The Addition of Organometallic Reagents to Azabicyclic Ketones[1]

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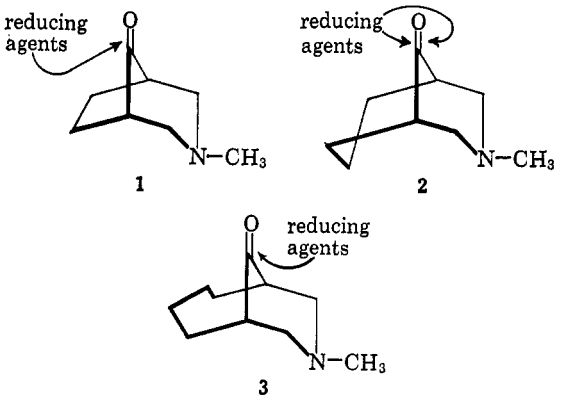
The additions of organomagnesium and organolithium compounds to the azabicyclic ketones **1**, **2**, and **3** have been studied. Addition to the ketone **1** yielded the β-alcohol **4**, addition to the ketone **3** yielded the α-alcohols **8**, and addition to ketone **2** yielded mixtures of α-alcohols **7** and β-alcohols **6**. These results suggest that the nitrogen atom exerts little effect on the direction of addition of these organometallic reagents. Selective acylation of the β isomers **4** and **6** with either *p*-nitrobenzoyl chloride or *p*-nitrobenzoic anhydride was used to establish the stereochemistry of the various amino alcohols.

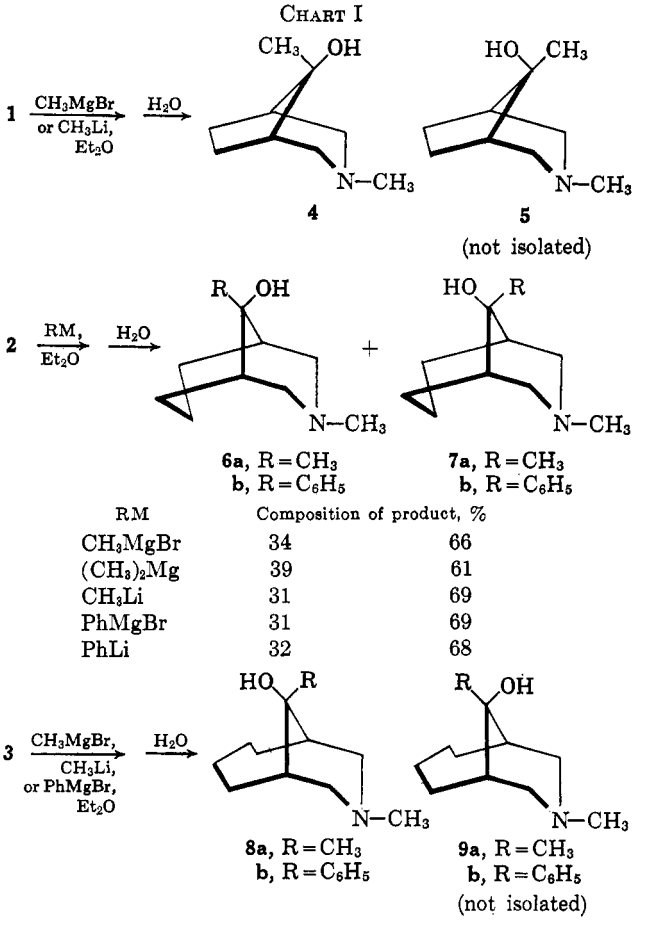
In earlier studies[2] we described the preparation of the azabicyclic ketones **1–3** as well as the stereochemical results observed when these ketones were reduced with various reagents. The stereochemical course of these reductions, summarized in structures **1–3**, was influenced only slightly by the nearby nitrogen atom irrespective of whether it was present as a tertiary amine or as quaternary ammonium salt; instead, the reduction stereochemistry was readily explicable in terms of approach of the reducing agent from the less hindered side of the carbonyl function. It appeared



possible that we would be more successful in finding examples in which the nitrogen atom would direct the steric course of addition of a nucleophilic reagent to the carbonyl function by examining reactions with organolithium and organomagnesium reagents. Since these reagents show a pronounced tendency to form coordinate bonds to both ethers and tertiary amines, it might be supposed that reaction would proceed from an initial coordination complex of the amine and the organometallic reagent. This circumstance would result in the predominant addition of the organometallic reagent from that side of the molecule in which the amine function was located. To examine this possibility, the reactions of amino ketones **1–3** with methyl and phenyl derivatives of magnesium and lithium have been studied.

The results of these studies are summarized in Chart I. The stereochemical results obtained will be noted to conform rather closely to the previously studied reductions. Thus, addition of the organometallic compound to the ketone **1** gave the β-alcohol **4** with no α isomer **5** being isolated and the additions to ketone **3** gave the α-alcohols **8**, no β isomer **9** being isolated.[3] From the ketone **2**, mixtures of the two stereoisomers **6** and **7** were obtained. The composition of this mixture was influenced to a relatively small extent by changes in the nature of the organometallic reagents (*e.g.*, dimethylmagnesium or methylmagnesium bromide), suggesting that factors such as coordination of the amino function with magnesium bromide in certain of the reaction mixtures do not alter the steric course of the addition to any appreciable extent. Consequently, these results, like the earlier data with various reducing agents, indicate that participation of the

CHART I



RM	Composition of product, %	
CH_3MgBr	34	66
$(CH_3)_2Mg$	39	61
CH_3Li	31	69
PhMgBr	31	69
PhLi	32	68

(1) This research has been supported by research grants from the National Institutes of Health (Grant No. GM-08761) and the Petroleum Research Fund.

(2) (a) H. O. House, P. P. Wickham, and H. C. Müller, *J. Am. Chem. Soc.*, **84**, 3139 (1962); (b) H. O. House and H. C. Müller, *J. Org. Chem.*, **27**, 4436 (1962); (c) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *ibid.*, **28**, 2407 (1963).

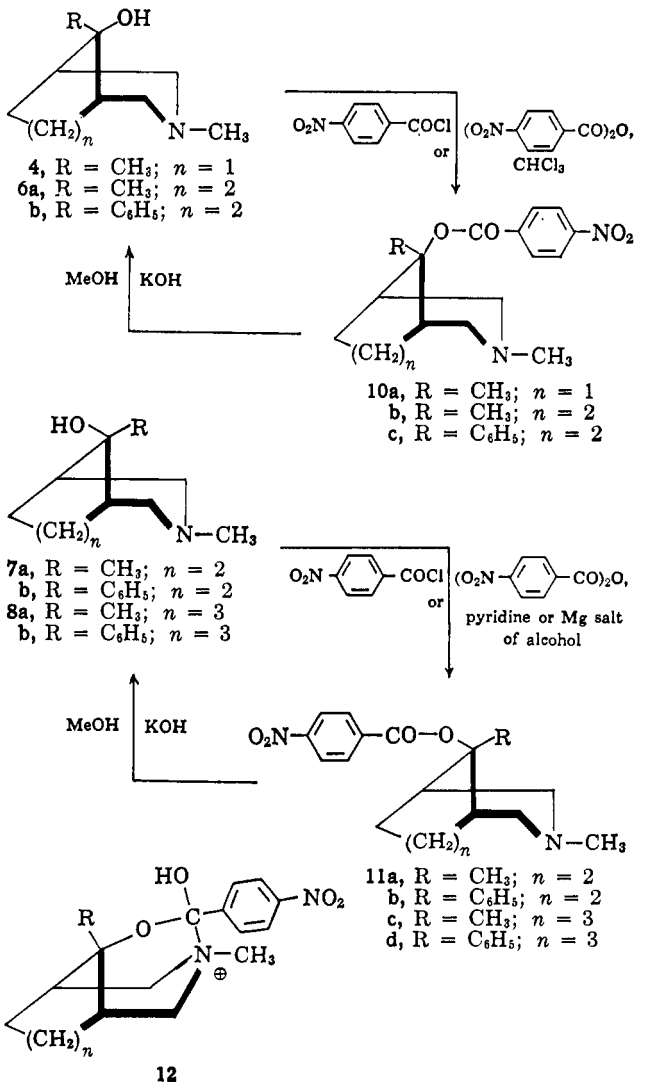
(3) As in our previous paper (ref. 2c), we are following the configurational designation for amino alcohols proposed by G. Fodor and K. Nador [*J. Chem. Soc.*, 721 (1953)] in which those isomers with the hydroxyl function oriented toward the nitrogen atom are called β isomers (*e.g.*, **4**, **6**, and **9**) and those isomers with the hydroxyl function oriented away from nitrogen are called α isomers (*e.g.*, **5**, **7**, and **8**).

nitrogen atom in the addition of organolithium or organomagnesium reagents is of minor importance, the stereochemical course of the addition being controlled largely by steric factors which favor addition of the reagent from the less hindered side of the carbonyl function.[4,5]

The configurations of the various amino alcohols, **4** and **6–8** produced in this study were assigned primarily by use of the previously discovered[2c] selective acylation procedure. Thus, the β-alcohols **4** and **6** were acylated with *p*-nitrobenzoyl chloride or *p*-nitrobenzoic anhydride to form *p*-nitrobenzoates **10** under conditions where the α isomers **7** and **8** failed to react; more vigorous reaction conditions did suffice to produce the α-alcohol *p*-nitrobenzoates **11**. The greater reactivity of the β-alcohols, attributable to an intramolecular acylation mechanism (as in structure **12**), not only permitted us to make stereochemical assignments, but offered a practical method for the separation of amino alcohols **6** and **7**. Thus, this procedure is useful for the tertiary alcohols encountered in this study as well as for the previously studied[2c] secondary alcohols.

The physical constants of the amino alcohols prepared in this study are summarized in Table I. As was noted earlier[2c] for the analogous secondary alcohols, within any one stereochemical family the basicity diminishes in the higher homologs (*i.e.*, **4** > **6a**, **7a** > **8a**, **7b** > **8b**). As was also the case for the analogous alcohols, the β isomer of any stereochemical pair is the stronger base (*i.e.*, **6a** > **7a**, **6b** > **7b**).[6] It might also be noted that the α isomer **7** of the stereochemical pairs of tertiary alcohols is eluted more rapidly from silicic acid than is the corresponding β isomer **6**, an additional point of similarity to the analogous secondary alcohols.

Each of the amine alcohols studied (**4** and **6–8**) as well as the *p*-nitrobenzoates **10** and **11** exhibits intense infrared absorption in the region 2600–2800 cm.$^{-1}$ characteristic of amines in which at least two α-C–H bonds are *trans* and coplanar to the free electron pair on nitrogen.[7] In addition, none of the amino alcohols in dilute solution (5×10^{-3} *M* or less) exhibits any significant amount of infrared absorption attributable to intramolecular hydrogen bonding. From these observations we conclude that the preferred conformations of these amino alcohols, like previously studied analogs,[2c] are those indicated in which the piperidine ring adopts a chair conformation.[8] It is also of interest



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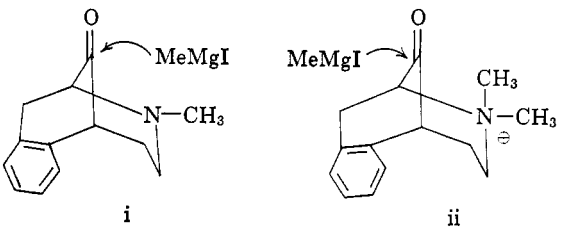
(4) The additions of organometallic reagents to certain amino ketones (*e.g.*, i) and the corresponding quaternary ammonium salts (*e.g.*, ii) have been found to give different stereochemical results: (a) E. L. May and H. Kugita, *J. Org. Chem.*, **26**, 188 (1961); (b) E. L. May, H. Kugita, and J. H. Ager, *ibid.*, **26**, 1621 (1961); (c) S. Saito and E. L. May, *ibid.*, **26**, 4536 (1961). In view of our results, we believe the differences observed with ketones such as i and ii should be attributed to differences in the steric hindrance encountered by the attacking organometallic reagent.



i ii

(5) We observed no products indicative of a fragmentation process of the type recently observed with certain strained amino esters: see L. Weintraub, A. Wilson, D. L. Goldhamer, and D. P. Hollis, *J. Am. Chem. Soc.*, **86**, 4880 (1964).

(6) It has been suggested [H. S. Aaron and C. P. Rader, *J. Org. Chem.*, **29**, 3426 (1964)] that the epimeric amino alcohol in which the C–O bond and axis of the free electron pair on nitrogen are arranged *anti* to one another will be the stronger base by about 0.4 pK_a unit. In other words, that isomer in which the dipole of the free electron pair on nitrogen is oriented in the same direction as the dipole of the C–O bond is expected to be the weaker base. Our results are certainly consistent with this idea. Our relative basicity data are also consistent with the idea that the β isomers are stronger bases because the salts are stabilized by intramolecular hydrogen bonding [V. Prelog and O. Häfliger, *Helv. Chim. Acta*, **33**, 2021 (1950); T. A. Geissman, B. D. Wilson, and R. D. Medz, *J. Am. Chem. Soc.*, **76**, 4182 (1954); B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964)]. Although we have been able to establish the absence of any significant amount of intramolecular hydrogen bonding in the β-alcohol free bases, we have not been able to establish the presence or absence of such intramolecular bonding in the amine salts.

(7) (a) F. Bohlman, *Chem. Ber.*, **91**, 2157 (1958); (b) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

(8) An X-ray crystal structure determination on the hydrobromide salt of 3-azabicyclo[3.3.1]nonane indicated that the conformation of this material in the solid state has both six-membered rings in chair conformations: M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964). Similar results have been obtained with derivatives of the analogous carbocyclic system: W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964). On the other hand, C. Y. Chen and R. J. W. Le Fevre [*Tetrahedron Letters*, **No. 12**, 737 (1965)] have presented n.m.r. evidence suggesting that the related 9-azabicyclo[3.3.1]nonane system present in 3α-granatanol exists predominantly in a boat–chair conformation.

TABLE I

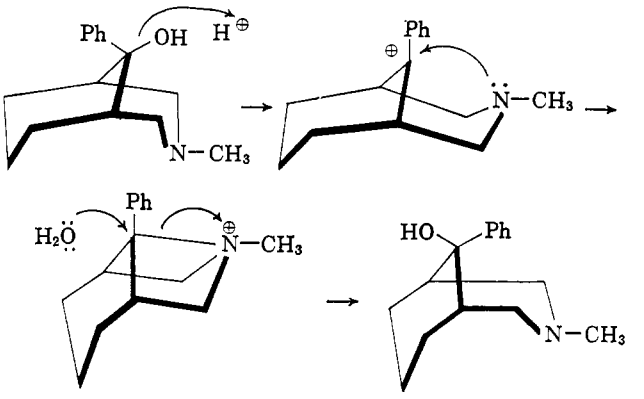
PHYSICAL PROPERTIES OF THE AMINO ALCOHOLS AND THEIR DERIVATIVES

Alcohols (m.p., °C.)	pK^*_{MCS}[a]	N.m.r. peaks, δ[b,c] N-Me	C-Me	*p*-Nitrobenzoates Compd. (m.p., °C.)	N.m.r. peaks, δ[b] N-Me	C-Me
4 (74.5–75.5)	8.56	2.37 (2.87)	1.31 (1.36)	**10a** (145–146)	2.23	1.58
6a (59.5–60.5)[d]	8.48	2.24 (2.91)	1.35 (1.47)	**10b** (136–137)	2.10	1.70
7a (92.5–93.5)[d]	7.54	2.20 (2.96)	1.36 (1.53)	**11a** (153.5–154.5)	2.20	1.74
8a (58.5–59.5)	7.08	2.23 (2.83)	1.40 (1.48)	**11c** (156–157)	2.17	1.77
6b (90.5–91.5)[d]	8.16	2.24 (2.99)	...	**10c** (170–171)	2.23	...
7b (84.5–85.5)[d]	7.30	1.96 (2.63)	...	**11b** (154–155)	2.04	...
8b (40–41)	6.73	1.97 (2.67)	...	**11d** (132–133)	2.14	...

[a] The apparent pK_a value in 80% Methyl Cellosolve and 20% water. See ref. 19. [b] Determined as a solution in deuteriochloroform. [c] The values in parentheses were determined for the ammonium salts obtained by solution of the amines in 20% deuterium chloride in deuterium oxide. [d] The α isomers **7** were eluted from silicic acid more rapidly than the β isomers **6**.

to note that the positions of the N–Me signal in the n.m.r. spectra for the various amino alcohols and for their salts are relatively constant except for those compounds, **7b** and **8b**, in which the N-methyl group lies under the benzene ring. In each of these cases the chemical shift of the N-methyl group is shifted upfield approximately 0.2 p.p.m., an observation which is clearly consistent with the stereochemical assignments made. A discussion of the mass spectral fragmentation patterns of these amino alcohols and related compounds will be published elsewhere.

In a recent study of the reaction products from the ketone **2** and phenylmagnesium bromide,[9a] the major product, eluted first when chromatographed on alumina and assigned structure **7b** in this paper, was converted by refluxing 10% aqueous hydrochloric acid to the minor product, m.p. 88–90° (eluted second on chromatography and assigned structure **6b** in this paper). Although the basis for assignment was not stated, the authors[9a] made stereochemical assignments just the reverse of those presented in this paper. We presume that the authors derived their stereochemical assignments from the idea that the conversion of one isomer to another by aqueous hydrochloric acid is a kinetically controlled process of the sort represented in the accompanying equations. This sequence, which would involve participation of the amine (as in **13**), is similar to the kinetically controlled reaction of certain tropane derivatives with nucleophiles.[9b] We can confirm the observation that the amino alcohol **7b** is converted to a mixture containing predominantly the isomeric alcohol **6b** by 10% aqueous hydrochloric acid (rapidly at reflux or slowly at room temperature). However, this transformation is not a kinetically controlled process because either pure isomer **6b** or **7b** is converted by aqueous hydrochloric acid to the same equilibrium



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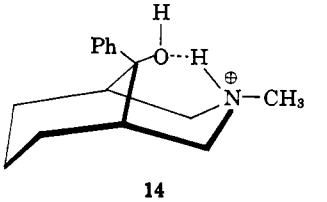
mixture of amino alcohols (91% **6b** and 9% **7b**). Thus, any argument such as the foregoing based on the assumption of a kinetically controlled isomerization in aqueous acid is not valid. We are currently studying the solvolysis of derivatives of amino alcohols **6** and **7** as well as related compounds to learn what the products will be. However, we believe the data presented in this paper clearly define the configuration of amino alcohols **6b** and **7b** and are in no way contradicted by the equilibration data in aqueous hydrochloric acid. The position of this equilibrium between the protonated forms of **6b** and **7b** could be regarded as evidence for the idea that the ammonium salt derived from **6b** is stabilized by an intramolecular hydrogen bond (as in **14**, *cf.* ref. 6).



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(9) (a) Sankyo Co., Ltd., British Patent 952,137 (March 11, 1964); *Chem. Abstr.*, **61**, 5614 (1964). (b) For studies of the reaction of 3-chloro- and 2-acetoxytropanes with nucleophiles, see S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg, and M. J. Unser, *J. Am. Chem. Soc.*, **79**, 6337 (1957); **80**, 4677 (1958); S. Archer, T. R. Lewis, M. R. Bell, and J. W. Schulenberg, *ibid.*, **83**, 2386 (1961).

Experimental Section[10]

Preparation of Starting Materials.—The Mannich condensation procedures described earlier[2a] were employed for the preparation of ketones **1**, **2**, and **3**; however, the modified isolation procedure which follows was adopted. The crude, basic product [93.66 g., b.p. 70–100° (0.7 mm.)] from reaction of 196.3 ml. (2.0 moles) of cyclohexanone, 135 g. (2.0 moles) of methylamine hydrochloride, and 450 ml. (6 moles) of 40% aqueous formaldehyde in 3.0 l. of acetic acid was redistilled in a Holtzmann column to separate 47.97 g. of the crude ketone **2**, b.p. 102–122° (19 mm.), $n^{25}D$ 1.4939. A solution of this fraction in pentane was stirred with 35 ml. of cold aqueous 48% hydrobromic acid and the pentane layer was separated. The cold aqueous phase was diluted with acetone and then filtered to separate 58.6 g. (12.5%) of the hydrobromide of ketone **2**, m.p. 200–206° dec. Recrystallization from an ethanol–ether mixture afforded hydrobromide as white prisms, m.p. 220–221° dec. This material is apparently either the hydrate or the ethanol hemiketal of the ketone **2** hydrobromide since it exhibits no absorption in the 6-μ region[11] attributable to a carbonyl function. After a cold, aqueous solution of 44.25 g. (0.19 mole) of this hydrobromide had been neutralized with sodium hydroxide, the aqueous phase was saturated with sodium chloride and extracted with pentane. The pentane extract was dried, concentrated, and distilled to separate 21.22 g. of the pure amino ketone **2**, b.p. 83–85.5° (8 mm.), $n^{25}D$ 1.4894–1.4895 [lit.[2a] b.p. 88° (7 mm.), $n^{25}D$ 1.4898]. This product, which exhibits a single peak on gas chromatography,[12] was identified with previous samples[2] by comparison of infrared spectra. Similarly, the crude, basic product [54.9 g., b.p. 40–110° (0.1 mm.)] obtained from 168 g. (2.0 moles) of cyclopentanone was redistilled, and the fraction, 15.82 g., b.p. 71–86° (18 mm.), $n^{25}D$ 1.4950, was converted to the hydrobromide of ketone **1** as 8.75 g. (4%) of white needles, m.p. 216–218° dec. Recrystallization from an ethanol–ether mixture sharpened the decomposition point to 217–218°. The infrared spectrum[11] of this salt also lacks carbonyl absorption in the 6-μ region indicating the existence of the salt as a hydrate or a hemiketal. Following the previous procedure, 6.456 g. (27 mmoles) of this hydrobromide was converted to 2.724 g. of the free ketone **1**, b.p. 91.5–92.5° (18 mm.), $n^{25}D$ 1.4806 [lit.[2a] b.p. 66° (5 mm.), $n^{25}D$ 1.4839], identified with previous samples[2] by comparison of infrared and n.m.r. spectra. The crude, basic product [119.5 g., b.p. 70–130° (1.0–1.5 mm.)] from 112 g. (1.0 mole) of cycloheptanone was redistilled to separate 38.58 g. of crude amino ketone, b.p. 88–107° (9 mm.), $n^{25}D$ 1.4940–1.4945, which yielded 30.12 g. (12.1%) of the **hydrobromide of ketone 3**, m.p. 230–233° dec. Recrystallization from a mixture of methanol and isopropyl alcohol afforded the pure hydrobromide as slender white prisms, m.p. 238–240° dec., with infrared absorption[11] at 1720 cm.$^{-1}$ (C=O) and n.m.r. absorption[13] in the regions δ 3.5–4.0 (4H, apparently the center peaks of an AB pattern, $-CH_2-N<^{\oplus}$) and 1.5–2.2 (8H, aliphatic C–H) and a singlet at δ 3.10 superimposed on a complex multiplet in the region δ 2.8–3.4 (5H, $CH_3-N<^{\oplus}$ and bridgehead C–H).

Anal. Calcd. for $C_{10}H_{18}BrNO$: C, 48.40; H, 7.31; Br, 32.20; N, 5.64. Found: C, 48.63; H, 7.41; Br, 32.22; N, 5.58.

Following the usual procedure, 12.4 g. (50 mmoles) of the hydrobromide salt of **3** was converted to 6.927 g. (83%) of the pure[12] amino ketone **3**, b.p. 113–114.5° (13 mm.), $n^{25}D$ 1.4933 [lit.[2a] b.p. 106° (7 mm.), $n^{25}D$ 1.4938]. This product was identified with previously described samples[2] by comparison of infrared and n.m.r. spectra.

p-Nitrobenzoic anhydride was prepared as previously described,[14] m.p. 192–194° (lit.[14] m.p. 193°).

Ethereal solutions of methyllithium, methylmagnesium bromide, phenyllithium, and phenylmagnesium bromide were prepared in the usual way; the ethereal solution of dimethylmagnesium was prepared from magnesium and dimethylmercury. The stock solutions of organomagnesium reagents were standardized by titration of the total base liberated when aliquots were hydrolyzed. In the case of the organolithium reagents, standardization involved titrating both the total base liberated on hydrolysis and the residual base liberated on hydrolysis after the lithium reagents had been consumed by reaction with 1,2-dibromoethane.

Reactions of 3-Methyl-3-azabicyclo[3.2.1]octan-8-one (1). A. With Methylmagnesium Bromide.—The addition of a solution of 2.45 g. (17.6 mmoles) of the ketone **1** in 15 ml. of ether to 25 ml. of an ethereal solution containing 41.2 mmoles of methylmagnesium bromide resulted in the immediate separation of a white precipitate. The resulting suspension was stirred overnight, at room temperature and under a nitrogen atmosphere, and then treated successively with saturated, aqueous ammonium chloride and aqueous sodium hydroxide. The ether layer was separated, combined with the ethereal extract of the aqueous phase, dried, and concentrated. The residual yellow liquid (2.73 g.) exhibited one major peak on gas chromatography[12] accompanied by a very small peak (<2%) which was eluted more rapidly. This minor, unidentified component has the same retention time as the starting ketone **1** but could be the second stereoisomeric amino alcohol **5**. A solution of the crude product in pentane deposited 1.77 g. (65%) of the **amino alcohol 4** as white prisms, m.p. 73.5–75.5°. Recrystallization sharpened the melting point to 74.5–75.5°. The product has infrared absorption[15] at 3600 and 3440 (broad) cm.$^{-1}$ (unassociated and associated O–H) with no absorption in the 6-μ region attributable to a carbonyl function; in dilute solution (1×10^{-2} and 5×10^{-3} *M*)[16] the material exhibits only the band at 3600 cm.$^{-1}$ with no indication of intramolecular hydrogen bonding. The n.m.r. spectrum[17] has a singlet at δ 1.31 (3H, CH_3–C), a multiplet in the region δ 1.6–2.0 (6H, aliphatic C–H), and a singlet at δ 2.37 (3H, CH_3–N<) superimposed on a multiplet in the region δ 2.2–3.2 (5H, $-CH_2$–N and O–H); in acid solution,[18] the sample has n.m.r. peaks at δ 1.36 (3H singlet, CH_3–C), in the region δ 1.7–2.3 (6H multiplet, aliphatic C–H), at δ 2.87 (3H singlet, $CH_3-\overset{\oplus}{N}D<$), and a pair of doublets (J = 12.5 c.p.s.) with further splitting apparent but not resolved at δ 3.28 and 3.56 (4H, $-CH_2-\overset{\oplus}{N}D<$). The mass spectrum of the product has a molecular ion peak at *m/e* 155 with abundant fragment peaks at *m/e* 154, 95, 74, 71, 58, 57, 44, 43, 42, and 41. The pK^*_{MCS} value for the sample was 8.56.[19]

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.42; H, 11.00; N, 8.88.

B. With Methyllithium.—After 65 ml. of an ethereal solution containing 65 mmoles of methyllithium had been added to a solution of 2.71 g. (20 mmoles) of the ketone **1** in 50 ml. of ether, the resulting solution was stirred overnight at room temperature and under a nitrogen atmosphere. After the addition of water the ether layer was separated, combined with the ethereal extract of the aqueous phase, dried, and concentrated to leave 2.92 g. (96%) of the crude amino alcohol **4**, m.p. 71–73°. Recrystallization from pentane afforded 2.58 g. (85%) of the pure **amino alcohol 4**, m.p. 73–74°, identified with the previously described sample by comparison of infrared spectra. As in the previous experiment, the gas chromatogram[12] of the crude product exhibited one major peak corresponding to the alcohol **4** and a second minor peak (<2%), attributable to the unchanged ketone **1** or, possibly, the isomeric alcohol **5**.

(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 Mc. with a Varian Model A-60 n.m.r. spectrometer. The mass spectra were obtained with a CEC Model 21-130 mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(11) Determined as a Nujol mull.

(12) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb W was employed for this analysis.

(13) Determined as a solution in deuterium oxide.

(14) E. Berliner and L. H. Allschul, *J. Am. Chem. Soc.*, **74**, 4110 (1952).

(15) Determined as a solution in chloroform.

(16) Determined as a solution in carbon disulfide.

(17) Determined as a solution in deuteriochloroform.

(18) A 20% solution of deuterium chloride in deuterium oxide was employed.

(19) (a) The values pK^*_{MCS}, the apparent pK_a values in a mixture of 80% Methyl Cellosolve and 20% water, were determined by Dr. W. Simon. (b) For discussion, leading references, and compilations of data, see W. Simon, *Angew. Chem. Intern. Ed. Engl.*, **3**, 661 (1964); W. Simon, G. H. Lyssy, A. Mörikofer, and E. Heilbronner, "Zusammenstellung von scheinbaren Dissoziationskonstanten im Lösungsmittelsystem Methylcellosolve/Wasser," Vol. 1, Juris-Verlag, Zürich, 1959; P. F. Sommer and W. Simon, *ibid.*, Vol. 2, 1961; and W. Simon and P. F. Sommer, *ibid.*, Vol. 3, 1963.

The mother liquor from the above recrystallization was found by thin layer chromatography[20] to contain predominantly the amino alcohol **4** (eluted more slowly) accompanied by a second minor component (eluted more rapidly) which may be either the starting ketone **1** or the amino alcohol **5**. A solution of 246 mg. (1.6 mmoles) of this material and 0.90 g. (4.9 mmoles) of *p*-nitrobenzoyl chloride in 10 ml. of chloroform[20c] was stirred, at room temperature and under a nitrogen atmosphere, for 4 days. The resulting mixture contained[20] predominantly the *p*-nitrobenzoate **10a** (eluted most rapidly) accompanied by small amounts of the two components originally present. After 0.15 ml. of concentrated hydrochloric acid had been added, the mixture was concentrated to dryness under reduced pressure and then extracted with ether to remove the unchanged *p*-nitrobenzoyl chloride. Recrystallization from ethanol afforded 248 mg. of the **hydrochloride of 10a** as a white solid, m.p. 263–265° dec. This salt was mixed with aqueous sodium hydroxide and extracted with ether; drying and subsequent concentration of the ethereal extract left 227 mg. of the ***p*-nitrobenzoate 10a**, m.p. 142–145°. Recrystallization from an ether–pentane mixture afforded the pure ester as pale yellow prisms, m.p. 145–146°. The material has infrared absorption[15] at 1720 cm.$^{-1}$ (conjugated ester C=O) with an ultraviolet maximum[21] at 258 mμ (ε 13,800) and an n.m.r. peak[17] at δ 8.35 (4H, aryl C–H) as well as singlets at δ 1.58 (3H, CH_3–C) and 2.23 (3H, CH_3–N) superimposed upon complex absorption in the region δ 1.2–3.1 (10H, aliphatic C–H).

Anal. Calcd. for $C_{15}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.11; H, 6.65; N, 9.20.

A solution of 152 mg. (0.50 mmoles) of the ester **10a** and 142 mg. (2.5 mmoles) of potassium hydroxide in 7 ml. of methanol was refluxed for 4 days and then concentrated under reduced pressure. After the crude product had been partitioned between ether and water, the ether solution was dried and concentrated to leave 30 mg. (39%) of the crude amino alcohol **4**, m.p. 64–67°. Recrystallization from an ether–pentane mixture gave a sample of the alcohol **4**, m.p. 72–73.5°, which was identified with the previously described samples by comparison of infrared spectra, mass spectra, gas chromatographic retention times, and by a mixture melting point determination.

Reactions of 8-Methyl-8-azabicyclo[4.3.1]decan-10-one (3). A. With Methylmagnesium Bromide.—After 65 ml. of an ethereal solution containing 107 mmoles of methylmagnesium bromide had been added to a solution of 7.83 g. (47 mmoles) of the ketone **3** in 50 ml. of ether, the resulting suspension was subjected to the previously described reaction and isolation procedures. The crude product, 8.36 g. (97%) of the amino alcohol **8a** melting at 50–54°, exhibited a single peak on gas chromatography.[12] Recrystallization from pentane afforded 5.01 g. of the pure **amino alcohol 8a** as white prisms, m.p. 57.5–59.5°, identified with the subsequently described sample by comparison of infrared spectra and gas chromatographic retention times.

In a subsequent experiment, the heterogenous reaction mixture from 3.225 g. (19.3 mmoles) of the ketone **3** and 19.3 mmoles of methylmagnesium bromide in 100 ml. of tetrahydrofuran and 11.7 ml. of ether was stirred, under a nitrogen atmosphere and at room temperature, for 24 hr. and then treated with a solution of 3.58 g. (19.3 mmoles) of *p*-nitrobenzoyl chloride in 75 ml. of tetrahydrofuran. After the resulting mixture had been stirred for an additional 24 hr., the clear, yellow solution was concentrated under reduced pressure and partitioned between water and ether. Drying and concentration of the ether phase resulted in the deposition of 4.892 g. (76%) of fractions of the *p*-nitrobenzoate **11c** melting within the range 154–156.5°. Recrystallization from an ether–hexane mixture afforded the pure ***p*-nitrobenzoate 11c** as yellow prisms, m.p. 156–157°. The product has infrared absorption[15] at 1715 cm.$^{-1}$ (conjugated ester C=O) with an ultraviolet maximum[21] at 259 mμ (ε 14,100) and an n.m.r. peak at δ 8.31 (4H, aryl C–H) as well as two singlets at δ 2.17 (3H, CH_3–N) and 1.77 (3H, CH_3–C) superimposed upon complex absorption in the region δ 1.2–2.9 (aliphatic C–H).

Anal. Calcd. for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.12; H, 7.33; N, 8.28.

(20) A plate coated with silica gel was employed. The eluent was a 2:3 (by volume) methanol–chloroform mixture containing 1% of aqueous ammonia.

(21) Determined as a solution in 95% ethanol.

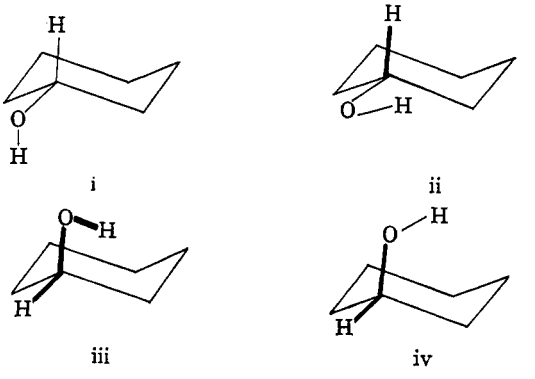
B. With Methyllithium.—A solution prepared from 6.77 g. (41 mmoles) of the ketone **3** and 90 mmoles of methyllithium in 270 ml. of ether was subject to the previously described reaction and isolation procedures. The crude product, 7.288 g. (98%) of the amino alcohol **8a** melting at 54–56°, was recrystallized from pentane to give 6.2 g. (83%) of the **alcohol 8a** as white prisms, m.p. 57–60°. Further recrystallization sharpened the melting point to 58.5–59.5°. The product has infrared absorption[15] at 3610 (shoulder), 3590, and 3440 (broad) cm.$^{-1}$ (unassociated and associated O–H); in dilute solution (4.5×10^{-3} *M*) only bands at 3610 (shoulder) and 3590 cm.$^{-1}$ attributable to an unassociated hydroxyl function remain.[22] The sample has n.m.r. singlets[17] at δ 2.23 (3H, CH_3–N<), 1.58 (1H, OH, shifted by the addition of pyridine) and 1.40 (3H, CH_3–C) superimposed on a complex multiplet in the region δ 1.2–2.9 (aliphatic C–H); in acid solution[18] the methyl singlets are found at 2.83 (CH_3–$\overset{\oplus}{N}$D<) and 1.48 (CH_3–C) and the signal attributable to the two methylene groups adjacent to nitrogen appears as a partially resolved AB pattern in the region δ 2.8–3.6. The mass spectrum of the product has a molecular ion peak at *m/e* 183 with abundant fragment peaks at *m/e* 74, 71, 58, 44, 43, 42, and 41. The pK^*_{MCS} value[19] for the amino alcohol **8a** is 7.08.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.82; H, 11.54; N, 7.45.

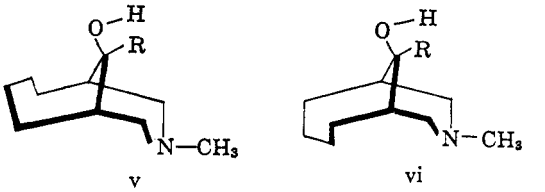
After the bulk of the pure alcohol **8a** had been separated, the mother liquors were found to contain the amino alcohol **8a** as the predominant constituent accompanied by a minor component which was eluted more rapidly on gas chromatography[12] and more slowly on thin layer chromatography.[20] From the chromatographic behavior of this minor component, it could be either the unchanged ketone **3** or the second stereoisomeric alcohol **9a**. A solution of 498 mg. (2.7 mmoles) of this crude mixture and 1.5 g. (8.1 mmoles) of *p*-nitrobenzoyl chloride in 30 ml. of chloroform was stirred for 100 hr. at room temperature and then subjected to the isolation procedure described previously. The crude hydrochloride salt (496 mg.) which remained contained[20] predominantly the salt of unchanged amine alcohol **8a**; however, the minor component had been converted to some other substance which we were unsuccessful in separating from the reaction mixture.

A solution of 916.5 mg. (5.0 mmoles) of the amino alcohol **8a** and 1021 mg. (5.5 mmoles) of *p*-nitrobenzoyl chloride in 10 ml. of anhydrous pyridine was refluxed for 20 hr. and then cooled and

(22) A multiplicity of unassociated O–H stretching frequencies has been noted previously in cyclohexanols with an equatorial hydroxyl function: H. S. Aaron and C. P. Rader, *J. Am. Chem. Soc.*, **85**, 3046 (1963). This multiplicity was ascribed to comparable population of conformers i and ii



(and a second equivalent conformation) with different stretching frequencies in equatorial isomers whereas only two equivalent conformations (*e.g.*, iii) were expected for axial isomers because conformation iv would be sterically unfavorable. In our tertiary alcohols **8**, a conformation analogous to iv would appear to be more favorable than would be the case for a simple cyclohexane system; alternatively, two or more stretching frequencies may be observed because of conformational changes elsewhere in the molecule; for example, structures v and vi might be considered.



diluted with ether. The solid which separated was taken up in boiling methanol, decolorized with activated charcoal, and cooled to deposit the crude hydrochloride of *p*-nitrobenzoate **11c** as brown prisms, m.p. 220–225° dec. This salt was partitioned between aqueous sodium bicarbonate and ether; the ether solution was dried and concentrated to leave the crude *p*-nitrobenzoate **11c** (220 mg.) which was recrystallized from an ether–pentane mixture to separate 31 mg. of the ester **11c**, m.p. 152–154°, which was identified with the previously described sample by comparison of infrared and n.m.r. absorption.

A solution of 166 mg. (0.5 mmole) of the ester **11c** and 142 mg. (2.5 mmoles) of potassium hydroxide in 20 ml. of methanol was refluxed for 1 week and then subjected to the previously described isolation procedure. The crude product (96 mg., m.p. 36–40°) was sublimed to separate 52 mg. of the amino alcohol **8a**, m.p. 59–60°, which was identified with the previously described sample by a mixture melting point determination and by comparison of infrared and mass spectra.

C. With Phenylmagnesium Bromide.—The mixture obtained from 10.1 g. (60.5 mmoles) of the ketone **3** and 88 mmoles of phenylmagnesium bromide in 205 ml. of ether was stirred overnight, at room temperature and under a nitrogen atmosphere, and then subjected to the usual isolation procedure. The crude product, 15.28 g. of yellow oil, exhibited a single peak on gas chromatography[12]; however, the infrared spectrum of a collected sample of this peak indicated that decomposition had occurred in the gas chromatography column. Crystallization of the crude product from pentane afforded 5.84 g. (39%) of fractions of the amino alcohol **8b** as white prisms melting within the range 37–40°. Recrystallization separated the pure **amino alcohol 8b** as white prisms, m.p. 40–41°. The product has infrared absorption[15] at 3595 and 3450 (broad) cm.$^{-1}$ (unassociated and associated O–H); in dilute solution (1×10^{-2} to 5×10^{-3} *M*),[16] only unassociated hydroxyl absorption was present with peaks at 3595, 3605 (shoulder), and 3620 (shoulder) cm.$^{-1}$.[22] The material has a series of weak (ϵ 172 to 239) ultraviolet maxima[21] in the region 250–270 mμ with intense end absorption and a molecular ion peak in the mass spectrum at *m/e* 245 with abundant fragment peaks at *m/e* 105, 58, 57, 55, 44, 43, 42, and 41. The n.m.r. spectrum[17] has a singlet at δ 1.97 (3H, CH_3–N) superimposed on a complex multiplet in the region δ 1.3–2.8 (15H, aliphatic CH and O–H) as well as a multiplet in the region δ 6.7–7.4 (5H, aryl C–H). In acid solution[18] the n.m.r. peak attributable to the N-methyl group was shifted to δ 2.67 and the patterns of the remaining multiplets were altered. The pK^*_{MCS} value[19] for the amino alcohol is 6.73.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.44; H, 9.44; N, 5.69.

From a comparable reaction employing 4.13 g. (24.7 mmoles) of the ketone **3** and 24.7 mmoles of phenylmagnesium bromide in 100 ml. of tetrahydrofuran and 14.6 ml. of ether, the resulting reaction solution was treated with a solution of 4.58 g. (24.7 mmoles) of *p*-nitrobenzoyl chloride in 100 ml. of tetrahydrofuran. After the resulting reaction mixture had been stirred, at room temperature and under a nitrogen atmosphere, for 1 day, the mixture was concentrated under reduced pressure and partitioned between water and ether. After the ether solution had been dried and concentrated, crystallization of the residue from pentane separated 5.27 g. (54%) of the crude *p*-nitrobenzoate **11d** as yellow prisms, m.p. 120–131°. The product was chromatographed on 50 g. of silicic acid and the fractions eluted with ethyl acetate were recrystallized from pentane to separate the pure ***p*-nitrobenzoate 11d** as yellow prisms, m.p. 132–133°. The material has infrared absorption[15] at 1720 cm.$^{-1}$ (conjugated ester C=O) with an ultraviolet maximum at 258 mμ (ϵ 16,100) and an n.m.r. singlet[17] at δ 2.14 (3H, CH_3–N) superimposed on a multiplet in the region δ 1.5–3.6 (14H, aliphatic C–H) as well as a multiplet in the region δ 7.2–8.5 (9H, aryl C–H).

Anal. Calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.09; H, 6.62; N, 6.85.

Treatment of the amino alcohol **8b** with *p*-nitrobenzoyl chloride in chloroform, either at reflux or at room temperature, or in pyridine at room temperature, did not yield the *p*-nitrobenzoate **11d**; the majority of the alcohol **8b** remained unchanged.[20] A solution of 395 mg. (1.0 mmole) of the *p*-nitrobenzoate and 280 mg. (5 mmoles) of potassium hydroxide in 20 ml. of methanol was refluxed for 4 days. The crude basic product, 244 mg. of yellow oil separated as described previously, was distilled in a short-path still (120–160° at 0.3 mm.). Crystallization of the distillate from hexane afforded the amino alcohol **8b** as colorless prisms, m.p. 35–38°, identified with the previously described sample by comparison of infrared and mass spectra.

Reactions of 3-Methyl-3-azabicyclo[3.3.1]nonan-9-one (2).

A. With Methyllithium.—After a solution prepared from 10.83 g. (71 mmoles) of the ketone **2** and 90 mmoles of methyllithium in 280 ml. of ether had been stirred, at room temperature and under a nitrogen atmosphere, for 5 hr., saturated aqueous sodium chloride was added and the ether-soluble products were separated. The crude product, 12.01 g. (100%) of white solid, m.p. 57–67°, with no absorption[15] in the 6-μ region attributable to a carbonyl function, contained[12] 31% of the β isomer **6a** (retention time 50.8 min.) and 69% of the α isomer **7a** (retention time 56.8 min.). These two stereoisomers **6a** and **7a** were also resolved by thin layer chromatography,[20] the α isomer **7a** being eluted more rapidly. The gas chromatography equipment used[12] for analysis of the mixtures of amino alcohols **6a** and **7a** was calibrated with known mixtures prepared from authentic samples.

A solution of 6.623 g. (39 mmoles) of this mixture of amino alcohols **6a** and **7a** and 4.43 ml. (39 mmoles) of 48% aqueous hydrobromic acid in 25 ml. of ethanol deposited 4.84 g. of the **hydrobromide of isomer 7a** as white needles, m.p. 218–222° dec. Similarly, the **hydrochloride of isomer 7a** separated from ethanol as white prisms, m.p. 230–236° dec. After 385 mg. of this hydrochloride had been treated with a mixture of aqueous sodium bicarbonate and ether, the ether solution of the free base was dried and concentrated. Recrystallization of the residual solid from hexane afforded 161 mg. of the **alcohol 7a** as white needles, m.p. 92–93°; further recrystallization raised the melting point to 92.5–93.5°. The amino alcohol **7a** has infrared absorption[15] at 3595 and 3450 (broad) cm.$^{-1}$ (unassociated and associated O–H); only the unassociated O–H bond band at 3595 cm.$^{-1}$ remains in dilute solution (9.9×10^{-3} *M*).[16] The product has n.m.r singlets[17] at δ 1.36 (3H, CH_3–C) and 2.20 (3H, CH_3–N) superimposed upon complex absorption in the region δ 1.2–3.2 (OH and aliphatic C–H); in acid soution[18] these singlets are found at δ 1.53 (CH_3–C) and 2.96 (CH_3–$\overset{\oplus}{N}$D<) and a multiplet (AB pattern with further splitting partially resolved) is present in the region δ 3.2–4.0 (4H, –CH_2–$\overset{\oplus}{N}$D<).

The mass spectrum has a molecular ion peak at *m/e* 169 with abundant fragment peaks at *m/e* 168, 71, 58, 44, 43, 42, and 41. The pK^*_{MCS} value[19] for this amine is 7.54.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.86; H, 11.37; N, 8.23.

Chromatography of 1.91 g. of this mixture of alcohols **6a** and **7a** on 60 g. of silicic acid (Davidson, 200–328 mesh) separated 1099 mg. of the pure[20] α isomer **7a** in fractions eluted with ether, ethyl acetate, and ethyl acetate containing 2.5% methanol. Recrystallization from pentane afforded 822 mg. of the pure α isomer **7a** as white prisms, m.p. 93.5–95.5°. Subsequent fractions (179 mg.), eluted with ethyl acetate–methanol mixtures and with methanol, contained[20] mixtures of **6a** and **7a**. The last fractions (117 mg.), eluted with methanol, contained[20] the pure β isomer **6a** as white prisms, m.p. 60.5–62.5°, identified with the subsequently described sample by comparison of infrared and mass spectra.

B. With Methylmagnesium Bromide.—After a solution obtained from 7.74 g. (51 mmoles) of the ketone **2** and 81 mmoles of methylmagnesium bromide in 149 ml. of ether had been stirred overnight in the usual manner, an aqueous solution of ammonia and ammonium chloride was added and the crude basic product was isolated as in previous cases. The crude product, 8.34 g. (99%) of white solid melting at 58–68°, lacked absorption in the 6-μ region attributable to a carbonyl function and contained[12] 34% of the β isomer **6a** and 66% of the α isomer **7a**. A solution of 7.74 g. (46 mmoles) of this crude product (**6a** + **7a**) and 28 g. (150 mmoles) of *p*-nitrobenzoyl chloride in 75 ml. of chloroform was stirred for 4 days at room temperature and then treated with 3.8 ml. (46 mmoles) of concentrated hydrochloric acid and concentrated to dryness under reduced pressure. After the residual solid had been extracted with ether, it was recrystallized from ethanol to separate 3.85 g. of the **hydrochloride of *p*-nitrobenzoate 10b** as yellow needles, m.p. 194–197°. By following the course of this reaction with thin layer chromatography,[20] it was shown that the β isomer **6a** (eluted most slowly) was converted to the ester **10b** (eluted most rapidly) while the α isomer **7a** remained unchanged. The mother liquors from the above crystallization were concentrated and the residue (5.5 g.) was partitioned between aqueous sodium hydroxide and ether. After this ethereal solution had been dried and concentrated,

fractional crystallization of the residue from benzene separated 4.26 g. of the amino alcohol **7a** melting within the range 91.5–95°, the ester **10b** remaining in the mother liquors.

The aforementioned hydrochloride was converted to the free base **10b** in the usual manner. Combined samples of this crude free base from several runs were chromatographed on silicic acid and the ester **10b** eluted with benzene, was washed with aqueous sodium hydroxide and then recrystallized from pentane to separate the pure ***p*-nitrobenzoate 10b** as yellow prisms, m.p. 136–137°. This product has infrared absorption[15] at 1715 cm.$^{-1}$ (conjugated ester C=O) with an ultraviolet maximum[21] at 259 mμ (ε 14,200) and n.m.r. singlets[17] at δ 1.70 (3H, CH_3–C) and 2.10 (3H, CH_3–N) superimposed on a multiplet in the region δ 1.2–3.2 (12H, aliphatic C–H) as well as a multiplet in the region δ 7.5–8.0 (4H, aryl C–H).

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.15; H, 7.09; N, 8.71.

A solution of 1.66 g. (5 mmoles) of the ester **10b** and 1.49 g. (26.5 mmoles) of potassium hydroxide in 70 ml. of methanol was refluxed for 4 days and then subjected to the usual isolation procedure. A solution of the crude basic product (822 mg. of yellow oil) in benzene was filtered through silicic acid and then sublimed to separate 607 mg. (71%) of the amino alcohol **6a** as white plates, m.p. 59–61°. A second sublimation sharpened the melting point of the **amino alcohol 6a** to 59.5–60.5°. The product has infrared absorption[15] at 3595, 3420 (broad), and 3200 (broad) cm.$^{-1}$ (unassociated and associated O–H). As the solution[16] was diluted, the broad band at 3420 cm.$^{-1}$ diminished rapidly and the longer wave length band (at *ca.* 3260 cm.$^{-1}$) diminished in intensity more rapidly than the band at 3595 cm.$^{-1}$. In the most dilute solution (1.15×10^{-3} *M*)[16] studied, the band at 3260 cm.$^{-1}$ had not completely disappeared and may indicate the presence of a small amount of intramolecularly hydrogen-bonded amino alcohol in this case.[23] The sample has n.m.r. singlets[17] at δ 1.35 (CH_3–C) and 2.24 (CH_3–N) superimposed upon complex absorption in the region δ 1.0–3.4 (aliphatic C–H); in acid solution,[18] the singlets are found δ 1.47 (3H, CH_3–C) and 2.91 (3H, CH_3–$\overset{\oplus}{N}D<$) and are accompanied by broad peaks in the region δ 3.2–3.8 (4H, $-CH_2-\overset{\oplus}{N}D<$) and 1.2–2.2 (8H, aliphatic C–H). The mass spectrum of the sample has a molecular ion peak at *m/e* 169 with abundant fragment peaks at *m/e* 168, 108, 74, 71, 58, 57, 44, 43, 42, and 41. The pK^*_{MCS} value[19] for this amine is 8.48.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.85; H, 11.29; N, 8.11.

A solution of 4.00 g. (24.0 mmoles) of the amino alcohol **7a** and 4.83 g. (26.0 mmoles) of *p*-nitrobenzoyl chloride in 70 ml. of anhydrous pyridine was heated to 90° for 12 hr. and then cooled and diluted with ether to precipitate 7.20 g. of the **hydrochloride of *p*-nitrobenzoate 11a** as tan prisms, m.p. 228–231° dec. After this material had been treated with a mixture of aqueous sodium hydroxide and ether, the ethereal solution of the free base was dried and concentrated to leave 6.05 g. of the crude *p*-nitrobenzoate **11a**, m.p. 111–125°. Consecutive recrystallizations from ether and from an ether–methanol mixture afforded 3.133 g. of the *p*-nitrobenzoate **11a** as yellow platelets, m.p. 151–153°. An additional recrystallization from an ether–pentane mixture afforded the pure **ester 11a** as yellow plates, m.p. 153.5–154.5°. The product has infrared absorption[15] at 1715 cm.$^{-1}$ (conjugated ester C=O) with an ultraviolet maximum[21] at 259 mμ (ε 13,400) and n.m.r. singlets[17] at δ 1.74 (3H, CH_3–C) and 2.20 (3H, CH_3–N) superimposed on a multiplet in the region δ 1.2–3.1 (12H, aliphatic CH) as well as a multiplet in the region δ 8.0–8.5 (4H, aryl C–H).

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.12; H, 7.04; N, 8.48.

A solution of 66 mg. (0.21 mmole) of the *p*-nitrobenzoate **11a** and 56.1 mg. (1.0 mmole) of potassium hydroxide in 5 ml. of methanol was refluxed for 4 days and then subjected to the previously described isolation procedure. The crude basic product, 37 mg. melting at 86–88°, was sublimed to afford the pure alcohol **7a** as white crystals, m.p. 93–94°, which was identified with the previously described sample by a mixture melting point determination and by comparison of infrared spectra, mass spectra, and gas chromatographic retention times.

C. With Dimethylmagnesium.—A mixture obtained from 555 mg. (3.63 mmoles) of the ketone **2** and 4.92 mmoles of dimethylmagnesium in 10 ml. of ether was stirred for 4 hr. at room temperature and under a nitrogen atmosphere and then subjected to the usual isolation procedure. The crude basic product, 560 mg. (91%) of white prisms melting at 61–68°, contained[12] 39% of the β isomer **6a** and 61% of the α isomer **7a**. This sample was combined with 250 mg. of a mixture of amino alcohols from a comparable reaction and chromatographed on 50 g. of silicic acid to separate, after recrystallization, 460 mg. of the pure α isomer **7a** as white needles, m.p. 91–93°, and 80 mg. of the β isomer **6a** as white prisms, m.p. 60–62°.

D. With Phenyllithium.—A solution prepared from 1.26 g. (8.25 mmoles) of the ketone **2** and 10.0 mmoles of phenyllithium in 60 ml. of ether was stirred, at room temperature and under a nitrogen atmosphere, for 30 min. and then poured into a mixture of aqueous ammonium chloride and ice. The ether layer was separated and the aqueous phase was made basic with aqueous sodium hydroxide and again extracted with ether. The combined ethereal solutions were extracted with cold 5% aqueous hydrochloric acid and the resulting aqueous extract was immediately made basic (pH >10) with aqueous sodium hydroxide and extracted with ether.[24] The final ethereal solution was dried and concentrated to leave 1.65 g. (87%) of a mixture of alcohols **6b** and **7b** as an oil which solidified on standing, m.p. 54–58°. This material gave only two spots on thin layer chromatography[20] corresponding to alcohols **6b** and **7b**. The composition of this mixture, 67% of **7b** and 33% of **6b**, was determined from its n.m.r. spectrum[17] by measuring the areas under the two N-methyl peaks arising from the two isomers **6b** and **7b**. The validity of this analytical method was established by measuring a series of known mixtures prepared from authentic samples of the two amino alcohols. A 215.5-mg. sample of this mixture was distilled in a short-path still (120–150° at 0.3 mm.) to give 210 mg. (97.5% recovery) of the mixture as an oil which solidified on standing. The composition of this distilled sample, determined from its n.m.r. spectrum,[17] was 68% of **7b** and 32% of **6b**. In a duplicate experiment, the crude product (95% yield) contained 69% of **7b** and 31% of **6b** and the distilled sample contained 66% of **7b** and 34% of **6b**. Our efforts to analyze these mixtures by gas chromatography were unsuccessful because the compounds were unstable on our columns at the temperatures required for elution.

A 1.1-g. sample of this mixture of amino alcohols **6b** and **7b** was chromatographed on 50 g. of silicic acid (Davidson, 200 mesh). The initial fractions (807 mg.), eluted with ether and ether–ethyl acetate mixtures, contained[20] the α isomer **7b**. Later fractions (40 mg.) eluted with ethyl acetate–methanol mixtures contained[20] mixtures of **6b** and **7b**, and the final fractions (117 mg.), eluted with methanol, contained[20] the β isomer **6b**. Recrystallization of the early fractions from pentane afforded 597 mg. of alcohol **7b** melting within the range 82–86°. An additional recrystallization, accompanied by treatment with decolorizing carbon, gave the pure **amino alcohol 7b** as white needles, m.p. 84.5–85.5°. This product has infrared absorption[15] at 3590 and 3430 (broad) cm.$^{-1}$ (unassociated and associated O–H); only the unassociated O–H peak at 3590 cm.$^{-1}$ remains in dilute solution (4×10^{-3} *M*).[16] The sample has a series of low-intensity (ε 153–249) ultraviolet maxima[21] in the region 245–270 mμ with intense end absorption and a molecular ion peak in the mass spectrum at *m/e* 231 with abundant fragment peaks at *m/e* 230, 136, 77, 58, 57, 55, 44, 42, and 41. The n.m.r. spectrum[17] has a multiplet in the region δ 7.1–7.7 (5H, aryl C–H) with singlets at δ 1.96 (3H, CH_3–N) and 1.49 (1H, O–H) superimposed on a multiplet in the region δ 1.3–3.0 (12H, aliphatic C–H); in acid solution the multiplets are in the regions δ 7.3–7.9 (aryl C–H) and 1.3–4.0 (aliphatic C–H) with the N-methyl singlet at δ 2.63 (CH_3–$\overset{\oplus}{N}D<$). The pK^*_{MCS} value[19] for this amine is 7.30.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.98; H, 9.23; N, 5.86.

The latter fractions from the above chromatogram were sublimed to separate 70 mg. of the alcohol **6b**, m.p. 86–88°. Recrystallization from pentane afforded the pure **amino alcohol**

(23) Essentially the same results were obtained earlier[2c] with the secondary alcohol (*i.e.*, **6** where R = H) analogous to **6a**.

(24) This extraction procedure was necessary to separate the alcohols **6b** and **7b** from biphenyl, a contaminant of the phenyllithium and the phenylmagnesium bromide reagents.

6b as white prisms, m.p. 90.5–91.5°. This material has infrared absorption[15] at 3590 and 3440 (broad) cm.$^{-1}$ (unassociated and associated O–H); in dilute solution (1.3×10^{-3} *M*) only the absorption at 3590 cm.$^{-1}$ attributable to an unassociated hydroxyl function remains. The product has a series of low-intensity (ϵ 161 to 244) ultraviolet maxima[21] in the region 245–265 mμ with intense end absorption and a molecular ion peak in the mass spectrum at *m/e* 231 as well as abundant fragment peaks at *m/e* 170, 105, 77, 74, 58, 57, 55, 44, 42, and 41. The n.m.r. spectrum[17] has a multiplet in the region δ 7.2–7.6 (5H, aryl C–H) with a singlet at δ 2.24 (3H, CH_3–N) superimposed on a multiplet in the region δ 1.1–3.3 (13H, OH and aliphatic C–H). In acid solution,[18] the N-methyl singlet appears at δ 2.99 (CH_3–$\overset{\oplus}{N}D<$). The pK^*_{MCS} value[19] for the amine is 8.16.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.95; H, 9.13; N, 5.92.

E. With Phenylmagnesium Bromide.—The reaction mixture from 1.477 g. (9.6 mmoles) of the ketone **2** and 16.9 mmoles of phenylmagnesium bromide in 30 ml. of ether was stirred for 30 min., at room temperature and under a nitrogen atmosphere, and then subjected to the isolation procedure described above for the phenyllithium reaction. The crude basic product, 1.91 g. (86%) of white crystals melting at 56–61°, contained (n.m.r. analysis) 66% of the α isomer **7b** and 34% of the β isomer **6b**; the thin layer chromatogram of this product had two spots corresponding to **6b** and **7b**. After a 1.03-g. portion of this material had been distilled in a short-path still (150–170° at 4 mm.), the distillate (993 mg.) contained 69% of **7b** and 31% of **6b**. From a duplicate experiment the crude basic product (60% yield, m.p. 53–64°) contained 66% of **7b** and 34% of **6b**; after distillation the composition was 69% of **7b** and 31% of **6b**.

The reaction of either of the tertiary alcohols **6b** or **7b** with *p*-nitrobenzoyl chloride in chloroform was found not to be a satisfactory procedure because the hydrochloride of the starting alcohol was formed in each case. However, the corresponding acid anhydride was useful. With this reagent the β isomer **6b** could be selectively acylated in refluxing chloroform and the epimer **7b** could be acylated in pyridine at elevated temperatures.[25] The following procedures are illustrative.

A solution of 750 mg. (3.26 mmoles) of the above mixture of epimeric alcohols **6b** and **7b** and 515 mg. (1.63 mmoles) of *p*-nitrobenzoic anhydride in 42 ml. of alcohol-free[26] chloroform was refluxed, with stirring, for 64 hr. The reaction was followed by thin layer chromatography[20]; the β isomer **6b** (eluted most slowly) was converted to the *p*-nitrobenzoate **10c** (eluted most rapidly and not resolved from the isomeric ester **11b**), while the α alcohol **7b** remained unchanged. The chloroform solution was washed with aqueous sodium bicarbonate and concentrated under reduced pressure. An ether solution of the residual semisolid was filtered and diluted with methanol to precipitate 216 mg. of the crude ester **10c**, m.p. 165–168°. Recrystallization from an ether–methanol mixture afforded 189 mg. of the ***p*-nitrobenzoate 10c** as yellow prisms, m.p. 172–174°, identified with the subsequently described sample by a mixture melting point determination and comparison of infrared spectra. After the mother liquors from the separation had been concentrated, distillation of the residue in a short-path still (120–150° at 0.3 mm.) afforded 334 mg. of a semisolid distillate. A 150-mg. portion of this distillate was chromatographed on silicic acid to separate 125 mg. of the α alcohol **7b**, m.p. 78–81°. Recrystallization from pentane separated the pure alcohol **7b** as white needles, m.p. 84–86°, identified with the previous sample by a mixture melting point determination and by comparison of infrared and mass spectra.

A solution of 334 mg. (2.0 mmoles) of *p*-nitrobenzoic acid, 476 mg. (2.5 mmoles) of *p*-toluenesulfonyl chloride,[25a] and 462 mg. (2.0 mmoles) of the amino alcohol **7b** in 5 ml. of anhydrous pyridine was heated to 100° for 5 hr. and then cooled and poured onto ice. The crude product (260 mg., m.p. 139–143°) was collected and recrystallized from hexane to separate 167 mg. (22%) of the *p*-nitrobenzoate **11b** as yellow prisms, m.p. 152–155°. Recrystallization afforded the pure ***p*-nitrobenzoate 11b**, m.p. 154–155°. The product has infrared absorption[15] at 1720 cm.$^{-1}$ (conjugated ester C=O) with an ultraviolet maximum[21] at 260 mμ (ϵ 15,100) and an n.m.r. multiplet[17] in the region δ 7.1–8.5 (9H, aryl C–H) as well as a singlet at δ 2.04 (3H, CH_3–N) superimposed on a multiplet in the region δ 1.2–3.6 (12H, aliphatic C–H).

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.53; H, 6.41; N, 7.17.

A solution of 190 mg. (0.50 mmole) of this *p*-nitrobenzoate **11b** and 140 mg. (2.5 mmoles) of potassium hydroxide in 10 ml. of methanol was refluxed for 4 days and then the crude product was isolated as in previous cases. The crude basic product (105 mg. or 91%, m.p. 74–79°) was distilled in a short-path still (125–155° at 0.25 mm.) and then recrystallized from hexane to separate 62.6 mg. of the amino alcohol **7b**, m.p. 84–86°, identified with the previously described sample by a mixture melting point determination and by comparison of infrared and mass spectra.

A solution of 175 mg. (1.05 mmoles) of *p*-nitrobenzoic acid, 247 mg. (1.3 mmoles) of *p*-toluenesulfonyl chloride,[25a] and 242 mg. (1.05 mmoles) of the β-alcohol **6b** in 3 ml. of anhydrous pyridine was heated to 95° for 9 hr. and then cooled and poured onto ice. The crude product (215 mg., m.p. 158–160°) was collected and recrystallized from an ether–methanol mixture to separate 169 mg. (42%) of the **ester 10c** as yellow prisms, m.p. 169–170.5°. An additional recrystallization raised the melting point to 170–171°. The product has infrared absorption[15] at 1720 cm.$^{-1}$ (conjugated ester C=O) with an ultraviolet maximum[21] at 259 mμ (ϵ 14,600) and an n.m.r. multiplet[17] in the region δ 7.1–8.5 (9H, aryl C–H) as well as a singlet at δ 2.23 (3H, CH_3–N) superimposed on a multiplet in the region δ 1.1–3.6 (12H, aliphatic C–H).

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.32; H, 6.40; N, 7.34.

A solution of 145 mg. (0.38 mmole) of the *p*-nitrobenzoate **10c** and 140 mg. (2.5 mmoles) of potassium hydroxide in 8 ml. of methanol was refluxed for 4 days and then subjected to the usual isolation procedure. The crude basic product (96.5 mg., m.p. 64–70°) was recrystallized from hexane to separate 55 mg. (63%) of the β-alcohol **6b**, m.p. 88–90°, which was identified with the previously described sample by a mixture melting point determination and by comparison of infrared and mass spectra.

Acid-Catalyzed Equilibration of the Amino Alcohols 6b and 7b.—A solution of 293.6 mg. (1.27 mmoles) of the β-alcohol **6b** in 11 ml. of 10% aqueous hydrochloric acid was refluxed, with stirring, for 5 hr. and then cooled and made basic with aqueous sodium hydroxide. The ether extract of the resulting mixture was dried and concentrated to leave 287.2 mg. of a mixture of amino alcohols as white prisms, m.p. 65–80°, which contained[27] both the α isomer **7b** (minor component eluted first) and the β isomer **6b** (major component eluted second). Use of the previously described n.m.r. analytical technique indicated the composition of the mixture to be 91% of **6b** and 9% of **7b**.

Similarly, a solution of 500 mg. (2.15 mmoles) of the α-alcohol **7b** in 10 ml. of 10% aqueous hydrochloric acid was refluxed, with stirring, for 5 hr. and then subjected to the same isolation procedure. The crude product (500 mg., m.p. 52–70°) contained (thin layer chromatography[27] and n.m.r. analysis) 91% of the β isomer **6b** and 9% of the α isomer **7b**. Solutions of the α-alcohol **7b** in 10% aqueous hydrochloric acid were either heated to 100° or allowed to stand at room temperature. Aliquots were withdrawn, made basic, and analyzed[27] at various time intervals. After 5 min. at 100°, the mixture of amino alcohols recovered contained predominantly the β isomer **6b**. After 20 min. at room temperature, the recovered amino alcohol contained only traces of the β isomer **6b**; a mixture of approximately equal amounts of **6b** and **7b** was present in a sample recovered after 28 hr. and the β isomer **6b** was the major constituent in a sample recovered after 44 hr. at room temperature. Thus, the equilibration of amino alcohols **6b** and **7b** in 10% aqueous hydrochloric acid is rapid (half-life <5 min.) at 100° but relatively slow (half-life ~30 hr.) at 25°.

A solution of 495 mg. (2.15 mmoles) of the equilibrium mixture of **6b** and **7b** and 700 mg. (2.2 mmoles) of *p*-nitrobenzoic

(25) The ability of *p*-nitrobenzoic anhydride in pyridine to acylate even very sensitive tertiary alcohols has been noted previously: (a) J. H. Brewster and C. J. Ciotti, *J. Am. Chem. Soc.*, **77**, 6214 (1955); (b) G. F. Hennion and S. O. Barrett, *ibid.*, **79**, 2146 (1957).

(26) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1957, p. 283.

(27) Thin layer chromatographic plates coated with either silicic acid or alumina were employed. When eluted with a 1:1 (by volume) mixture of methanol and ethyl acetate, the α isomer **7b** was eluted more rapidly than the β isomer **6b** with either adsorbent.

anhydride in 40 ml. of alcohol-free[26] chloroform was refluxed for 48 hr. and then subjected to the previously described isolation procedure. The crude product, 715 mg. of yellow prisms melting at 160–165°, contained[27] the alcohol **7b** and the ester **10c**. Two crystallizations from ether–methanol mixtures afforded 449 mg. (55%) of the ester **10c**, m.p. 169–170.5°, identified with an authentic sample by a mixture melting point determination and by comparison of infrared spectra.

Synthesis of Bicyclo[4.4.0]decanones and Bicyclo[3.3.1]nonanones *via* the Wichterle Reaction

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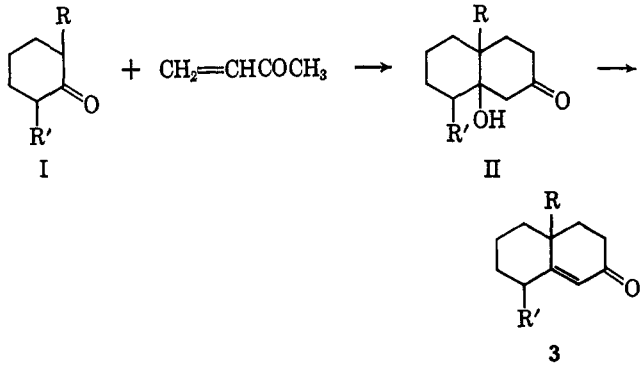
The preparation of *trans*-8,10-dimethyl-1(9)-octal-2-one (**3c**) utilizing the Wichterle reaction was explored. The sequence initially investigated involved alkylation of 2,6-dimethylcyclohexanone with 1,3-dichloro-*cis*-2-butene to give 2,6-dimethyl-2-(γ-chlorocrotyl)cyclohexanone (**1c**). Hydrolysis of this γ-chlorocrotylcyclohexanone under mild conditions in sulfuric acid afforded none of the desired dione, 2,6-dimethyl-2-(3-oxobutyl)-cyclohexanone (**2c**); instead, the bridged product, 1,2,5-trimethylbicyclo[3.3.1]non-2-en-9-one (**4c**), was exclusively formed. Changes in the reaction conditions gave no useful result and therefore the sequence was modified. To this end, 2,6-dimethyl-2-(γ-chlorocrotyl)-5-cyclohexenone (**5b**), obtained from 2,6-dimethyl-2-(γ-chlorocrotyl)cyclohexanone (**1c**) by bromination and dehydrobromination, gave the corresponding dione, 2,6-dimethyl-2-(3-oxobutyl)-5-cyclohexenone (**6b**), upon hydrolysis in sulfuric acid. The desired octalone **3c** was prepared by catalytic hydrogenation of unsaturated dione **6b** followed by base-catalyzed aldol cyclization of the resulting saturated dione **2c**. The same sequence of reactions was investigated using 2-methylcyclohexanone as the starting material. In contrast to the aforementioned 2,6-dimethyl-2-(γ-chlorocrotyl)cyclohexanone (**1c**) case, conditions were found whereby 2-methyl-2-(γ-chlorocrotyl)cyclohexanone (**1a**) and 2-methyl-6-(γ-chlorocrotyl)cyclohexanone (**1b**) could be converted to the respective diones, 2-methyl-2-(3-oxobutyl)cyclohexanone (**2a**) and 2-methyl-6-(3-oxobutyl)cyclohexanone (**2b**). 8,10-Dimethyl-1(9),7-hexal-2-one (**7b**) and 10-methyl-1(9),7-hexal-2-one (**7a**) were prepared from the unsaturated diones **6b** and **6a** in order to demonstrate an additional application of the reaction sequence.

We recently described a modified Robinson annelation of cyclohexanones whereby the ketol intermediates (*e.g.*, II) are isolated and purified prior to dehydration.[1] Although this modification offers distinct advantages for the preparation of octalones derived from 2-methylcyclohexanones, it fails in the case of 2,6-dimethylcyclohexanone (I, R = R′ = CH_3). In fact, all attempts to prepare *trans*-8,10-dimethyl-1(9)-octal-2-one (**3c**) *via* the Robinson annelation route were unsatisfactory; impure bicyclic material was formed in less than 20% yield.



I II 3

Since a large amount of octalone **3c** was required as a starting material for synthetic studies, we considered alternative methods for its preparation. To this end, the scheme devised by Wichterle[2] presented certain desirable features. This method utilizes 1,3-dichloro-*cis*-2-butene[3] (DCB) as a methyl vinyl ketone equivalent and thus circumvents the undesirable condensations and polymerizations which often attend Michael reactions between unactivated cyclohexanones and vinyl ketones. An application of the Wichterle sequence which commanded our attention involves the alkylation of cyclohexanone with DCB followed by hydrolysis of the resulting γ-chlorocrotylcyclohexanone **1** (R = R′ = H) in sulfuric acid to give the octalone **3** (R = R′ = H)[2c] presumably *via* the dione intermediate **2** (R = R′ = H).[2b]

Julia[2c] noted an alternative reaction pathway in the hydrolysis of 2-methyl-2-(γ-chlorocrotyl)cyclohexanone (**1a**). In this case aldol condensation of the intermediate dione **2a** (not isolated) gave the bicyclo[3.3.1]-nonanone **4a** rather than the bicyclo[4.4.0]decanone **3a**. Although the same reaction course is open to the precursor of octalone **3c**, we hoped to suppress the formation of the bicyclo[3.3.1]nonane **4c** by employing mild conditions for the hydrolysis step (**1** → **2**) such that dione **2c** could be isolated. Subsequent base-catalyzed aldol condensation of this intermediate would then yield the desired octalone **3c**. Diones **2a** and **2b** were of interest in connection with another problem and we therefore also planned to utilize the above route to prepare these materials.

Chlorocrotylcyclohexanones **1a** and **1b** were prepared from 2-methylcyclohexanone by alkylation with DCB using sodamide in benzene. The resulting mixture of monoalkylated 2-methylcyclohexanones contained 80% of the 2,2 isomer **1a** and 20% of the 2,6 isomer **1b** estimated by evaluation of the integrated n.m.r. spectrum. These isomers were separated by the hydroxymethylation method,[4] and the pure 2,2-

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(3) L. F. Hatch and S. G. Ballin, *J. Am. Chem. Soc.*, **71**, 1041 (1949).

(4) W. J. Bailey and M. Madoff, *ibid.*, **76**, 2707 (1954).