with the oxime tosylates of aliphatic ketones. The rearrangement, however, was considerably slower, thereby allowing the competing reaction of the tosylate with the Grignard reagent to form the anil 31 to occur. This competing reaction could occur by addition of the Grignard reagent to the carbon-nitrogen double bond of the tosylate with subsequent loss of tosylate ion with rearrangement of a phenyl group or the ring methylene or by a direct displacement of tosylate ion by the Grignard reagent (Fig. 10).

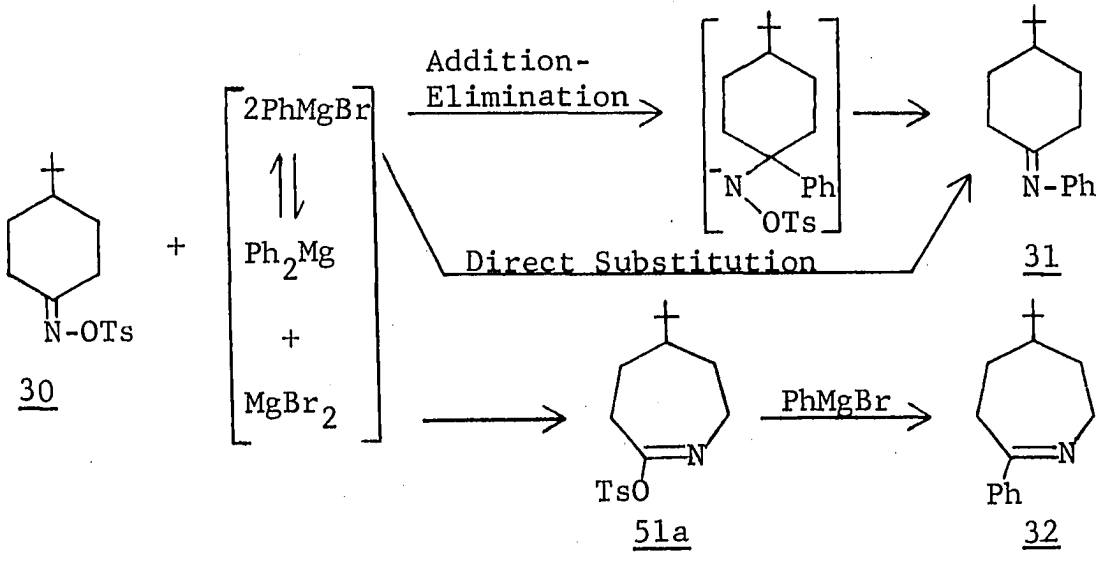


Fig. 10 Mechanism B of the Reaction of 4-t-Butylcyclohexanone Oxime Tosylate with Phenylmagnesium Bromide.

Table III

Reactions of Tosylates with Diorganomagnesium Reagents

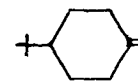
Reaction Number	Oxime Tosylate of	Diorganomagnesium Reagent	Products[a]	Relative Yields[b]
I		Ph_2Mg	$PhNH_2$	100
II	$CH_3COC_2H_5$	Ph_2Mg	$PhNH_2$	99
			$PhCOCH_3$	1
III	$PhCOCH_3$	$(C_2H_5)_2Mg$	$PhCOCH_3$	74
			$PhNH_2$	26
IV	p-Cl-$C_6H_4COCH_3$	$(C_2H_5)_2Mg$	p-Cl-$C_6H_4COCH_3$	76
			p-Cl-$C_6H_4NH_2$	24
V	p-Cl-$C_6H_4COCH_3$	Ph_2Mg	$PhNH_2$	69
			p-Cl-$C_6H_4NH_2$	31
VI	$PhCOCH_3$	$(p\text{-Cl-}C_6H_4)_2Mg$	p-Cl-$C_6H_4NH_2$	minor[c]
			$PhNH_2$	major

Table III (continued)

Reaction Number	Oxime Tosylate of	Diorganomagnesium Reagent	Products[a]	Relative Yields[b]
VII	$PhCOCH_3$	$(p\text{-}CH_3\text{-}C_6H_4)_2Mg$	$p\text{-}CH_3\text{-}C_6H_4NH_2$	39
			$PhNH_2$	61
			$PhCOCH_3$	42
			$p\text{-}CH_3\text{-}C_6H_4COCH_3$	58

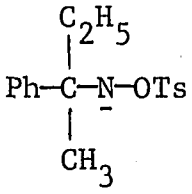
[a] Reactions were hydrolyzed with dilute hydrochloric acid to insure complete hydrolysis of the Schiff's bases to their respective amine and ketone fragments.

[b] Calculated for the higher boiling component (amine or corresponding ketone) and represent the area under the respective peak in the gas chromatogram.

[c] Relative yields could not be obtained since the reaction was hydrolyzed with ammonium chloride solution and $p\text{-}Cl\text{-}C_6H_4\text{-}C(CH_3)=N\text{-}Ph$ (66) (36%) was isolated.

In order to distinguish between these two possible mechanisms, a series of reactions of tosylates with diorganomagnesium reagents was studied. Previously described reactions of diphenylmagnesium with 4-t-butylcyclohexanone oxime tosylate (30) and methyl ethyl ketoxime tosylate (54) showed this reagent to cause little or no rearrangement prior to reaction with the organometallic reagent (see reactions I and II in Table III). The results of these diorganomagnesium reactions are given in Table III and are best explained by a direct displacement mechanism, for the amine (or corresponding ketone) expected from the direct displacement was consistently the major product in reactions I-V.

The results of reactions II and III, when evaluated together, support a direct displacement mechanism. If an addition-elimination mechanism were operating, then the product ratios would be expected to be identical, since both reactions would proceed through the same intermediate 67 resulting from addition of the organometallic reagent to the carbon-nitrogen double bond. However, the relative yields were reversed, and the major product from both reactions was the one expected from a direct displacement. Secondly, if an addition-elimination mechanism were operating, the product ratios in reactions III and IV would be determined by the migratory aptitudes of the substitutents (phenyl $\gg$ methyl and ethyl).[33] The product ratios, however, are contrary to those predicted on this basis and again are consistent with a direct displacement mechanism.



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Since the diorganomagnesium reagents are Lewis acids, it is not surprising that substantial amounts of product resulting from rearrangement of the tosylate prior to reaction with the diorganomagnesium reagent were observed. A comparison of the relative yields suggests that the amount of product formed by rearrangement is proportional to the Lewis acid strength of the diorganomagnesium reagent. This trend can be seen in reactions IV-VI in which the Lewis acid strength of the diorganomagnesium reagent probably increases in the order diethylmagnesium < diphenylmagnesium < p,p'-dichlorophenylmagnesium estimated from the relative acidities of beryllium compounds.[34] The relative yield of the product of rearrangement also increased in this order.

The structure of the tosylate appears to be a second factor in determining the amount of product formed by rearrangement. The oxime tosylates of aliphatic ketones apparently do not undergo rearrangement readily in the presence of a Lewis acid (see reactions I and II), while the oxime tosylates of aryl ketones do undergo rearrangement readily. Consider, for example, the reaction of benzophenone oxime tosylate (48) mentioned previously. Thus the reaction of alkyl aryl oxime tosylates with diarylmagnesium reagents may be expected to give greater amounts of product of rearrangement rather than direct displacement as was observed in reactions VI and VII.

Reactions of 1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate with Organometallic Reagents

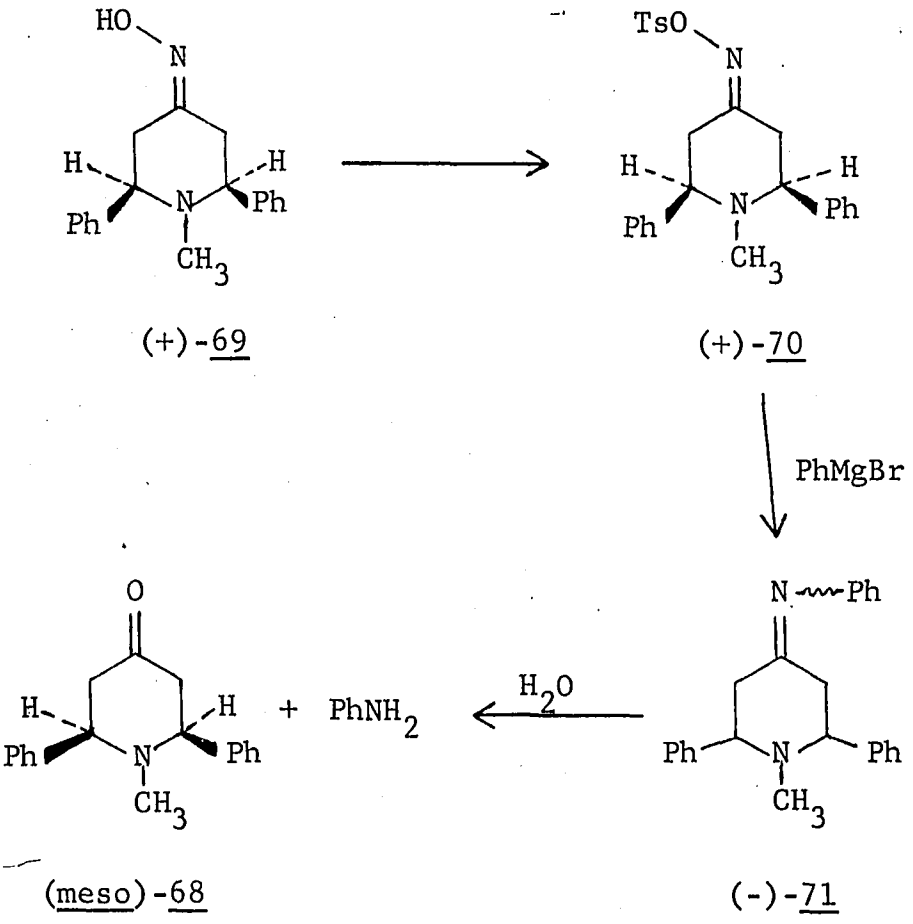
Resolution of 1-methyl-2,6-diphenyl-4-piperidone oxime (69) prepared from the meso piperidone 68 has been reported by Lyle and Lyle[35] to give the dextrorotatory isomer. The optical activity of (+)-69 was caused by the molecular asymmetry of the unsymmetrically substituted carbon-nitrogen double bond of the oximino function. Subsequently, the absolute configuration of the dextrorotatory isomer of 69 was established by Lyle and Tyminski[36] (see Fig. 11).

The reaction of the tosylate of such an optically active oxime with a Grignard reagent offered a means of distinguishing between an addition -elimination mechanism and a direct displacement mechanism. If the reaction occurred with addition of the Grignard reagent to the carbon-nitrogen double bond followed by loss of tosylate ion with rearrangement of the migrating group, the molecular asymmetry of the tosylate would be lost resulting in the formation of optically inactive product. On the other hand, a direct displacement of tosylate ion by the Grignard reagent would be expected to lead to the formation of optically active product, if the displacement were stereospecific, and the resulting displacement product were optically stable under the reaction conditions.

Initially the reaction of 1-methyl-2,6-diphenyl-4-piperidone oxime tosylate (70) with diphenylmagnesium was studied to avoid the presence of magnesium bromide in the solution of the organometallic reagent. Unreacted 70, however, was recovered in a 54% yield. The infrared spectrum of the residual oil remaining after unreacted 70 was separated

contained strong bands at 3500, 3400, 1725, and 1670 cm^{-1} suggesting the presence of aniline, 1-methyl-2,6-diphenyl-4-piperidone (68), and 1-methyl-2,6-diphenyl-4-piperidone anil (71).

The reaction of 70 with phenylmagnesium bromide (1:2 molar ratio) was shown to give 1-methyl-2,6-diphenyl-4-piperidone anil (71). The infrared spectrum of 71 was consistent with this structure showing a strong band at 1675 cm^{-1}, indicative of the carbon-nitrogen double bond stretching vibration. An attempt to recrystallize 71 from hot 95% ethanol resulted in hydrolysis of the anil to 1-methyl-2,6-diphenyl-4-piperidone (68) and aniline, thereby confirming its structure. Therefore, no rearrangement of tosylate 70 occurred prior to reaction with the Grignard reagent. The exclusive formation of 71 was not expected in view of the results obtained in the reactions of the carbocyclic analogs. The absence of rearrangement of 70 prior to reaction with the Grignard reagent may be due to the unusual stability of 70. It was previously mentioned that 70 was relatively unreactive toward diphenylmagnesium with the recovery of unchanged 70. Lyle[37] was unable to effect a satisfactory Beckmann rearrangement of 1-methyl-2,6-diphenyl-4-piperidone oxime (69) with acidic conditions. On the other hand, 4-t-butylcyclohexanone oxime (22) readily underwent a Beckmann rearrangement, and its tosylate 30 was converted by phenylmagnesium bromide to a product of rearrangement (Table I). Any participation of the basic nitrogen of 70 by coordination with magnesium bromide would probably effect the Schlenk equilibrium of the Grignard reagent and cannot be ruled out as a factor in determining the course of the reaction.



(+)-69 (+)-70

(meso)-68 (-)-71

Fig. 11 Reaction of (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate with Phenylmagnesium Bromide.

1-Methyl-2,6-diphenyl-4-piperidone oxime (69) was readily resolved according to the procedure described by Lyle and Lyle[35] to give the dextrorotatory isomer with a specific rotation of +31.2 to +32.8°. The preparation of optically active tosylate 70 was more difficult due to racemization under the reaction conditions. A modification of the procedure described by Hatch and Cram[10b] proved to be the most successful giving optically active tosylate with a specific rotation of +5.6 to +7.4°.

The reaction of (+)-70 ($[\alpha]_D^{23}$ +7.4°) with phenylmagnesium bromide following the procedure described for the reaction of racemic 70 gave (-)-1-methyl-2,6-diphenyl-4-piperidone anil (71) ($[\alpha]_D^{23}$ -2.1°) in a 4% yield, while reaction of (+)-70 ($[\alpha]_D^{23}$ +5.6°) with phenylmagnesium bromide at ice-salt bath temperature gave (-)-71 ($[\alpha]_D^{23}$ -1.4°) in a 52% yield. The reaction temperature did not effect the optical purity of (-)-71, but did increase the yield of (-)-71 by a factor of thirteen.

The optical rotatory dispersion curve of a freshly prepared solution of (-)-71 in dioxane showed a plain negative curve (Fig. 12). The same solution after standing for three days, however, showed no negative curve, but only a zero rotation line. Also a solution of (-)-71 in 95% aqueous dioxane produced no rotation of plane polarized light. This loss of optical rotation indicated that the optical activity exhibited by (-)-71 was indeed due to the molecular asymmetry caused by the unsymmetrically substituted carbon-nitrogen double bond.

The mechanism of the reaction of (+)-70 with phenylmagnesium bromide must account for the formation of (-)-71. An addition-elimination mechanism must be rejected for the formation of intermediate 72 would destroy the molecular asymmetry of the molecule and would lead to the formation of racemic product. Because of the formation of (-)-71, the most probable mechanism appeared to be a direct displacement of tosylate ion by the Grignard reagent. The mechanism probably involved initial coordination of the Grignard reagent with the free pair of electrons on the nitrogen atom to give an intermediate complex which collapsed to form product with production of the N-Ph bond and breaking of the N-OTs bond. Whether this direct displacement occurred with

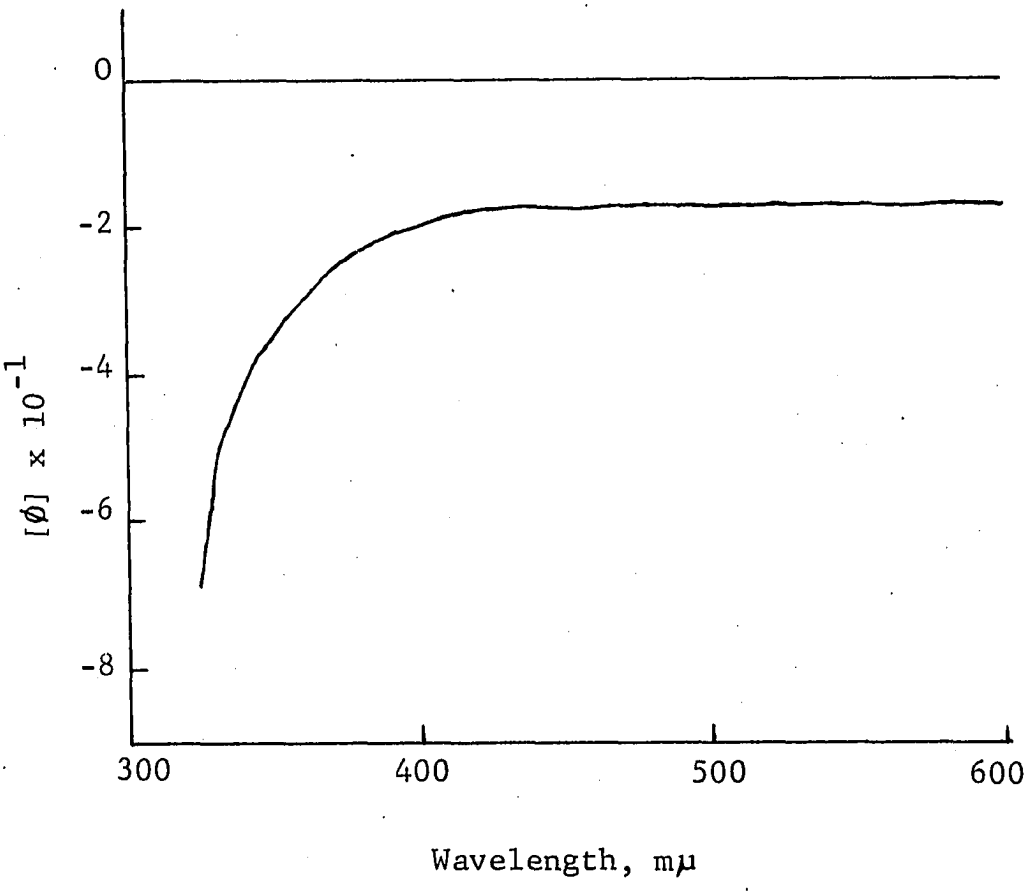
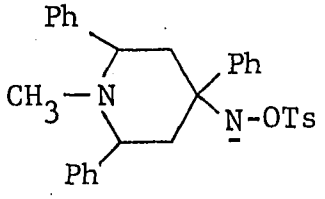


Fig. 12 Optical Rotatory Dispersion Curve of (-)-1-Methyl-2,6-diphenyl-4-piperidone Anil.

retention or inversion of configuration cannot be determined from these results for the absolute configuration of (-)-71 has not been established. Nucleophilic displacement reactions at vinylic carbon[38] have been found to give products of predominantly retained configuration, and the experimental evidence favors an intermediate complex mechanism rather than a concerted mechanism as in displacement reactions at saturated carbon.



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A similar reaction most likely occurred with the oxime tosylates of aliphatic ketones. The formation of anil 31 from the reaction of 4-t-butylcyclohexanone oxime tosylate (30) with phenylmagnesium bromide most likely occurred by a direct displacement of tosylate ion by the Grignard reagent (Fig. 10). The rearrangement of 30 in the presence of a Lewis acid to give the O-tosyl derivative of the lactam (51a), however, was considerably faster. The O-tosyl derivative (51a) then underwent rapid reaction with the Grignard reagent, most likely by an addition-elimination mechanism, to give the Schiff's base 32.

EXPERIMENTAL

General

Melting Points. Melting points were determined using a Kofler hot-stage melting point apparatus equipped with a polarizing microscope and are uncorrected.

Infrared Absorption Spectra.[39,40] The infrared absorption spectra were determined using a Perkin-Elmer Model 137B infracord spectrophotometer equipped with sodium chloride optics or a Perkin-Elmer Model 21 infrared spectrophotometer equipped with sodium chloride optics at settings of resolution, 927; response, 1; gain, 5.5-6.0; speed, 4-6; supression, 0; scale, standard. The spectra determined on the Model 137B are indicated by No., and those determined on the Model 21 are indicated by $No._{21}$. The spectra of liquids were determined as films, and the spectra of solids were determined as mulls in Halocarbon oil from 4000 cm^{-1} to 1300 cm^{-1} and in Nujol from 1300 cm^{-1} to 650 cm^{-1}. All of the bands listed were strong except those indicated weak (w) or medium (m), and the location of the bands is given in frequency units, cm^{-1}.

Ultraviolet Absorption Spectra.[41,42] The ultraviolet absorption spectra were determined using a Perkin-Elmer Model 4000 recording spectrophotometer. The spectra were determined in the solvents indicated, and the wavelengths are given in millimicrons, mμ.

Optical Rotation Data. Optical rotations were determined on a Franz Schmidt and Haensch polarimeter using a sodium

vapor lamp as a light source, and all measurements were made in a 2 dcm. tube. The solvent and concentration (g. per 100 ml. of solution) are indicated for each measurement.

Optical Rotatory Dispersion Data. The optical rotatory dispersion curves were determined on a Rudolph recording spectropolarimeter Model 260/655/850/810-614 using a 0.1 dcm. tube. The solvent and concentration (g. per 100 ml. of solution) are indicated for each curve, and data are given as molecular rotations, $[\phi]_{\lambda}$.

Nuclear Magnetic Resonance Spectra.[43,44] The nuclear magnetic resonance spectra were determined using a Varian Model A-60 proton resonance spectrometer. The spectra were determined in the solvents indicated, and the chemical shifts are given in p.p.m. relative to tetramethylsilane as an internal standard.

Gas Chromatographic Analysis Data. The gas chromatographic analyses were determined on a Perkin-Elmer Model 154 vapor fractometer using helium as the carrier gas. The column packing, temperature and flow rate are indicated for each chromatogram. The yields of products are only relative yields, and no calibration curves were determined. The retention times of the products were determined using two different columns and in all cases were identical to the retention times of an authentic sample.

Analytical Data. Microanalyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, New York, and on a F and M Model 180 carbon, hydrogen and nitrogen analyzer. The microanalyses determined on the F and M analyzer are indicated by Found^{FM} and represent an average of three determinations.

Preparation and Reactions of 5α-Cholestan-3-one Oxime (8)

5α-Cholestan-3β-ol (10). A simple apparatus for catalytic hydrogenation was prepared from a suction flask fitted with a balloon on the side arm and a two-holed rubber stopper containing a stopcock for introduction of hydrogen and a small separatory funnel for introduction of sample. Platinum oxide (0.40 g.) was added to the hydrogenation flask, and the sides of the flask were washed with ethyl acetate. The mixture was stirred with a magnetic stirrer, and hydrogen was introduced to the system to reduce the catalyst. A solution of 20 g. of cholesterol and one drop of 70% perchloric acid in 500 ml. of ethyl acetate was added, and the mixture was stirred for 24 hrs. One drop of 50% sodium hydroxide was added, and the catalyst was removed by filtration. The ethyl acetate was removed by distillation under reduced pressure, and the residual solid was heated under reflux for 2 hrs. with 500 ml. of ethanol, 5.0 g. of sodium hydroxide and 20 ml. of water. The solvent was removed by distillation under reduced pressure, and the residual solid was washed with water, isolated by filtration and again washed with water. Recrystallization from methanol gave 17.5-18.6 g. (87-93%) of 5α-cholestan-3β-ol (10), m.p. 144-145.5°; lit.[45] m.p. 139-142°.

5α-Cholestan-3-one (11) was prepared according to the procedure described by Bruce[46] to give a 74-85% yield of 11, m.p. 131.5-133.5°; lit.[46] m.p. 129-130°.

5α-Cholestan-3-one Oxime (8) was prepared according to the procedure described by Shoppee[47] and Edward[48] to give a 98-99% yield of 8, m.p. 191-193°, $[\alpha]_D^{25}$ +31.4° (ethanol, c=0.2; lit.[49] m.p. 199°.

ORD Curve (No. 82, ethanol, c=0.208): $[\phi]_{690}$+193.1°,

$[\phi]_{589}$+173.8°, $[\phi]_{420}$+347.6°, $[\phi]_{310}$+733.8°, $[\phi]_{240}$+2317.0°.

5α-Cholestan-3-one Oxime, Methyl Ether (12). A mixture of 2.0 g. of 5α-cholestan-3-one, 1.7 g. of methoxyamine hydrochloride, and 2.0 g. of anhydrous sodium acetate in 200 ml. of 75% aqueous ethanol was heated under reflux for 4 hrs. Water was added, and the solid which precipitated was separated by filtration. The solid was recrystallized from methanol giving 1.0 g. (48%) of 5α-cholestan-3-one oxime, methyl ether (12), m.p. 91-93.5°, $[\alpha]_D^{23}$ +45.8° (ethanol, c=0.096).

Anal. Calcd. for $C_{28}H_{49}NO$: C, 80.90; H, 11.88; N, 3.37. Found[FM]: C, 80.72; H, 12.10; N, 3.45.

IR Spectrum (No.$_{21}$ 3683): 2904, 2840, 1635 (w), 1053, 891, 872.

ORD Curve (No. 98, ethanol, c=0.096): $[\phi]_{695}$+476.3° $[\phi]_{589}$+519.6°, $[\phi]_{300}$+1256°, $[\phi]_{260}$°2338°, $[\phi]_{240}$+3464°.

5α-Cholestan-3-one Oxime Benzoate (13). To a solution of 1.0 g. of 5α-cholestan-3-one oxime in 10 ml. of pyridine was added 1.0 g. of benzoyl chloride. The solution was stirred for 8 hrs. and allowed to stand overnight. Water was added, and the solid which precipitated was separated by filtration. The solid was added to a saturated solution of sodium bicarbonate, stirred for 3 hrs., separated by filtration, and washed with water. Recrystallization from methanol gave 0.7 g. (56%) of crude 5α-cholestan-3-one oxime benzoate, m.p. 138-158°, $[\alpha]_D^{25}$ +32.5° (ethanol, c=0.2), of which 0.20 g. was chromatographed on 5.0 g. of acidic alumina. Elution with 50 ml. of benzene-ether (1:1) gave 0.17 g. of pure 5α-cholestan-3-one oxime benzoate (13), m.p. 180-185°, $[\alpha]_D^{25}$ +125° (ethanol, c=0.083), after recrystallization from petroleum ether.

Anal. Calcd. for $C_{34}H_{51}NO_2$: C, 80.73; H, 10.17. Found: C, 80.53; H, 10.29.

IR Spectrum (No.$_{21}$ 3564): 2910, 2860, 1732, 1630 (m), 1279, 1262, 1250, 1085, 1065, 858, 702.

ORD Curve (No. 83, ethanol, c=0.201): $[\phi]_{690}$+251.6°, $[\phi]_{589}$+377.4°, $[\phi]_{450}$+905.8°, $[\phi]_{330}$+2,818°, $[\phi]_{283}$+5,887°, $[\phi]_{277}$+3,120°.

5α-Cholestan-3-one Oxime Acetate (14). A solution of 0.3 g. of 5α-cholestan-3-one oxime and 4 ml. of acetic anhydride in 30 ml. of dioxane was heated on a steam bath for 10.5 hrs. After cooling, water was added, and the solid which precipitated was separated by filtration. The solid was recrystallized from methanol giving 0.1 g. (30%) of 5α-cholestan-3-one oxime acetate (14), m.p. 124-143°.

Anal. Calcd. for $C_{29}H_{49}NO_2$; C, 78.50; H, 11.13; N, 3.16. Found^{FM}: C, 78.62; H, 11.56; N, 3.25.

IR Spectrum (No.$_{21}$ 3840): 2900, 2842, 1750, 1362, 1238, 1205, 997, 950, 927, 865.

Attempted Preparation of 5α-Cholestan-3-one Oxime Tosylate (15). (a). Attempts to prepare this tosylate according to the procedure described by Hatch and Cram[10b] were unsuccessful resulting in the isolation of unreacted oxime 8 and/or 3-aza-A-homo-5α-cholestan-4-one (16).

(b). The sodium salt of the oxime was prepared with sodium hydride dispersion in benzene and was treated with p-toluenesulfonyl chloride giving 3-aza-A-homo-5α-cholestan-4-one (16), m.p. 248-258°; lit.[50] m.p. 268-271°.

Beckmann Rearrangement of 5α-Cholestan-3-one Oxime (8).

(a). With Thionyl Chloride. The Beckmann rearrangement of 5α-cholestan-3-one oxime according to the procedure described by Shoppee and Sly[50] gave 3-aza-A-homo-5α-cholestan-

4-one (16), m.p. 265-272°; lit.[50] m.p. 268-271°, $[\alpha]_D$ +16° (chloroform, c=0.7).

(b). With Polyposphoric Acid. The rearrangement following the procedure described by Doorenbos and Wu[51] gave 3-aza-A-homo-5α-cholestan-4-one (16), m.p. 259-264°, $[\alpha]_D^{25}$ +15.4° (ethanol, c=0.2); lit.[51] m.p. 275.5-276.5°.

(c). With Base. A solution of 5.0 g. of 5α-cholestan-3-one oxime and 5.0 g. of p-toluenesulfonyl chloride in 170 ml. of pyridine was heated on a steam bath for 10 hrs. After cooling, 11 ml. of water was added, and the reaction mixture was poured into 220 ml. of cold 6 N. hydrochloric acid. The solid which precipitated was separated by filtration and recrystallized from methanol giving 2.0 g. (40%) of 3-aza-A-homo-5α-cholestan-4-one (16), m.p. 258-262°; lit.[50] m.p. 268-271°.

Preparation of Oximes

4-t-Butylcyclohexanone Oxime (22). A mixture of 30.0 g. of 4-t-butylcyclohexanone, 25.0 g. of hydroxylamine hydrochloride, and 28.9 g. of anhydrous sodium acetate in 1200 ml. of 75% aqueous ethanol was heated under reflux for 6 hrs. After cooling, the mixture was poured into one liter of cold water, and the solid which precipitated was separated by filtration giving 30.9-32.0 g. (94-98%) of 4-t-butylcyclohexanone oxime (22), m.p. 136-138°; lit.[15] m.p. 135-136°.

An ethereal solution of oxime 22 was treated with a solution of hydrogen chloride in ether. The solid which precipitated was separated by filtration giving a stable hydrochloride (23) which sublimed at 110-123°.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.37; H, 9.80; N, 6.81.

Found: C, 58.60; H, 10.09; N, 6.95.

IR Spectrum (No.$_{21}$ 4503): 2930, 2860, 2600-2440, 1905 (w), 1861 (w), 1835 (w), 1366, 1175, 1060, 976, 969, 774, 720.

Methyl Ethyl Ketoxime (53). A modified procedure of Marvel and Noyes[52] was employed for the preparation. A solution of 49 g. of hydroxylamine hydrochloride in 350 ml. of water, 50 g. of methyl ethyl ketone, and 38 g. of anhydrous sodium carbonate was allowed to stand at room temperature for 40 hrs., and the mixture was extracted with ether. The water layer was saturated with sodium chloride and again extracted with ether. The combined extracts were evaporated, and the residual oil was distilled under reduced pressure giving 48 g. (80%) of methyl ethyl ketoxime (53), b. p. 59-60° at 12.5 mm; lit.[52] b. p. 150-155°.

Benzophenone Oxime (47) was prepared according to the procedure described by Lachman[53] to give a quantitative yield of oxime, m.p. 145-146°; lit.[53] m.p. 141-142°.

Acetophenone Oxime (1) was prepared according to the procedure described by Campbell[4] to give a 79% yield of oxime, m.p. 55-58°; lit.[4] m.p. 59°.

p-Chloroacetophenone Oxime (61) was prepared according to the procedure described by Campbell[4] to give an 89% yield of oxime, m.p. 95-96.5°; lit.[54] m.p. 95°.

Reactions of Oximes with Phenylmagnesium Bromide

Reaction of 5α-Cholestan-3-one Oxime (8) with Phenylmagnesium Bromide. (a). Phenylmagnesium bromide was prepared from 21.0 g. of bromobenzene and 3.0 g. of magnesium in 60 ml. of dry ether. The reaction flask was fitted with a condenser for distillation and heated in an oil bath until the temperature reached 150° at which time 25-30 ml. of ether was recovered. The distillation condenser was replaced by a reflux condenser, and 5.0 g. of powdered 5α-cholestan-3-one oxime along with 30 ml. of ether and 30 ml. of toluene was added with stirring over a period of 20 minutes. The mixture was stirred at 150-155° (oil bath temperature) for 1 hr. and, after cooling, was hydrolyzed with a mixture of 30 ml. of concentrated hydrochloric acid and 120 g. of ice. The mixture was extracted with ether, and the combined extracts were dried over potassium carbonate. The solvent was removed by distillation under reduced pressure giving 2.9 g. (58%) of unreacted oxime 8, m.p. 192-199° after recrystallization from methanol.

The acidic water layer was filtered to separate 0.2 g. of an unidentified insoluble material (19), m.p. 252-257° after recrystallization from methanol.

Anal. Calcd. for $C_{33}H_{53}NO$: C, 82.61; H, 11.14. Found: C, 66.24; H, 10.04.

IR Spectrum (No.$_{21}$ 4137): 3350-3314, 2918-2838, 1664-1643 (w), 1627 (m), 1607 (m), 1535, 1084, 757, 697.

The aqueous acidic filtrate was made basic with ammonium hydroxide and extracted with ether. The combined extracts were dried over potassium carbonate and filtered to remove the drying agent. The clear ethereal filtrate was treated with hydrogen chloride until no more precipitate appeared giving 0.1 g. (6%) of aniline hydrochloride (17)

which was identical in every respect with an authentic sample.

The base of hydrochloride 17 was prepared by treatment of 17 with 5% sodium hydroxide and extraction of the mixture with ether. The combined extracts were dried over potassium carbonate, and the ether was evaporated giving a residual oil whose infrared spectrum was identical with that of pure aniline.

The benzamide of the product was prepared by treatment of the hydrochloride with 5% sodium hydroxide and benzoyl chloride giving benzanilide, m.p. 162-167°, which was identical in every respect with an authentic sample.

(b). The reaction of 5.0 g. of 5α-cholestan-3-one oxime with phenylmagnesium bromide prepared in tetrahydrofuran following the procedure described above gave 0.39 g. (24%) of aniline hydrochloride (17).

Reaction of 4-t-Butylcyclohexanone Oxime (22) with Phenylmagnesium Bromide. (a). A suspension of 4.2 g. of 4-t-butylcyclohexanone oxime in 25 ml. of dry ether was added with stirring to phenylmagnesium bromide prepared as in the reaction with 5α-cholestan-3-one oxime (a). The mixture was stirred at 165-175° for 1 hr. and, after cooling, was hydrolyzed with a mixture of 30 ml. of concentrated hydrochloric acid and 120 g. of ice. The mixture was extracted with ether, and the combined extracts were dried over potassium carbonate. The ether was removed by distillation under reduced pressure giving 5.6 g of a mixture of white solid and yellow oil. The solid was separated by filtration and washed with cold methanol giving 0.43 g. of unreacted oxime 22. The infrared spectrum of the residual oil (5.2 g.) from evaporation of the methanol mother liquor contained strong bands at 3370 and 1715 cm^{-1} suggesting the presence of unreacted oxime 22 and 4-t-butylcyclo-

hexanone along with the usual products from the Grignard reagent.

The acidic water layer was made basic and extracted with ether. The combined extracts were dried over potassium carbonate, and after the drying agent was separated by filtration, the clear filtrate was treated with hydrogen chloride until no more precipitate appeared. The precipitate was separated by filtration giving 0.19 g. (6%) of aniline hydrochloride which was identical in every respect with an authentic sample.

(b). A second reaction was hydrolyzed with a saturated solution of ammonium chloride. The mixture was extracted with ether, and the combined extracts were dried over potassium carbonate. The ether solution was concentrated and treated with a solution of hydrogen chloride in ether. The solid which precipitated was separated by filtration giving 3.0 g. (59%) of 4-t-butylcyclohexanone oxime hydrochloride (23), m.p. 139-141°. The infrared spectra of this material and the hydrochloride prepared from pure 4-t-butylcyclohexanone oxime were identical.

The oxime (22) was prepared by treating the hydrochloride with 5% sodium hydroxide and extracting the mixture with ether. Evaporation of the ether, after drying, gave 4-t-butylcyclohexanone oxime which was identical in every respect with an authentic sample.

Preparation and Reactions of 4-t-Butylcyclohexanone Oxime, Methyl Ether (24) with Organometallic Reagents.

4-t-Butylcyclohexanone Oxime, Methyl Ether (24). A mixture of 20.0 g. of 4-t-butylcyclohexanone, 12.0 g. of methoxyamine hydrochloride, and 11.8 g. of anhydrous sodium acetate in 600 ml. of 75% aqueous ethanol was heated under reflux for 8 hrs. After cooling, 300 ml. of water was added, and the resulting mixture was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation. The residual oil was distilled under reduced pressure giving 19.2 g. (81%) of 4-t-butylcyclohexanone oxime, methyl ether (24), b.p. 109° at 3 mm.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.06; H, 11.55; N, 7.64. Found: C, 71.90; H, 11.32; N, 7.87.

IR Spectrum (No.$_{21}$ 4496): 2940, 1640 (w), 1480 (m), 1468 (m), 1443 (m), 1367, 1053, 872.

Reaction of 4-t-Butylcyclohexanone Oxime, Methyl Ether (24) with Phenylmagnesium Bromide. 4-t-Butylcyclohexanone oxime, methyl ether (13.5 g.) was added with stirring to phenylmagnesium bromide prepared from 57.0 g. of bromobenzene and 9.0 g. of magnesium in 150 ml. of tetrahydrofuran as in the reaction with 5α-cholestan-3-one oxime. The mixture was stirred at 150-160° for 3 hrs. and, after cooling, was hydrolyzed with a saturated solution of ammonium chloride. The mixture was extracted with ether, and the combined extracts were dried over potassium carbonate. The solvent was removed by distillation, and the residual oil was distilled under reduced pressure giving 2.1 g. (11%) of distillate, b.p. 141-159° at 1.5 mm., which was tentatively identified as N-methoxy-4-t-butyl-1-phenylcyclohexylamine (25). Gas chromatographic

analysis showed this material to be contaminated with aniline and biphenyl.

IR Spectrum (No.$_{21}$ 4462): 3290 (m), 3005 (m), 2935-2852, 1643 (w), 1597 (m), 1495 (m), 1473 (m), 1447 (m), 1365, 1053 (m), 1022 (m), 757, 695.

A solution of 2.1 g. of 25 in dry ether was treated with hydrogen chloride. The light yellow solution became dark red, and the white solid which was deposited with excess hydrogen chloride was separated by filtration giving 0.7 g. (29%) of a hydrochloride (26), m.p. 195-203°.

Anal. Calcd. for $C_{17}H_{28}ClNO$: Cl, 11.90. Found: Cl, 12.99.

IR Spectrum (No. 2934): 3020-2900, 2645 (m), 1610 (m), 1560 (m), 1500, 1370, 1143, 1027 (m), 902 (m), 765, 700.

The base of the hydrochloride 26 was prepared by treatment of 26 with 5% sodium hydroxide and extraction of the mixture with ether. Evaporation of the ether, after drying, gave a residual oil whose infrared spectrum was nearly identical to that of compound 25.

Reaction of 4-t-Butylcyclohexanone Oxime, Methyl Ether (24) with Phenyllithium. 4-t-Butylcyclohexanone oxime, methyl ether (4.5 g.) was added with stirring to phenyllithium prepared from 0.86 g. of lithium and 19.4 g. of bromobenzene in 60 ml. of dry ether. The mixture was heated under reflux for 8 hrs. and, after cooling, was poured into 200 ml. of cold water. The mixture was extracted with ether, and the combined extracts were dried over potassium carbonate. The solvent was removed by distillation, and the residual oil was distilled under reduced pressure. A solution of the distillate, b.p. 90-151° at 2.0 mm., in ether was treated with a solution of

hydrogen chloride in ether. The solid which precipitated was separated by filtration giving 0.20 g. (6%) of aniline hydrochloride which was identical in every respect with an authentic sample.

The ethereal filtrate was washed with dilute sodium hydroxide solution and dried over potassium carbonate. The ethereal solution was evaporated, and the residual oil was dissolved in ethanol and treated with 2,4-dinitrophenylhydrazine reagent. The orange solid which precipitated was separated by filtration giving 0.05 g. (1%) of 4-t-butylcyclohexanone 2,4-dinitrophenylhydrazone (29), m.p. 154-157°, which was identical in every respect with an authentic sample.

Preparation of Tosylates of Oximes

The procedure described by Hatch and Cram[10b] was employed for the preparation of oxime tosylates, but purification of the tosylates on a preparative scale proved difficult due to their instability. The wet oxime tosylate, therefore, was dissolved in benzene, the water layer was separated in a separatory funnel, and the benzene layer was dried over anhydrous magnesium sulfate. The benzene solution of the oxime tosylate was then treated with the Grignard reagent.

The following oxime tosylates were prepared, and the yields were calculated from the air-dried, crude products. Since the tosylates could not be purified, no elemental analyses were made, and identification was based on the infrared absorption spectra.

4-t-Butylcyclohexanone Oxime Tosylate (30) (74-86%), m.p. 78-80°.

IR Spectrum (No.$_{21}$ 4502): 2935, 1637 (w), 1372, 1191, 1177, 1092, 846, 810, 752, 668.

Benzophenone Oxime Tosylate (48) (80-84%), m.p. 58-93°; lit.[55] m.p. 82-83°.

Methyl Ethyl Ketoxime Tosylate (54) (73-76%), m.p. 63-73°.

IR Spectrum (No. 4646): 2970 (m), 1640 (w), 1460 (m), 1366, 1192, 1174, 874, 827, 773.

Acetophenone Oxime Tosylate (59) (86-90%), m.p. 68-71°; lit.[55] m.p. 73-74.5°.

p-Chloroacetophenone Oxime Tosylate (62) (78-83%), m.p. 84-85.5°, recrystallized from ether.

IR Spectrum (No. 7081): 3060 (m), 2900 (m), 1381, 1198, 1182, 840, 827, 771, 683.

The tosylates of p-methoxy- and p-methylacetophenone oximes could not be prepared. These tosylates apparently underwent a Beckmann rearrangement with isolation of the corresponding amides.

Reactions of Tosylates with Grignard Reagents

Reaction of 4-t-Butylcyclohexanone Oxime Tosylate (30) with Phenylmagnesium Bromide. A solution of 4-t-butylcyclohexanone oxime tosylate (prepared from 12 g. of 4-t-butylcyclohexanone oxime) in 100 ml. of benzene was added with stirring at 10° to phenylmagnesium bromide prepared from 38.8 g. of bromobenzene and 6.0 g. of magnesium in 240 ml. of dry ether. The mixture was stirred at 10-15° for 2 hrs. and was hydrolyzed with a saturated solution of ammonium chloride. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation. The

residual oil was distilled under reduced pressure giving 8.9-9.4 g. (55-58% based on oxime) of a mixture of 4-t-butylcyclohexanone anil (31) and 4-t-butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32), b.p. 129-131° at 0.87 mm. Gas chromatographic analysis (2 m. 5% Silicone Oil 200 on Haloport F, 200°, 8 psi) showed the mixture to contain 21% of 31 and 79% of 32.

Anal. Calcd. for $C_{16}H_{23}N$: C, 83.77; H, 10.11. Found for the mixture: C, 83.56; H, 9.94.

IR Spectrum (No. 3135): 3000, 2910, 1665, 1635, 1475, 1445, 1365, 1235, 774, 693.

UV Spectrum: λ_{max}^{EtOH} 238 mμ (ε 12,200).

Reaction of Methyl Ethyl Ketoxime Tosylate (54) with Phenylmagnesium Bromide. A solution of 6.0 g. of methyl ethyl ketoxime tosylate in 75 ml. of benzene was added with stirring at 11° to phenylmagnesium bromide prepared from 16.3 g. of bromobenzene and 2.6 g. of magnesium in 50 ml. of dry ether. The mixture was stirred at 11-16° for 2 hrs. and was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the water layer was extracted with ether. The acidic water layer was made basic with sodium hydroxide solution and was extracted with ether. The extracts from the acidic and basic water layers were combined and dried over potassium carbonate. The solvent was removed by distillation under reduced pressure giving 2.9 g. of residual oil which was shown by gas chromatographic analysis (1 m. 5% Carbowax 20M on Chromosorb W in series with a 1 m. 5% Silicone Grease on Haloport F, 133°, 11 psi) to contain aniline (48%), acetophenone (42%) and propiophenone (10%).

Reaction of Benzophenone Oxime Tosylate (48) with Phenylmagnesium Bromide. A solution of benzophenone oxime tosylate (prepared from 9.8 g. of benzophenone oxime) in 100

ml. of benzene was added with stirring at 10° to phenylmagnesium bromide prepared from 38.8 g. of bromobenzene and 6.0 g. of magnesium in 200 ml. of dry ether. The mixture was stirred at 10-15° for 3 hrs. and was hydrolyzed with a saturated solution of ammonium chloride. The organic layer was separated, and the water layer was extracted with benzene. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving a residual oil which partially crystallized on standing. The residue was triturated with ether, and the solid was separated by filtration giving 4.0 g. of benzophenone anil (49), m.p. 113-117°. Four additional crops (5.0 g.) were obtained from the ethereal washings giving 9.0 g. (67% based on oxime) of benzophenone anil (49). Recrystallization from ether raised the melting point to 115-117°; lit.[56] m.p. 117°.

A mixture of 0.5 g. of benzophenone anil (49) and 30 ml. of 10% hydrochloric acid was heated on a steam bath for 1 hr. The cooled mixture was extracted with ether, and the ethereal extracts were dried over potassium carbonate. The ether was removed by distillation under reduced pressure giving 0.30 g. (86%) of benzophenone which was identical in every respect with an authentic sample.

The acidic water layer was made basic with sodium hydroxide solution and was extracted with ether. The ethereal extracts were dried over potassium carbonate, and the ether was removed by distillation under reduced pressure giving 0.14 g. (78%) of aniline which was identical in every respect with an authentic sample.

Reaction of Benzophenone Oxime Tosylate (48) with p-Substituted Phenylmagnesium Bromides. Benzophenone oxime tosylate which was prepared from 20.0 g. of benzophenone oxime was dissolved in 200 ml. of benzene, the water was separated in a separatory funnel, and the benzene solution was dried over anhydrous magnesium sulfate. The solution was divided into four equal portions and each portion was added to 0.076 mole of Grignard reagent in 80 ml. of dry ether. The mixture was stirred at 10-15° for 2 hrs. and was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the water layer was washed with ether. The acidic water layer was made basic with sodium hydroxide solution and was extracted with ether. The ethereal extracts were dried over potassium carbonate, and the ether was removed by distillation under reduced pressure giving a residual oil which was analyzed by gas chromatography.

Reaction of benzophenone oxime tosylate with p-tolylmagnesium bromide gave 1.10 g. (47% based on oxime) of a residual oil; p-anisylmagnesium bromide, 1.04 g. (44%); p-chlorophenylmagnesium bromide, 0.90 g. (38%); and p-trifluoromethylphenylmagnesium bromide, 0.77 g. (33%). The residual oil from each reaction was shown to be aniline, and its purity was established by gas chromatographic analysis. The infrared spectrum of each product was identical with the infrared spectrum of pure aniline.

A liquid ketone isolated from the non-basic fraction of the p-tolylmagnesium bromide reaction was identified as phenyl p-tolyl ketone. The infrared spectra of this product and an authentic sample were identical as were the 2,4-dinitrophenylhydrazone derivatives.

Reaction of Benzophenone Oxime Tosylate (48) with p-Tolyllithium.

A solution of benzophenone oxime tosylate (prepared from 9.9 g. of benzophenone oxime) in 100 ml. of benzene was added with stirring at 10° to p-tolyllithium prepared from 25.6 g. of p-bromotoluene and 2.1 g. of lithium wire in 80 ml. of dry ether. The mixture was stirred at 10-14° for 2 hrs. and was poured into 200 ml. of cold water. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were dried over potassium carbonate. After the solvent was removed by distillation under reduced pressure, the solid residue was triturated with ether and was separated by filtration giving 4.4 g. of p,p'-ditolylsulfone (57), m.p. 155-159°; lit.[57] m.p. 158°. Four additional crops were collected from the ethereal washings giving a total of 10.5 g. (86% based on oxime) of p,p'-ditolylsulfone.

Proof of Structure of 4-t-Butylcyclohexanone Anil (31) and 4-t-Butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32)

Reduction of the Mixture of 4-t-Butylcyclohexanone Anil (31) and 4-t-Butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32) with Lithium Aluminum Hydride. A solution of 2.75 g. of Schiff's base mixture 31 and 32 in 30 ml. of dry ether was added to a stirred suspension of 0.45 g. of lithium aluminum hydride in 60 ml. of dry ether. The mixture was warmed during the addition and then heated under gentle reflux for 0.5 hr. After cooling, the excess lithium aluminum hydride was decomposed with wet ether (10 ml.) and water (30 ml.), and the mixture was extracted with ether. The ether was evaporated giving a residual oil which was treated with 5% hydrochloric acid. The resulting mixture was washed with

ether, made basic with sodium hydroxide solution, and extracted with ether. The ethereal extracts were dried over potassium carbonate, and the ether was removed by distillation. The residual oil was distilled under reduced pressure giving 1.84 g. (67%) of a mixture of 1-anilino-4-t-butylcyclohexane (33) and 5-t-butyl-2-phenylhexamethylenimine (34), b.p. 130.5° at 1.15 mm.

Anal. Calcd. for $C_{16}H_{25}N$: C, 83.05; H, 10.89. Found for the mixture: C, 82.93; H, 11.10.

IR Spectrum (No. 3256): 3350 (w), 3065 (m), 2970, 2900, 1600 (m), 1460, 1448, 1362, 1140, 752, 699.

UV Spectrum: λ_{max}^{EtOH} (ϵ): 292(156), 246(1310).

Benzoylation of the product mixture with 5% sodium hydroxide and benzoyl chloride gave a glassy material which could not be crystallized. The infrared spectrum (No. 3289) contained strong bands at 2900, 1630, 755 and 698 cm^{-1}.

Hydrolysis of the Mixture of 4-t-Butylcyclohexanone Anil (31) and 4-t-Butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32). A mixture of 2.18 g. of Schiff's base mixture 31 and 32 and 50 ml. of 10% hydrochloric acid was heated on a steam bath for 20 minutes and allowed to cool to room temperature with occasional shaking. The mixture was extracted with ether, and the combined ethereal extracts were dried over potassium carbonate. The ether was removed by distillation giving 0.36 g. (24.5% assuming the 2.18 g. to be only 31) of 4-t-butylcyclohexanone which was identical in every respect with an authentic sample.

The acidic water layer was made basic with potassium hydroxide solution and was extracted with ether. The combined ethereal extracts were dried over potassium carbonate,

and the ether was removed by distillation giving 1.61 g. (74% represents ratio of isolated basic material to starting mixture) of residual oil which was shown by gas chromatographic analysis to consist of 32 and aniline.

A second hydrolysis of 2.43 g. of Schiff's base mixture 31 and 32 which was heated for 6 hrs. to insure complete hydrolysis gave 1.87 g. (77% recovery) of the same product mixture (32 and aniline).

Distillation under reduced pressure of the mixture of 32 and aniline gave only a partial separation as indicated by gas chromatographic analysis.

1-Benzoyl-4-t-butyl-2,3,4,5-tetrahydro-7-phenyl-1H-azepine (35). To a solution of 2.1 g. of 4-t-butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine(32) (contaminated with aniline from the hydrolysis of the mixture of 31 and 32) in 20 ml. of chloroform was added 20 ml. of 5% sodium hydroxide and 1 ml. of benzoyl chloride. The mixture was stirred for 8 hrs. and allowed to stand overnight. The chloroform layer was separated, washed with water, 5% hydrochloric acid, and again with water. After drying over potassium carbonate, the chloroform was removed by distillation under reduced pressure giving a yellow residual oil which was crystallized with n-hexane. Two recrystallizations from methanol gave 0.6 g. (20%) of 1-benzoyl-4-t-butyl-2,3,4,5-tetrahydro-7-phenyl-1H-azepine (35), m.p. 144-145.5°.

Anal. Calcd. for $C_{23}H_{27}NO$: C, 82.87; H, 8.16. Found: C, 82.95; H, 8.27.

IR Spectrum (No. 3903): 3140 (w), 3020 (m), 2940 (m), 1665, 1640, 1392, 763, 730, 692.

UV Spectrum: λ_{max}^{EtOH} 251 (ϵ 17,100).

NMR Spectrum (CCl_4, No. 530): 0.8-2.5 (multiplet, 16 protons), 5.83 (triplet, 1 vinyl proton), 7.1 (multiplet, 10

aromatic protons).

5-t-Butyl-2-phenylhexamethylenimine (34). A solution of 7.5 g. of 4-t-butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32) (contaminated with aniline from the hydrolysis of the mixture of 31 and 32) in 50 ml. of dry ether was added to a stirred suspension of 1.4 g. of lithium aluminum hydride in 100 ml. of dry ether. The mixture was heated under reflux for 2 hrs., and the excess lithium aluminum hydride was decomposed with water. The mixture was extracted with ether, and the combined ethereal extracts were evaporated giving a colorless residual oil. Treatment of the residual oil with 10% hydrochloric acid gave a white insoluble solid, 5-t-butyl-2-phenylhexamethylenimine hydrochloride, which was separated by filtration and washed with water. The hydrochloride was treated with sodium hydroxide solution, and the mixture was extracted with ether. The ethereal extracts were dried over potassium carbonate, and the ether was evaporated. The residual oil was distilled under reduced pressure giving 4.8 g. (64%) of 5-t-butyl-2-phenylhexamethylenimine (34), b.p. 151-2° at 2.9 mm.

Anal. Calcd. for $C_{16}H_{25}N$: C, 83.05; H, 10.89. Found: C, 83.79; H, 10.73.

IR Spectrum (No. 3616): 3400 (w), 3090 (w), 3000, 2910, 1482, 1465, 1368, 1148, 758, 702.

UV Spectrum: λ_{max}^{EtOH} (ϵ): 263(157), 257(213), 252(198).

NMR Spectrum: (CCl_4, No. 193): 0.87 (singlet), 1.36-1.92 (multiplet), 2.48-3.36 (multiplet), 3.84 (triplet), 7.23 (multiplet).

Treatment of 2 ml. of 5-t-butyl-2-phenylhexamethylenimine (34) with 10 ml. of 10% sodium hydroxide and 2 ml. of

benzenesulfonyl chloride gave an insoluble benzenesulfonamide which melted at 102-104° after one recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{29}NO_2S$: C, 71.12; H, 7.87. Found: C, 71.03; H, 7.83.

IR Spectrum (No. 3609): 3110 (w), 3080 (w), 2995, 2910, 1330, 1165, 1100, 940, 752, 732, 704, 697, 688.

5-t-Butyl-1-methyl-2-phenylhexamethylenimine (37).

Method A. To 2.0 g. of 98-100% formic acid[58] in a 50 ml. flask in a cold water bath was added slowly 2.8 g. of 5-t-butyl-2-phenylhexamethylenimine (34). To the resulting solution was added 2.0 g. of 37% formaldehyde solution, and the flask fitted with a reflux condenser was heated on a steam bath for 13 hrs. After cooling, 8 ml. of 4 N. hydrochloric acid was added, and the solution was evaporated to dryness under reduced pressure giving a white solid residue which was dissolved in 30 ml. of water. The resulting solution was made basic with potassium hydroxide solution and was extracted with ether. The ethereal extracts were dried over potassium carbonate, and the ether was evaporated giving 2.6 g. (92%) of 5-t-butyl-1-methyl-2-phenylhexamethylenimine (37). Recrystallization from acetone gave an analytical sample, m.p. 61-62°.

Anal. Calcd. for $C_{17}H_{27}N$: C, 83.20; H, 11.09. Found: C, 83.13; H, 11.15.

IR Spectrum (No. 3653): 3110 (m), 3000, 2890, 2800, 1450, 1367, 1212, 1097, 1023, 754, 748, 702.

NMR Spectrum (CCl_4, No. 195): 0.86 (singlet), 1.37-1.95 (multiplet), 2.13 (singlet), 2.73 (triplet), 3.30 (triplet), 7.25 (multiplet).

Method B. A mixture of 1.0 g. of 4-t-butyl-2,3,4,5-tetrahydro-1-methyl-7-phenyl-1H-azepine (43) and 0.3 g. of sodium borohydride in 15 ml. of anhydrous tetrahydrofuran was stirred while 1 ml. of glacial acetic acid[20] was added dropwise over a period of 0.5 hr. The mixture was heated under reflux for 1.5 hrs., cooled, made basic with sodium hydroxide solution, and extracted with ether. The combined extracts were washed with water, a saturated sodium chloride solution, and were dried over sodium sulfate. The solvent was evaporated to give a residual solid (amine-borane) which was dissolved in 20 ml. of dioxane and heated on a steam bath with 5 ml. of glacial acetic acid for 2 hrs. The cooled mixture was made basic with sodium hydroxide solution and was extracted with ether. The combined extracts were washed with water, a saturated sodium chloride solution, and were dried over sodium sulfate. Evaporation of the solvent gave 0.81 g. of a colorless residual oil which crystallized on standing. Recrystallization from methanol gave 0.51 g. (51%) of 5-t-butyl-1-methyl-2-phenylhexamethylenimine (37), m.p. 61-62°, which was identical in every respect with that prepared by method A above. A mixture melting point of the two solids showed no depression.

5-t-Butyl-1-methyl-2-phenylhexamethylenimine Methiodide (38). (a). A solution of 2.3 g. of 5-t-butyl-1-methyl-2-phenylhexamethylenimine (37) (prepared from 34) in 40 ml. of acetone was heated under reflux with 3.0 g. of methyl iodide for 1 hr. and allowed to stand overnight. After cooling with ice, the white solid which precipitated was separated by filtration giving 2.4 g. (67%) of 5-t-butyl-1-methyl-2-phenylhexamethylenimine methiodide (38), m.p. 203.5-205°.

Anal. Calcd. for $C_{18}H_{30}IN$: C, 55.81; H, 7.81. Found: C, 55.76; H, 7.56.

IR Spectrum (No. 3659): 3040 (m), 2995, 2915 (m), 1479 (m), 1458 (m), 1368 (m), 1022 (m), 940 (m), 895 (m), 766, 710.

(b). A solution of 0.22 g. of 5-t-butyl-1-methyl-2-phenylhexamethylenimine (37) (prepared from 43) in 10 ml. of acetone was heated under reflux with 2.0 g. of methyl iodide for 10 minutes. After cooling to room temperature, the white solid which precipitated was separated by filtration giving 0.18 g. (52%) of 38, m.p. 197.5-200.5°. Recrystallization from acetone gave a sample, m.p. 204-205°, which was identical in every respect with that prepared by method (a) above. A mixture melting point of the two solids showed no depression.

(3-t-Butyl-6-phenyl-5-hexenyl)dimethylamine (40). To a solution of 2.3 g. of 5-t-butyl-1-methyl-2-phenylhexamethyleninime methiodide (38) in 350 ml. of water (required warming for dissolution) 2.8 g. of silver oxide[14] was added with stirring. The mixture was stirred for 8 hrs., at which time a negative test for the presence of iodide ion was obtained with chloroform and chlorine water, and was filtered into a Claisen flask. The water was evaporated, and the residual oil was heated at 70-200° at 1.5 mm. giving 0.46 g. of distillate. The reaction flask was washed with ether, and the combined ethereal washings were dried over potassium carbonate. The ether was evaporated giving 0.46 g. of residual oil which was identical with the distillate. The combined oily product was distilled under reduced pressure giving 0.55 g. (36%) of (3-t-butyl-6-phenyl-5-hexenyl)dimethylamine (40), b.p. 140° at 1.45 mm. Due to the small amount of material,

40 was purified by the preparation of the picrate derivative.

Anal. Calcd. for $C_{18}H_{29}N$: C, 83.33; H, 11.27. Found: C, 82.43; H, 11.72.

IR Spectrum (No. 3695): 3055 (m), 2995, 2890, 2840, 2795, 1745 (m), 1650 (w), 1600 (m), 1460, 1363, 1236, 1045, 970, 743, 693.

UV Spectrum λ_{max}^{EtOH} (ϵ): 292(831), 284(1360), 252(16,800).

NMR Spectrum (CCl_4, No. 122): 0.93 (singlet, 9 protons), 2.10 (singlet, 6 protons), 6.30 (doublet, 1 proton), 7.22 (multiplet, 6 protons).

A solution of 0.22 g. of (3-t-butyl-6-phenyl-5-hexenyl)dimethylamine (40) in 5 ml. of ethanol was warmed with 4 ml. of a saturated ethanolic solution of picric acid. On cooling overnight, the solution deposited a solid which was collected by filtration to give 0.22 g. (53%) of (3-t-butyl-6-phenyl-5-hexenyl)dimethylamine picrate, m.p. 118-125°. Recrystallization from ethanol gave an analytical sample, m.p. 122.5-125°.

Anal. Calcd. for $C_{24}H_{32}N_4O_7$: C, 59.00; H, 6.60. Found: C, 59.25; H, 6.94.

IR Spectrum (No. 4051): 3080 (m), 3000, 2765, 1660, 1630, 1560, 1468, 1365, 1340, 1312, 1268, 1163 (m), 1078 (m), 788 (m), 744, 710 (m), 693 (m).

4-t-Butylhexamethylenimine (45). A suspension of 2.8 g. of 5-t-butylhexahydro-2H-azepin-2-one (41) in 300 ml. of dry ether was added to a stirred suspension of 0.8 g. of lithium aluminum hydride in 50 ml. of dry ether. The mixture was warmed during the addition and then heated under reflux for 3.5 hrs. After cooling, the excess lithium aluminum hydride was decomposed with water, and the mixture was extracted with ether. The ether was evaporated giving a residual oil which was treated with

200 ml. of 5% hydrochloric acid. The resulting mixture was washed with ether, made basic with potassium hydroxide solution, and was extracted with ether. The ethereal extracts were dried over potassium carbonate, and the ether was removed by distillation. The residual oil was distilled under reduced pressure giving 1.3 g. (51%) of 4-t-butylhexamethylenimine (45), b.p. 49° at 1.1 mm.

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.33; H, 13.63. Found: C, 77.01; H, 13.74.

IR Spectrum (No. 3273): 3355 (m), 2990, 2910, 2785 (m), 1470, 1440, 1365, 1150.

Attempted Reaction of 5-t-Butylhexahydro-2H-azepin-2-one (41) with Phenylmagnesium Bromide. A solution of 4.2 g. of 5-t-butylhexahydro-2H-azepin-2-one in 100 ml. of benzene was added with stirring at 10° to phenylmagnesium bromide prepared from 19.4 g. of bromobenzene and 3.0 g. of magnesium in 120 ml. of dry ether. The mixture was stirred at 10-13° for 2.5 hrs. and was hydrolyzed with a saturated solution of ammonium chloride. The organic layer was separated, the water layer was extracted with ether, and the combined extracts were dried over potassium carbonate. After the solvent was removed by distillation under reduced pressure, the solid residue was triturated with ether and was separated by filtration giving 2.6 g. of unreacted 41. An additional 0.2 g. was obtained from the ethereal washings giving 2.8 g. (67%) of unreacted 41. The infrared spectra of the product and starting material were identical.

Alternate Synthesis of 5-t-Butyl-1-methyl-2-phenylhexamethyl-enimine (37).

5-t-Butylhexahydro-2H-azepin-2-one (41) was prepared by a Beckmann rearrangement of 4-t-butylcyclohexanone oxime tosylate to give a 56-70% yield of 41, m.p. 160-161°; lit.[15] m.p. 155-156°.

5-t-Butylhexahydro-1-methyl-2H-azepin-2-one (42). A suspension of 5.9 g. of 54.5% sodium hydride dispersion in 200 ml. of dry benzene was stirred vigorously while 22.6 g. of 5-t-butylhexahydro-2H-azepin-2-one (41) was added in portions. After stirring for 2 hrs., 8.4 g. of dimethyl-sulfate was added in portions. The mixture was stirred over-night, and 100 ml. of water was added. The benzene layer was separated, and the water layer was extracted with benzene. The combined benzene extracts were washed with 5% potassium hydroxide and water and were dried over potassium carbonate. The benzene was evaporated, and the residual oil was distilled under reduced pressure giving 15.6 g. (64%) of 5-t-butylhexa-hydro-1-methyl-2H-azepin-2-one (42), b.p. 100-101.5° at 0.85 mm.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55. Found: C, 71.87; H, 11.38.

IR Spectrum (No. 4336): 2990, 2890, 1665, 1499, 1401, 1372, 1270 (m), 1217 (m), 1180 (m), 1092, 1019 (m), 980 (m).

NMR Spectrum (neat, No. 194): 0.88 (singlet), 2.90 (singlet).

4-t-Butyl-2,3,4,5-tetrahydro-1-methyl-7-phenyl-1H-azepine (43). A solution of 15.6 g. of 5-t-butylhexahydro-1-methyl-2H-azepin-2-one (42) in 50 ml. of dry ether was added with stirring to a refluxing solution of phenylmagnesium bro-

mide prepared from 13.5 g. of bromobenzene and 2.1 g. of magnesium in 100 ml. of dry ether. The mixture was heated under reflux for 8 hrs. and was hydrolyzed with dilute hydrochloric acid. The ethereal layer was separated, and the water layer was extracted with ether. The combined ethereal extracts were dried over potassium carbonate, and the ether was evaporated. The residual oil was distilled under reduced pressure giving 8.3 g. (40%) of 4-t-butyl-2,3,4,5-tetrahydro-1-methyl-7-phenyl-1H-azepine (43), b.p. 130-136° at 1.15 mm.

IR Spectrum (No. 4358): 3060 (m), 3025 (m), 2990, 2890, 1680 (m), 1625, 1600 (m), 1475, 1445, 1387, 1368, 1108, 1068, 801 (m), 769, 750 (m), 702.

To a solution of 1.02 g. of 4-t-butyl-2,3,4,5-tetrahydro-1-methyl-7-phenyl-1H-azepine (43) in 10 ml. of ether a mixture (1:1 by volume) of perchloric acid[17] and ethanol was added dropwise until the resulting mixture was acid to Congo red paper at which time a white solid was deposited. After cooling the mixture with ice, the solid was collected by filtration and was washed with ether giving 1.15 g. (80%) of 4-t-butyl-3,4,5,6-tetrahydro-1-methyl-7-phenyl-2H-azepinium perchlorate (44), m.p. 137-144°. Recrystallization from ethanol gave an analytical sample, m.p. 140.5-142°.

Anal. Calcd. for $C_{17}H_{26}ClNO_4$: C, 59.37; H, 7.62. Found: C, 59.30; H, 7.65.

IR Spectrum (No. 4360): 2940 (m), 2860 (m), 1651, 1445 (m), 1370, 1115-1070, 778, 713.

5-t-Butyl-1-methyl-2-phenylhexamethylenimine (37) was prepared by reduction of 43 with sodium borohydride and glacial acetic acid as previously described (method B).

Ultraviolet Absorption Spectra of Tosylates

Effect of Drying Agents on Benzophenone Oxime Tosylate (48). A solution of benzophenone oxime tosylate in wet ether was divided into three portions. One portion was dried over potassium carbonate, the second over magnesium sulfate and the third portion was not dried. After standing for 2 hrs., the solutions were filtered from the drying agents. The ultraviolet absorption spectra (No. 71) of the three solutions were nearly identical showing maxima at 249 mμ. The absorption spectrum (No. 71) of benzophenone oxime showed a maximum at 250 mμ and benzanilide at 265 mμ. The absorption spectrum (No. 71) of an equimolar mixture of benzophenone oxime and p-toluenesulfonyl chloride showed a maximum at 241 mμ.

Reaction of Benzophenone Oxime Tosylate (48) with Magnesium Bromide. Benzophenone oxime tosylate (4.9 mg., m.p. 91-124° from anhydrous ether) was weighed into a 25 ml. volumetric flask, and 3-5 ml. of anhydrous ether was added for dissolution. A filtered ethereal solution of magnesium bromide (prepared from 1 magnesium turning and 2-3 drops of ethylene bromide) was added, and the resulting turbid solution was diluted to a total volume of 25 ml. An aliquot (1,2 or 5 ml.) was removed and treated with 3-4 drops of dioxane. The resulting mixture was filtered into a volumetric flask (all glassware washed) and appropriately diluted with ether. The ultraviolet absorption spectrum (No. 181) of the clear solution showed maxima at 315 mμ (ε 2,680) and 245 mμ (ε 19,300). A duplicate sample showed an absorption maximum at 315 mμ (ε 2,525). The 245 mμ band was not recorded on this spectrum, since the solution was too concentrated. The absorption spectrum (No. 180) of pure benzophenone oxime tosylate showed a maximum at 249 mμ (ε 16,100).

Reaction of 4-t-Butylcyclohexanone Oxime Tosylate (30) with Magnesium Bromide. An ethereal solution of 4-t-butylcyclohexanone oxime tosylate (0.0285 g., m.p. 72-78° from ether) which was treated with magnesium bromide in the same manner as benzophenone oxime tosylate showed a maximum at 271 mμ (ε 2,260) in the ultraviolet absorption spectrum (No. 183). The absorption spectrum (No. 183) of pure 4-t-butylcyclohexanone oxime tosylate showed maxima at 272(415), 265(582), 262(593), and 256 mμ (ε 470).

Reaction of p-Toluenesulfonyl Chloride with Magnesium Bromide. An ethereal solution of p-toluenesulfonyl chloride (0.0478 g.) which was treated with magnesium bromide in the same manner as benzophenone oxime tosylate showed maxima at 278 sh (700), 270 sh (1,350), and 242 mμ (ε 9,700) in the ultraviolet absorption spectrum (No. 183). The absorption spectrum (No. 183) of pure p-toluenesulfonyl chloride was nearly identical showing maxima at 278 sh (780), 270 sh (1,470), and 242 mμ (ε 10,300).

Reactions of Tosylates with Magnesium Bromide and Phenylmagnesium Bromide

Reaction of 4-t-Butylcyclohexanone Oxime Tosylate (30) with Magnesium Bromide and Phenylmagnesium Bromide. (a). A solution of 4-t-butylcyclohexanone oxime tosylate (prepared from 6.0 g. of 4-t-butylcyclohexanone oxime) in 75 ml. of benzene was added to an anhydrous magnesium bromide solution (prepared from 6.7 g. of ethylene bromide and 0.85 g. of magnesium in 50 ml. of dry ether), and the mixture was allowed to stand at room temperature for 17 hrs. The resulting mixture was added with stirring at 11° to phenylmagnesium bromide prepared from 16.8 g. of bromobenzene and 2.6 g. of magnesium in

50 ml. of dry ether. The mixture was stirred at 11-15° for 2 hrs. and was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were dried over potassium carbonate. The solvent was removed by distillation under reduced pressure giving a residual oil which was shown by gas chromatographic analysis (2 m. 5% Silicone Oil 200 on Haloport F, 198°, 10 psi) to contain 5-t-butylhexahydro-2H-azepin-2-one (41).

The acidic water layer was made basic with a sodium hydroxide solution and was extracted with ether. The combined extracts were dried over potassium carbonate. The solvent was removed by distillation under reduced pressure giving 0.34 g. of a residual oil which was shown by gas chromatographic analysis (same conditions as above) to consist of 4-t-butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32) and 5-t-butylhexahydro-2H-azepin-2-one (41) in a 5:1 ratio respectively. No evidence for the presence of 4-t-butylcyclohexanone or aniline was obtained.

(b). This series of reactions was repeated with only one difference in procedure; namely, the Grignard reaction mixture was hydrolyzed with a saturated solution of ammonium chloride instead of dilute hydrochloric acid. The residual oil obtained was distilled under reduced pressure. The fraction, b.p. 63-124° at 1.8 mm., was shown by gas chromatographic analysis (2 m. 5% Silicone Oil 200 on Haloport F, 198°, 10 psi) to consist of biphenyl, phenol, and bromobenzene. The fraction, b.p. 144-150° at 1.8 mm., (0.28 g.) was shown to contain 4-t-butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32), 5-t-butylhexahydro-2H-azepin-2-one (41), and a trace of biphenyl. The majority of the residual oil could not be distilled

and was left as a brown tar. Again no evidence for the presence of 4-t-butylcyclohexanone or aniline was obtained.

Reaction of Methyl Ethyl Ketoxime Tosylate (54) with Magnesium Bromide and Phenylmagnesium Bromide. A solution of 6.0 g. of methyl ethyl ketoxime tosylate in 200 ml. of dry ether was added to an anhydrous magnesium bromide solution prepared from 6.5 g. of ethylene bromide and 0.85 g. of magnesium in 35 ml. of dry ether, and the mixture was allowed to stand at room temperature for 16 hrs. The resulting mixture was added with stirring at 11° to phenylmagnesium bromide prepared from 16.3 g. of bromobenzene and 2.6 g. of magnesium in 50 ml. of dry ether. The mixture was stirred at 11-15° for 2 hrs. and was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the acidic water layer was extracted with ether, made basic with sodium hydroxide solution, and again extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 3.2 g. of residual oil which was shown by gas chromatographic analysis (1 m. 5% Carbowax 20 M on Chromosorb W in series with a 1 m. 5% Silicone Grease on Haloport F, 133°, 11 psi) to contain acetophenone (82%) and propiophenone (18%). No evidence for the presence of aniline was obtained.

Reactions of Tosylates with Diorganomagnesium Reagents

Reaction of 4-t-Butylcyclohexanone Oxime Tosylate (30) with Diphenylmagnesium. Phenylmagnesium bromide was prepared from 64.0 g. of bromobenzene and 9.9 g. of magnesium in 280 ml. of dry ether under a nitrogen atmosphere. Dropwise addition of a mixture (140 ml.; 1:1 by volume) of anhydrous dioxane[29,30]

and ether to the stirred Grignard reagent produced a white precipitate which was allowed to settle. The resulting mixture was filtered through a sintered glass filter with nitrogen pressure into a flamed-out, 3-necked flask (Grignard apparatus). The precipitate was washed with 50 ml of ether, and the mixture was filtered as before. A solution of 4-t-butylcyclohexanone oxime tosylate (prepared from 6.0 g. of 4-t-butylcyclohexanone oxime) in 100 ml. of benzene was added with stirring at 10° to the diphenylmagnesium solution. The mixture was stirred at 10-15° for 2 hrs. and was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 5.0 g. of residual oil which was shown by gas chromatographic analysis (2 m. 5% Silicone Oil 200 on Haloport F, 198°, 8 psi) to contain 4-t-butylcyclohexanone.

The acidic water layer was made basic with sodium hydroxide solution and was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 1.3 g. (40% based on oxime) of residual oil which was shown by gas chromatographic analysis (same conditions as above) to consist of aniline and a trace amount of dioxane.

Reaction of Methyl Ethyl Ketoxime Tosylate (54) with Diphenylmagnesium. A solution of 6.4 g. of methyl ethyl ketoxime tosylate in 100 ml. of benzene was added with stirring at 11° to diphenylmagnesium prepared as in the reaction with 4-t-butylcyclohexanone oxime tosylate. The mixture was stirred at 11-15° for 2 hrs. and was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the

water layer was extracted with ether, made basic with sodium hydroxide solution, and again extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 4.6 g. of residual oil which was shown by gas chromatographic analysis (1 m. 5% Carbowax 20M on Chromosorb W in series with a 1 m. 5% Silicone Grease on Haloport F, 134°, 11 psi) to contain aniline (99%) and acetophenone (1%).

Reaction of Acetophenone Oxime Tosylate (59) with Diethylmagnesium. A solution of 10.0 g. of acetophenone oxime tosylate in 100 ml. of benzene was added with stirring at room temperature to diethylmagnesium prepared from 38.6 g. of ethyl bromide and 8.6 g. of magnesium in 240 ml. of dry ether and 120 ml. of dioxane-ether (1:1 by volume) following the procedure previously described for the preparation of diphenylmagnesium. The mixture was stirred for 2 hrs. and was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the water layer was extracted with ether, made basic with sodium hydroxide solution and again extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving a residual oil which was shown by gas chromatographic analysis (1 m. 5% Carbowax 20M on Chromosorb W in series with a 1 m. 5% Silicone Grease on Haloport F, 120°, 15 psi) to contain acetophenone (74%) and aniline (26%).

The residual oil was dissolved in 20 ml. of ether and washed three times with 5% hydrochloric acid (75 ml.). The water layer was extracted with ether, and the combined extracts were dried over potassium carbonate. The solvent was removed by distillation under reduced pressure giving 1.9 g. of residual oil which gave only one peak on gas chromatographic

analysis with the same retention time as acetophenone. The infrared spectrum was similar to that of pure acetophenone, but contained additional small bands at 3000-2900 cm^{-1}.

The acidic water layer was made basic with sodium hydroxide solution and was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 0.98 g. of residual oil which gave only one peak on gas chromatographic analysis with the same retention time as aniline. The infrared spectrum was similar to that of pure aniline, but contained additional small bands at 3000-2900 and 1680 cm^{-1}.

Reaction of p-Chloroacetophenone Oxime Tosylate (62) with Diethylmagnesium. A solution of 11.5 g. of p-chloroacetophenone oxime tosylate in 100 ml. of benzene was added with stirring at room temperature to diethylmagnesium prepared as in the reaction with acetophenone oxime tosylate. The mixture was stirred for 1.5 hrs. and was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 3.7 g. of residual oil which was shown by gas chromatographic analysis (2 m. 5% Silicone Oil 200 on Haloport F, 174°, 10 psi) to contain p-chloroacetophenone and a trace amount of p-chloroaniline.

The acidic water layer (contained in a 3-necked flask fitted with a stopper, dropping funnel and glass tube connected to a 5% hydrochloric acid trap) was made basic with a hot sodium hydroxide solution, and the system was swept with nitrogen gas. Evaporation of the solution from the acid trap gave a white semi-solid residue in an insufficient amount for definite characterization as ethylamine hydrochloride.

The basic water layer was extracted with ether, and

the combined extracts were dried over potassium carbonate. The solvent was removed by distillation under reduced pressure giving 0.83 g. of residual oil which was shown by gas chromatographic analysis (same conditions as above) to consist of p-chloroaniline and a trace amount of p-chloroacetophenone.

The residual oils from extraction of the acidic and basic water layers were combined, and the flasks were washed with ether. The ether was evaporated, and gas chromatographic analysis (1 m. 5% Carbowax 20M on Chromosorb W in series with a 1 m. 5% Silicone Grease on Haloport F, 170°, 10 psi) showed the mixture to consist of p-chloroacetophenone (76%) and p-chloroaniline (24%).

Reaction of p-Chloroacetophenone Oxime Tosylate (62) with Diphenylmagnesium. A solution of 11.5 g. of p-chloroacetophenone oxime tosylate in 100 ml. of benzene was added with stirring at room temperature to diphenylmagnesium prepared in half the amount as in the reaction with 4-t-butylcyclohexanone oxime tosylate. The mixture was stirred for 2 hrs. and was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the water layer was washed with ether. The acidic water layer was made basic with sodium hydroxide solution and was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 0.6 g. of residual oil which was shown by gas chromatographic analysis (1 m. 5% Carbowax on Chromosorb W in series with a 1 m. 5% Silicone Grease on Haloport F, 152°, 10 psi) to consist of aniline (69%) and p-chloroaniline (31%).

Reaction of Acetophenone Oxime Tosylate (59) with p,p'-Dichlorophenylmagnesium. A solution of 18.5 g. of aceto-

phenone oxime tosylate in 100 ml. of benzene was added with stirring at room temperature to p,p'-dichlorophenylmagnesium prepared from 78.0 g. of 1-bromo-4-chlorobenzene and 9.9 g. of magnesium in 300 ml. of dry ether and 140 ml. of dioxane-ether (1:1 by volume) following the procedure previously described for the preparation of diphenylmagnesium. The mixture was stirred for 2 hrs. and was hydrolyzed with a saturated solution of ammonium chloride. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving a residual oil which partially crystallized with petroleum ether. The solid was triturated with ether and was collected by filtration. Four additional crops were obtained from the ethereal washings giving 5.3 g. (36%) of p-chloroacetophenone anil (66), m.p. 88-92°. Recrystallization from ether gave an analytical sample, m.p. 91.5-92.5°.

Anal. Calcd. for $C_{14}H_{12}ClN$: C, 73.20; H, 5.27; N, 6.10. Found[FM]: C, 73.20; H, 5.61; N, 5.88.

IR Spectrum (No. 6132): 2980, 1630, 1590, 1483, 1277, 1097, 1017, 842, 792, 750, 704.

The residual oil from evaporation of the ethereal washings was treated with 25 ml. of 10% hydrochloric acid. The mixture was heated on a steam bath for 10 minutes and was allowed to cool to room temperature with occasional shaking. The mixture was extracted with ether, and the combined extracts were dried over potassium carbonate. The solvent was removed by distillation under reduced pressure giving a residual oil which was shown by gas chromatographic analysis (1 m. 5% Carbowax 20M on Chromosorb W in series with a 1 m. 5% Silicone Grease on Haloport F, 133°, 11 psi) to contain

p-chloroactophenone (major component) and acetophenone (minor component).

The acidic water layer was made basic with sodium hydroxide solution and was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 2.5 g. of residual oil which was shown by gas chromatographic analysis (same conditions as above) to consist of aniline (major component) and p-chloroaniline (minor component).

A mixture of 0.50 g. of p-chloroacetophenone anil (66), m.p. 91.5-92.5°, and 30 ml. of 10% hydrochloric acid was heated on a steam bath for 10 minutes and was allowed to cool with occasional shaking. The mixture was extracted with ether, and the combined extracts were dried over potassium carbonate. The ether was removed by distillation under reduced pressure giving 0.29 g. (86%) of p-chloroacetophenone which was identical in every respect with an authentic sample.

The acidic water layer was made basic with sodium hydroxide solution and was extracted with ether. The ethereal extracts were dried over potassium carbonate, and the ether was removed by distillation under reduced pressure giving 0.17 g. (84%) of aniline which was identical in every respect with an authentic sample.

Reaction of Acetophenone Oxime Tosylate (59) with p,p'-Ditolylmagnesium. A solution of 10.3 g. of acetophenone oxime tosylate in 100 ml. of benzene was added with stirring at room temperature to p,p'-ditolylmagnesium prepared from 34.5 g. of p-bromotoluene and 5.0 g. of magnesium in 140 ml. of dry ether and 70 ml. of dioxane-ether (1:1 by volume) following the procedure previously described for the preparation of diphenylmagnesium. The mixture was stirred for 2.5 hrs. and

was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 7.65 g. of residual oil which was shown by gas chromatographic analysis (1 m. 5% Carbowax 20M on Chromosorb W in series with a 1 m. 5% Silicone Grease on Haloport F, 152°, 10 psi) to contain acetophenone (42%) and p-methylacetophenone (58%).

The acidic water layer was made basic with sodium hydroxide solution and was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 1.95 g. of residual oil which was shown by gas chromatographic analysis (same conditions as above) to consist of p-toluidine (39%) and aniline (61%).

Preparation and Reactions of (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate (70) with Organometallic Reagents

1-Methyl-2,6-diphenyl-4-piperidone (68) was prepared according to the procedure described by Lyle and Lyle[35] to give a 35-47% yield of piperidone 68, m.p. 146-150°; lit.[35] m.p. 151-153°.

1-Methyl-2,6-diphenyl-4-piperidone Oxime (69) was prepared according to the procedure described by Lyle[37] to give a 68-71% yield of oxime 69, m.p. 190-191°; lit.[35,37] m.p. 191-193°.

(+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime (69). The oxime was resolved according to the procedure described by Lyle and Lyle.[35] Reaction of 10.0 g. of racemic 1-methyl-

2,6-diphenyl-4-piperidone oxime with 10.0 g. of (+)-10-camphorsulfonic acid gave 16.4-18.1 g. (90-99%) of (+)-10-camphorsulfonic acid salt of the oxime, m.p. 165-167.5°, $[\alpha]_D^{22}$ +25.7 to +29.7° (95% ethanol, c=2.0); lit.[35] m.p. 167.5-172°, $[\alpha]_D^{25}$ +30.08° (95% ethanol, c=2.0). Neutralization of 16.4-18.1 g. of the (+)-salt of the oxime with aqueous potassium carbonate gave 8.0-8.8 g. (85-89%) of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (69), m.p. 191.5-192.5°, $[\alpha]_D^{22}$ +31.2 to +32.8° (95% ethanol, c=2.0); lit.[35] m.p. 188-192°, $[\alpha]_D^{25}$ +32.63° (95% ethanol, c=2.2).

(+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate (70). To a stirred suspension of 5.0 g. of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime ($[\alpha]_D^{22}$ +31.5°, 95% ethanol) in 50 ml. of acetone in an ice-salt bath 35 ml. of cold 1.37 N potassium hydroxide solution was added. To the resulting solution 3.4 g. of p-toluenesulfonyl chloride was added in portions producing a white precipitate. The mixture was stirred at -3° for 0.5 hr. and then poured into ice water. The solid was collected by filtration, triturated with ice water, and again collected by filtration giving, after drying, 7.2 g. (93%) of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime tosylate (70), m.p. 86-98°, $[\alpha]_D^{23}$ +6.5° (dioxane, c=2.1); lit.[37] m.p. 96-99°, $[\alpha]_D^{25}$ +4.77°, +10.03° (benzene, c=2.3, 3.2). Recrystallization from benzene and petroleum ether (30-60°) gave 5.2 g. (67%) of tosylate, m.p. 96-100°, $[\alpha]_D^{23}$ +7.4° (dioxane, c=2.0).

Attempted Reaction of 1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate (70) with Diphenylmagnesium. A solution of 7.8 g. of 1-methyl-2,6-diphenyl-4-piperidone oxime tosylate in 75 ml. of benzene was added with stirring at room temperature to diphenylmagnesium prepared from 2.5 g. of magnesium and 16.0 g. of bromobenzene in 70 ml. of dry ether and 36 ml.

of dioxane-ether (1:1 by volume) following the procedure previously described for the reaction with 4-t-butylcyclohexanone oxime tosylate. The mixture was stirred for 2 hrs. and was hydrolyzed with a saturated solution of ammonium chloride. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 7.9 g. of yellow residual oil. On treatment with petroleum ether, the residual oil partially crystallized giving 4.2 g. (54%) of unreacted 70. The infrared spectrum of the residual oil from concentration of the petroleum ether mother liquor contained strong bands at 3500, 3400, 1725, and 1670 cm^{-1} suggesting the presence of aniline, 1-methyl-2,6-diphenyl-4-piperidone (68), and 1-methyl-2,6-diphenyl-4-piperidone anil (71).

Reaction of 1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate (70) with Phenylmagnesium Bromide. A solution of 1-methyl-2,6-diphenyl-4-piperidone oxime tosylate (prepared from 7.0 g. of oxime) in 100 ml. of benzene was added with stirring at 10° to phenylmagnesium bromide prepared from 1.2 g. of magnesium and 7.9 g. of bromobenzene in 40 ml. of dry ether. The mixture was stirred at 10-14° for 2 hrs. and was hydrolyzed with a saturated solution of ammonium chloride. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure giving 9.3 g. of a brown residual oil which was treated with n-hexane. The n-hexane was evaporated, and the residual oil partially crystallized on standing overnight. The mixture was triturated with petroleum ether, and the yellow solid was collected by filtration giving 3.0 g.

(35% based on oxime) of 1-methyl-2,6-diphenyl-4-piperidone anil (71), m.p. 97-116°. Recrystallization from n-heptane raised the melting point to 110-118°.

A second reaction of 14.8 g. of 1-methyl-2,6-diphenyl-4-piperidone oxime tosylate with phenylmagnesium bromide gave 4.1 g. (35%) of 1-methyl-2,6-diphenyl-4-piperidone anil (71). An attempt to recrystallize 4.0 g. of anil 71 from hot 95% ethanol resulted in hydrolysis of the anil giving 1.8 g. of 1-methyl-2,6-diphenyl-4-piperidone (68) which was identical in every respect with an authentic sample. The mother liquor was evaporated, the residue was triturated with petroleum ether, and the semi-solid (1.1 g.) was separated by filtration. The infrared spectrum indicated this material to be a mixture of piperidone 68 and aniline. Evaporation of the petroleum ether mother liquor gave 0.8 g. of residual oil whose infrared spectrum was nearly identical with that of pure aniline, but contained weak additional bands at 2795 and 1718 cm^{-1} indicating the presence of piperidone 68.

Reaction of (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate (70) with Phenylmagnesium Bromide. (a). The reaction of 4.9 g. of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime tosylate, m.p. 96-100°, $[\alpha]_D^{23}$ +7.4° (dioxane, c=2.0), with phenylmagnesium bromide following the procedure previously described for the reaction with racemic tosylate gave 0.16 g. (4%) of (-)-1-methyl-2,6-diphenyl-4-piperidone anil(71), m.p. 110-118°, $[\alpha]_D^{23}$ -2.1° ±0.5° (dioxane, c=2.0) after recrystallization from acetonitrile.

ORD Curve (No. 546, dioxane, c=0.402): $[\phi]_{600}$ -17°, $[\phi]_{589}$ -17°, $[\phi]_{370}$ -25.5°, $[\phi]_{360}$ -29.5°, $[\phi]_{345}$ -38°, $[\phi]_{335}$ -46.5°, $[\phi]_{323}$ -68°.

After the solution of (-)-71 in dioxane was allowed to stand for 3 days, the optical rotatory dispersion curve (No. 552) showed only a zero rotation line.

(b). The reaction of 11.5 g. of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime tosylate, m.p. 91-99°, $[\alpha]_D^{23}$ +5.6° (dioxane, c=2.0), with phenylmagnesium bromide at ice-salt bath temperature gave 4.1 g. (47%) of (-)-1-methyl-2,6-diphenyl-4-piperidone anil (71), m.p. 111-116°, $[\alpha]_D^{23}$ -1.44° ±0.25° (dioxane, c=4.0). A second crop of anil (0.6 g., m.p. 109-119°) was obtained giving a total of 4.7 g. (52%) of anil 71. A solution of the anil 71 in 95% aqueous dioxane (c=4.34) produced no rotation of plane polarized light.

Anal. Calcd. for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11. Found[FM]: C, 84.23; H, 7.36.

IR Spectrum (No. 6104): 3035 (m), 2785 (m), 1675, 1595 (m), 1488 (m), 1453 (m), 1148, 808, 795, 768, 753, 701.

SUMMARY

5α-Cholestan-3-one oxime and 4-t-butylcyclohexanone oxime underwent reaction with concentrated solutions of phenylmagnesium bromide to produce aniline in poor yields.

The reaction of 4-t-butylcyclohexanone oxime, methyl ether with phenylmagnesium bromide occurred with addition to the carbon-nitrogen double bond to give a basic material which was tentatively identified as N-methoxy-4-t-butyl-1-phenylcyclohexylamine.

Tosylates of oximes underwent reaction readily with Grignard reagents to produce a mixture of Schiff's bases. The relative percentages of the Schiff's bases were found to be dependent on the nature of the tosylate and the organometallic reagent. The results summarized below required a mechanism with two competing reactions: (1) rearrangement of the tosylate in the presence of a Lewis acid to the O-tosyl derivative of the amide which underwent reaction with the Grignard reagent, most likely by an addition-elimination mechanism and (2) a direct displacement of tosylate ion by the Grignard reagent.

1. 4-t-Butylcyclohexanone oxime tosylate underwent reaction with phenylmagnesium bromide to give a mixture of 4-t-butylcyclohexanone anil (31) and 4-t-butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine (32). The structures were confirmed by hydrolysis of 31 and an alternate synthesis of a derivative of 32.
2. The reaction of methyl ethyl ketoxime tosylate with phenylmagnesium bromide gave, after hydrolysis, a mixture

of aniline, acetophenone, and propiophenone.

3. The reaction of benzophenone oxime tosylate (48) with phenylmagnesium bromide gave benzophenone anil. The reaction of 48 with a series of p-substituted phenylmagnesium bromides produced, after hydrolysis, aniline as the only product which contained nitrogen. These results required that complete rearrangement of the tosylate must have occurred prior to reaction with the Grignard reagent.

4. A study of the ultraviolet absorption of ethereal solutions of benzophenone oxime tosylate and 4-t-butylcyclohexanone oxime tosylate after treatment with anhydrous magnesium bromide showed a striking change in the ultraviolet absorption spectra indicative of the O-tosyl derivative of the corresponding amide.

5. Tosylates when pretreated with anhydrous magnesium bromide and then phenylmagnesium bromide gave only the products expected from a Beckmann-like rearrangement prior to reaction with the Grignard reagent. Thus 4-t-butylcyclohexanone oxime tosylate gave only 4-t-butyl-3,4,5,6-tetrahydro-7-phenyl-2H-azepine, and methyl ethyl ketoxime tosylate gave only acetophenone and propiophenone.

6. Tosylates underwent reaction with diorganomagnesium reagents to give predominantly the products expected from a direct displacement of tosylate ion by the diorganomagnesium reagent.

7. (+)-1-Methyl-2,6-diphenyl-4-piperidone oxime tosylate underwent reaction with phenylmagnesium bromide to produce (-)-1-methyl-2,6-diphenyl-4-piperidone anil. The formation of optically active anil required a direct displacement mechanism.

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