Amino Ketone Rearrangements. IV.[1] Thermal Rearrangements of α-Amino Methyl Ketones

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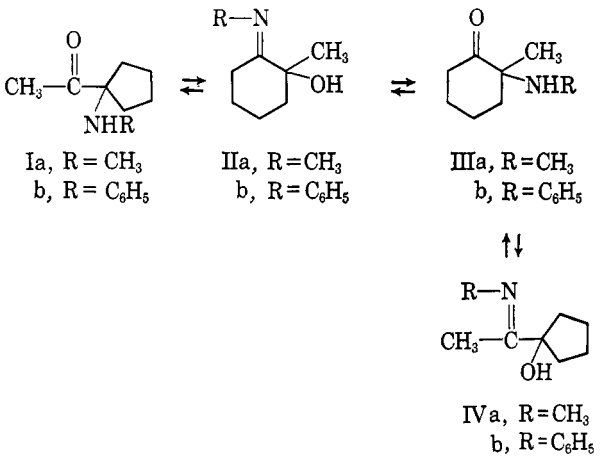
The four isomeric partners of the two equilibrium systems, I–IV (R = CH_3 and C_6H_5), were synthesized and pyrolyzed to determine their individual thermal rearrangement behavior. The generality of α-amino ketone rearrangements has been demonstrated with a simple, all-aliphatic carbon skeleton, and a qualitative survey of rearrangement from all four equilibrium positions has been obtained.

The thermal rearrangement of α-amino ketones bearing alkyl disubstitution at the α-carbon bearing nitrogen is believed to involve an equilibrium between four isomeric partners. This possibility is illustrated for the case of the cyclopentyl methyl ketone carbon skeleton in the equilibrium I–IV shown in Scheme I. Indeed, with other specific but analogous compounds, examples of rearrangement from and to all equilibrium positions have been observed.[3]

SCHEME I

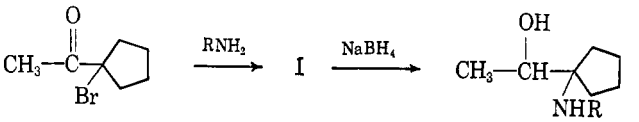


Ia, R = CH_3 IIa, R = CH_3 IIIa, R = CH_3
b, R = C_6H_5 b, R = C_6H_5 b, R = C_6H_5

IVa, R = CH_3
b, R = C_6H_5

For the dual purposes of extending the amino ketone rearrangement to systems with all-aliphatic carbon skeleton and of observing thermal behavior from all equilibrium positions, the eight compounds of the I–IV series were synthesized. The cyclopentyl methyl ketone was chosen because clean rearrangements were observed for the most part in the cyclopentyl *phenyl* ketone system,[1a,3] and it was hoped that comparable results here would enable a direct intersystem comparison. Further, by comparison of alkyl- and aryl-nitrogen substituents, insight into the part that nitrogen basicity and/or N–H acidity plays in the rearrangement might be obtained.

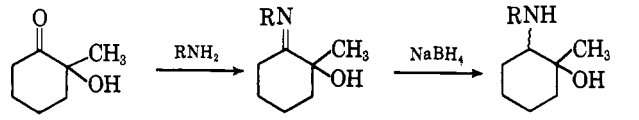
Synthetic Methods.—Cyclopentyl methyl ketone[4] was brominated at the methinyl position in 77% yield with N-bromosuccinimide and in 66% yield with bromine in carbon tetrachloride at reduced temperatures. The bromo ketone V was subsequently used for the synthesis of both Ia and b. Following the procedure of Mannich and Budde,[5] V was treated with methylamine in benzene solution at room temperature for 4 days, whereupon amino ketone Ia was isolated in 84% yield. The higher temperature required by the pro-



V VIa, R = CH_3
b, R = C_6H_5

cedure of Julian and co-workers[6] effected the displacement of the bromine atom of V by aniline and amino ketone Ib was isolated in 34% yield. Both structures Ia and b were confirmed by the isolation of cyclopentanone dinitrophenylhydrazone from the periodate cleavage reactions of the respective amino alcohols VIa and b. Also, the n.m.r. spectra of Ia and b revealed C-methyl singlets at τ 7.90 and 7.85, respectively. The N-phenyl region of the n.m.r. spectra of Ib was interesting with the *meta* (τ 2.88), *para* (τ 3.28), and *ortho* (τ 3.50) protons clearly visible. The splitting pattern was similar in appearance to that recorded for N-*sec*-butylaniline[7] with apparent $J_{m,p} \sim 7$ c.p.s., $J_{m,o} \sim 8$ c.p.s., and $J_{o,p} \sim 1.5$ c.p.s.

The synthesis of α-hydroxy imines IIa and b was accomplished readily through the intermediate 2-hydroxy-2-methylcyclohexanone (VII). This hydroxy ketone, prepared by the reaction of methylmagnesium iodide with cyclohexane-1,2-dione,[8] slowly dimerized on standing and consequently was prepared fresh shortly before intended use. The preparation of IIa was



VII II VIII

best effected by several successive 2-day treatments of VII with liquid methylamine at room temperature. The use of solid potassium hydroxide as a desiccant somewhat shortened the reaction time. Standard imine synthesis conditions were sufficient for the prepa-

(1) (a) Paper III: C. L. Stevens, A. Thuillier, and F. A. Daniher, *J. Org. Chem.*, **30**, 2962 (1965). (b) A portion of this work has been previously described: C. L. Stevens, R. D. Elliott, B. L. Winch, and I. L. Klundt, *J. Am. Chem. Soc.*, **84**, 2272 (1962).

(2) Abstracted in part from the Ph.D. Dissertation of I. L. Klundt, Wayne State University, 1963.

(3) Some synthetic and thermodynamic aspects of the amino ketone rearrangement in other carbon skeleton systems will be presented in future communications.

(4) C. G. Overberger and A. Leboriets, *J. Am. Chem. Soc.*, **76**, 2272 (1954).

(5) C. Mannich and H. Budde [*Arch. Pharm.*, **271**, 51 (1933)] prepared the analogous α-methylaminoisobutyrophenone.

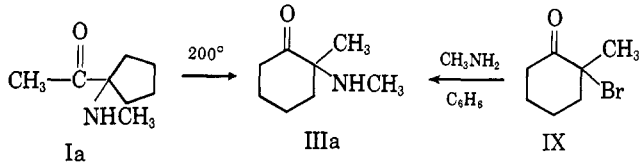
(6) P. L. Julian, E. W. Meyer, R. Magnani, and W. Cole, *J. Am. Chem. Soc.*, **67**, 1203 (1945).

(7) "N.M.R. Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963, Spectrum No. 568.

(8) C. C. Hach, C. V. Banks, and H. Diehl, *Org. Syn.*, **32**, 35 (1952). The dione is also available from the Aldrich Chemical Co.

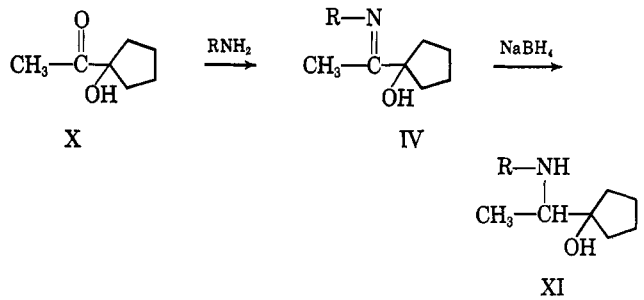
ration of N-phenylimine IIb in 88% yield. The C-methyl signals of IIa and b were very similar arising at τ 8.69 and 8.63, respectively. Further characterization of the hydroxy imines was attained by borohydride reduction to the corresponding amino alcohols VIII. The low yield (33%) of sharp-melting VIIIa and the wide melting range of analytically pure VIIIb, which was isolated in high yield, both indicate a lack of stereospecificity in the borohydride reduction.

Thermal rearrangement of Ia was initially employed for the synthesis of 2-methyl-2-methylaminocyclohexanone (IIIa).[1b] Thus, pyrolysis at 200° of neat Ia afforded the rearranged product in 34% yield. Alternatively, application of the technique of Mannich and Budde[5] to the case of 2-bromo-2-methylcyclohexanone[9] (IX) afforded IIIa in 43% yield. An n.m.r. spectrum of the hydrochloride salt of IIIa exhibited both C-methyl (τ 8.59) and N-methyl (τ 7.52) singlets which confirmed the structure of IIIa.



Amino ketone IIIb was only synthesized by thermal rearrangement of the α-hydroxy N-phenylimine (IVb). Using conditions previously described for the cyclopentyl *phenyl* ketone system,[1a] IVb afforded IIIb in 44% yield. In its n.m.r. spectrum IIIb exhibited a sharp C-methyl singlet (τ 8.65) and an N-phenyl region similar to but less well resolved than that of Ib.

The precursor of amino ketone IIIb was synthesized *via* hydroxy ketone X. 1-Acetylcyclopentanol[10] (X), prepared by the hydration of 1-ethynylcyclopentanol, was then converted to the N-phenylimine IVb by the standard acid-catalyzed imine preparation, albeit, in only 25% yield. The N-methyl analog IVa was prepared by the same technique used to prepare hydroxy imine IIa. Structures IV were confirmed by periodate cleavage of the borohydride reduction products.



Rearrangements.—The results of a qualitative survey of rearrangement reactions of the two series are shown in Tables I and II. The rearrangements of hydroxy imines of both series showed improvement when rearranged in the presence of acetic acid catalyst. These results are shown in Table III.

While no stringent comparison of reaction conditions is possible, it is apparent that the rearrangements of the hydroxy imines are subject to acid catalysis. Thus, for IIb a shorter reaction time in the presence of acid afforded a significantly higher yield of product Ib. Suppression of the reverse reaction by acid, for both N-phenyl cases, is probably not important since both products Ib and IIIb are fairly stable to thermal rearrangement in the absence of acid. Again, use of acetic acid for the conversion of IVb to IIIb caused a significant increase in yield at a lower conversion temperature. Acid catalysis in the present N-methyl cases is not as clear cut. The presence of acid could well slow down the reverse reactions in these cases, thus resulting in "apparent" acid catalysis. However, the irreversible rearrangement of hydroxy N-methylimine (XII) is 24% complete in 35 min. at 176° while its hydrochloride salt is *completely* converted to XIII in 30 min. at this same temperature.[11]

TABLE I

REARRANGEMENT OF N-METHYLAMINO KETONES AND HYDROXY IMINES[a]

Compd.	Rearrangement temp., °C.	Reaction time, hr.	Product	Yield, %
Ia	200	10	IIIa	34
IIa	170	10	IIIa	10–15
IIIa	190	18		Decomposes
IVa	110	42	IIIa	60

[a] No solvent was used.

TABLE II

REARRANGEMENT OF N-PHENYLAMINO KETONES AND HYDROXY IMINES

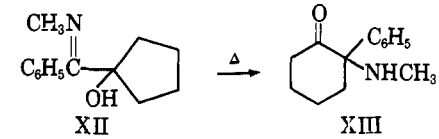
Compd.	Rearrangement temp., °C.	Reaction time, hr.	Solvent	Product	Yield, %
Ib	184	10	Decalin	Ib	71
IIb	190	45	Decalin	Ib	42
IIIb	180	24	None	IIIb	~50
IVb	190	4	Decalin	IIIb	44

TABLE III

REARRANGEMENT OF HYDROXY IMINES WITH ACID CATALYSIS

Compd.	Solvent[a]	Product	Yield, %	Reaction time, hr.
IIa	Xylene	IIIa	20[b]	8
IVa	Xylene	IIIa	62[b,c]	12
IIb	Decalin	Ib	60	23
IVb	Xylene	IIIb	47	4

[a] At reflux temperature; 10 ml. of solvent for each 0.1 g. of compound with 3–5 drops of glacial acetic acid added. [b] Isolated as the hydrochloride salt. [c] Without acetic acid for 12 hr.: 49%.

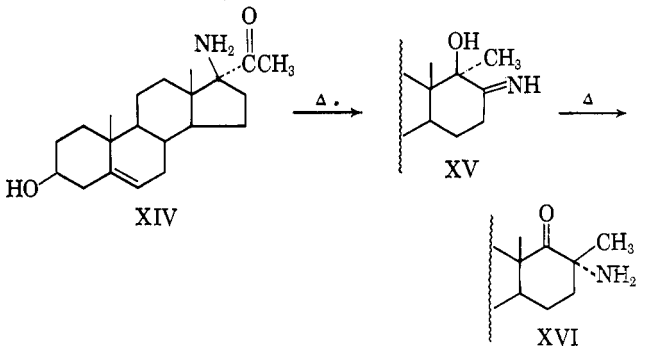


Turning to the rearrangements of amino ketones of the N-methyl series, aminocyclohexanone (IIIa) appears to be the most stable isomer. The formation of IIIa from amino ketone Ia must certainly proceed

(9) E. J. Corey, *J. Am. Chem. Soc.*, **77**, 5415 (1955).
(10) G. W. Stacy and R. A. Mikulec, *ibid.*, **76**, 524 (1954).

(11) (a) The authors thank Mr. Harry T. Hanson for these data. (b) The equilibrium constant, K = [XIII]/[XII], is high enough (≥ 25) so that, practically, the conversion XII → XIII may be considered as irreversible.

through the intermediate hydroxy imine IIa. Morrow and co-workers[12] have isolated the intermediate hydroxy imine XV in their rearrangement of 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (XIV) to its D-homo isomer XVI.[13] Thus, the yield of IIIa from the

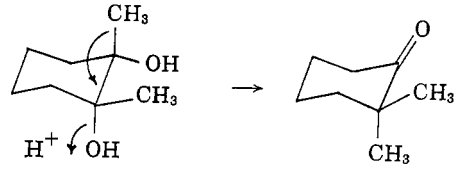


XIV XV XVI

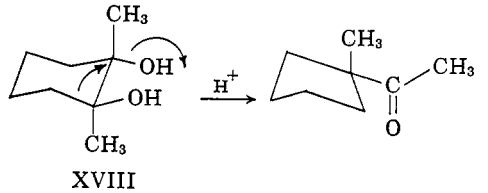
pyrolysis of IIa does not discredit the role of the hydroxy imine as a reaction intermediate. Aminocyclohexanone (IIIa), apparently, was reasonably stable at 140° (Table III, footnote *c*), but slowly decomposed at 190° over extended periods of time (Table I). The only isolable product after 18 hr. was the dinitrophenylhydrazone of 2-methylcyclohex-2-en-1-one which could have come from either IIa or IIIa.

The results of the N-phenyl series clearly indicate the lack of importance of NH acidity in amino ketone rearrangements. Thus, both Ib and IIIb, which are expected to be more acidic than their N-methyl analogs, are, by comparison, thermally stable. The rearrangements in this series appear to be governed by the greater stability of the α-amino ketone system over the isomeric α-hydroxy imine system. With both ring expansion and contraction being encountered, ring size effects have, clearly, been overridden, as would be expected.

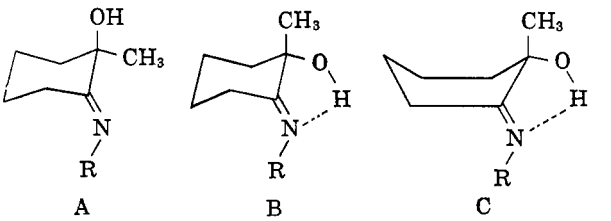
Comparison of the rearrangement products of IIa and IIb is interesting. It was hoped that clean pyrolysis of both IIa and IIb might give some clues as to the stereochemical requirements for their rearrangement. It seems reasonable to draw some analogy between the



XVII



XVIII



A B C

Figure 1.

rearrangement of hydroxy imines and the pinacol rearrangement. The stereochemical requirements for migration in the pinacol reaction are well documented. Thus, in the case of the *cis*-pinacol XVII, migration proceeds in a *trans* copolanar fashion with migration of a methyl group from an axial position.[15] Rearrangement of the *trans*-pinacol XVIII proceeds, again, in a *trans* coplanar fashion, but this time ring contraction results. After inspection of conformational isomers A and B (Figure 1) of imines II, one would expect methyl migration only from conformation B (or C), since only from this conformation can the methyl group attain any degree of coplanarity with the developing electron-deficient orbital at the imine carbon. Thus, if ground-state population controls product formation to any extent, then conformation B would result in methyl migration. Further, ground-state conformation B would be more favored with the more basic imine IIa, and from this imine methyl migration is observed. Ring contraction can almost certainly occur from all conformations.[16] Further, the migratory aptitude of the alkyl chain is expected to be greater than that of the methyl group, since the order of ethyl > methyl has been observed in an amino ketone rearrangement.[17]

Certainly, no firm mechanistic conclusions can be drawn from the experimental data thus far, and the factors governing the observed differences between the N-methyl and N-phenyl series require detailed study. Synthetically, the amino ketone rearrangement is finding wider application[12,14] and this paper serves to illustrate the scope in simple aliphatic systems.

Experimental

Melting points were obtained with a Thomas–Hoover melting point apparatus, but are uncorrected. Elemental analyses were performed by Midwest Microlab, Inc. Where they are recorded, n.m.r. C-methyl shifts were obtained on a Varian DP-60 spectrometer, infrared spectra on a Beckman IR-4, ultraviolet spectra in ethanol on a Cary 14 spectrometer. pK_a' values were obtained on apparatus previously described.[18] Thin layer chroma-

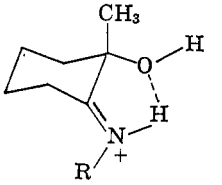
(12) D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 579 (1965).

(13) The reasons for the stereochemical course observed for the conversion of XIV to XVI are not clear. Further, in view of the complex base-catalyzed isomerizations known to occur in D-homo-α-hydroxy ketones, and in the absence of stability data for the C-17 epimer of XVI, any stereochemical conclusions for this and some analogous steroid cases must await further study. For discussions in this area, see N. L. Wendler, "Molecular Rearrangements, part 2," P. DeMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp. 1114–1121; ref. 14.

(14) D. F. Morrow, M. E. Brokke, G. W. Moersch, M. E. Butler, C. F. Klein, W. A. Neuklis, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 212 (1965).

(15) P. D. Bartlett and I. Pockel, *J. Am. Chem. Soc.*, **59**, 820 (1937); *cf.* also E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, N. Y., 1959, p. 601.

(16) Acid catalysis need not alter the stereochemical outcome of the rearrangements of IIa. For instance, the protonated imine would be stabilized in conformation i.



i

(17) C. L. Stevens, R. D. Elliot, and B. L. Winch, *J. Am. Chem. Soc.*, **85**, 1464 (1963).

(18) A. M. Wilson and M. E. Munk, *Anal. Chem.*, **34**, 443 (1962).

tography solvent was diethyl ketone–diisopropyl ketone–ligroin (100°), 6:3:1 (v./v.); spots were developed with sulfuric acid.

α-Bromocyclopentyl Methyl Ketone (V).—In a 1-l. flask was placed 30 g. (0.27 mole) of cyclopentyl methyl ketone,[4] 47.2 g. (0.27 mole) of N-bromosuccinimide, 4.8 g. of benzoyl peroxide, and 300 ml. of carbon tetrachloride. This reaction mixture was heated at reflux for 3 hr. An additional gram of benzoyl peroxide was added, and the reaction refluxed for an additional 3 hr. The succinimide which had formed was filtered off, the solvent was removed by distillation, and the black residue was fractionally distilled at reduced pressure. The bromo ketone distilled as a colorless liquid, b.p. 75–77° (8 mm.), $n^{25}D$ 1.4900. The product was isolated in 77% yield. The compound could also be prepared in 66% yield by bromination with bromine in carbon tetrachloride. Redistillation produced an analytical sample, b.p. 50° (2.8 mm.), $n^{25}D$ 1.4905, d^{25}_4 1.3825.

Anal. Calcd. for $C_7H_{11}BrO$: Br, 41.83. Found: Br, 42.11.

α-Methylaminocyclopentyl Methyl Ketone (Ia).—To 31 g. (0.16 mole) of α-bromocyclopentyl methyl ketone was added a mixture of 25 ml. (0.5 mole) of methylamine in 500 ml. of cold benzene. This was allowed to warm to room temperature and remain there for 91 hr. The benzene solution was extracted with dilute hydrochloric acid. The acid fraction was made basic by the addition of solid sodium hydroxide and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and filtered, and the solvent was removed by distillation. The residual material was fractionally distilled to yield a colorless oil, b.p. 63–64° (3 mm.), $n^{25}D$ 1.4656, in 89% yield. Redistillation gave an analytical sample, b.p. 51° (2 mm.), $n^{25}D$ 1.4633, d^{25}_4 0.9649.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.27; H, 10.83; N, 10.15.

The amino ketone was characterized by conversion to its hydrochloride salt with dry 2-propanol saturated with dry hydrogen chloride. The salt was recrystallized from acetone to yield white needles, m.p. 118–120°, λ_{max} 279 mμ (ε 22.19), n.m.r. (CCl_4) τ 7.90 (CCH_3) and 7.95 (NCH_3), pK_a' = 7.50 (50% methanol).

Anal. Calcd. for $C_8H_{16}ClNO$: C, 54.07; H, 9.08. Found: C, 54.03; H, 9.06.

1-(1-Methylaminocyclopentyl)ethanol Hydrochloride (VIa).—In a 50-ml. flask was placed 1.2 g. (8.5 mmoles) of Ia and 7 ml. of 95% ethanol. To this was added 0.4 g. (10.6 mmoles) of sodium borohydride. The reaction was allowed to stand 2 days at room temperature, then diluted with 25 ml. of 2 *N* hydrochloric acid, made basic, and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and filtered, and 2-propanol saturated with dry hydrogen chloride was added. The salt was recrystallized from ethanol–ether to yield a white solid, m.p. 113–114°, in 73% yield, pK_a' = 9.70 (50% methanol).

Anal. Calcd. for $C_8H_{18}ClNO$: C, 53.44; H, 10.09; Cl, 19.72; N, 7.89. Found: C, 53.12; H, 10.31; Cl, 19.59; N, 7.81.

Sodium Periodate Cleavage of 1-(1-Methylaminocyclopentyl)-ethanol Hydrochloride (VIa).—In a 50-ml. flask were placed 0.3 g. (1.7 mmoles) of VIa, 6 ml. of methanol, and 20 ml. of 0.1 *N* sodium periodate. The reaction was allowed to stand overnight at room temperature, neutralized with barium hydroxide, saturated with sodium chloride, and extracted with ether. The ether was dried over sodium sulfate, filtered, and removed on a steam bath. To the residue was added an alcoholic solution of 2,4-dinitrophenylhydrazine. The 2,4-dinitrophenylhydrazone which resulted was recrystallized from alcohol to yield a yellow solid, m.p. 142–143°. A mixture melting point with an authentic sample of cyclopentanone 2,4-dinitrophenylhydrazone showed no depression.

2-Methyl-2-methylaminocyclohexanone (IIIa).—In a steel bomb was placed 24.31 g. (0.17 mole) of α-amino ketone Ia. The reaction was heated at 200–215° for 10 hr. The reaction was allowed to cool, the bomb was opened, and the reaction mixture was taken up in ether and extracted with dilute hydrochloric acid. The acid layer was made basic by the addition of sodium hydroxide and extracted with four 100-ml. portions of ether and two 50-ml. portions of methylene chloride. The organic layers were combined, dried, and filtered, and the solvent was removed on a steam bath. The residual material was fractionally distilled to give a pale yellow liquid, b.p. 55–57° (2 mm.), $n^{25}D$ 1.4710. Redistillation produced an analytical sample, b.p. 52° (1.8 mm.), $n^{25}D$ 1.4689, d^{25}_4 0.9927.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.08; H, 10.69; N, 10.12.

The hydrochloride salt of IIIa was prepared as described for Ia. The solid was recrystallized from acetone to yield 10.55 g. (34.5%) of a white solid, m.p. 188–190°. An analytical sample was prepared: m.p. 191.4–191.8°, n.m.r. (D_2O) τ 8.59 (CCH_3), λ_{max} 283 mμ (ε 22.2), pK_a' = 8.40 (50% methanol).

2-Methyl-2-methylaminocyclohexanol.—Sodium borohydride reduction of 2-methyl-2-methylaminocyclohexanone (IIIa) was carried out as previously described for Ia. The reaction product was isolated by conversion to its hydrochloride salt in 47% yield, m.p. 144–145° after recrystallization from ethanol–ether.

Alternate Synthesis of 2-Methyl-2-methylaminocyclohexanone (IIIa).—In a 100-ml. flask were placed 3.5 g. (0.018 mole) of 2-bromo-2-methylcyclohexanone,[9] 75 ml. of benzene (cooled to about 7°), and 4 ml. of methylamine. The reaction mixture was allowed to warm slowly to room temperature and remain there for 50 hr. The reaction was filtered to remove the methylamine hydrobromide and extracted with three 25-ml. portions of 6 *N* hydrochloric acid. The aqueous acid solution was made basic with potassium hydroxide and extracted with three 50-ml. portions of ether and one 50-ml. portion of methylene chloride. The organic extracts were combined, dried over sodium sulfate, and filtered, and the solvent was removed. Anhydrous ether was added to the residue and 2-propanol saturated with dry hydrogen chloride was added to form the hydrochloride salt of the product. The salt which precipitated was recrystallized from acetone to yield 1.4 g. (43%) of white crystals, m.p. 190–192°. A mixture melting point with the previously prepared sample of 2-methyl-2-methylaminocyclohexanone hydrochloride was undepressed.

N-Methylimine of 1-acetylcyclopentanol (IVa).—In a steel bomb were placed 10 g. (0.078 mole) of 1-acetylcyclopentanol[10] and 70 ml. of methylamine. The reaction mixture was allowed to stand at room temperature for 18 hr. The bomb was opened, the reaction mixture was transferred in ether to a flask, and the solvent was removed *in vacuo*. The residue was dissolved in ether, dried over sodium sulfate, and filtered, and the ether was removed. The procedure described above was repeated four times until a carbonyl band was absent from the infrared spectrum. Distillation of the residue gave 5.0 g. (45%) of a colorless liquid, b.p. 31.5–32.5° (0.4 mm.), $n^{22}D$ 1.4747, d^{24}_4 0.9757, λ_{max} 233 mμ (ε 164.7), λ_{max} 3.10 and 6.02 μ, n.m.r. ($CDCl_3$) τ 8.15.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.26; H, 10.56; N, 9.68.

1-(2-N-Methylaminoethyl)cyclopentanol Hydrochloride (XIa).—In a 50-ml. flask were placed 900 mg. (6.3 mmoles) of IVa, 15 ml. of dioxane, and 300 mg. (8 mmoles) of sodium borohydride. The reaction mixture was allowed to stand at room temperature for 36 hr., heated on a steam bath for 2 hr., and diluted with 75 ml. of water. The reaction mixture was continuously extracted with ether for 18 hr. The ether was dried and filtered, and the hydrochloride salt was prepared. Filtration gave 900 mg. (75%) of white solid, m.p. 116–120°. Recrystallization from acetone gave an analytical sample, m.p. 121–122.5°, pK_a' = 9.82 (50% methanol).

Anal. Calcd. for $C_8H_{18}ClNO$: C, 53.47; H, 10.10; Cl, 19.73. Found: C, 53.30; H, 10.21; Cl, 19.52.

Sodium Periodate Cleavage of XIa.—An aqueous solution containing 500 mg. (2.8 mmoles) of Xa, 10 ml. of 0.4 *M* sodium periodate, and 670 mg. (8.0 mmoles) of sodium bicarbonate was allowed to stand at room temperature for 2 days. The aqueous solution was extracted with three 25-ml. portions of ether. The ether was distilled, and the residue was treated with a 2,4-dinitrophenylhydrazine solution. The solid which formed was passed over an alumina column in benzene. Crystallization of the product from alcohol gave 180 mg. (25% yield) of cyclopentanone 2,4-dinitrophenylhydrazone, m.p. 142–144°. A mixture melting point with an authentic sample was undepressed.

Pyrolysis of the N-Methylimine of 1-Acetylcyclopentanol (IVa).—In a sealed tube was placed 2.0 g. (14.2 mmoles) of IVa, which was heated at 115° for 42 hr. The tube was cooled and opened, and the contents was dissolved in 15 ml. of 3 *N* hydrochloric acid. The aqueous solution was heated at 50° for 15 min., cooled, extracted with ether, and made basic with sodium hydroxide. The basic solution was extracted with four 25-ml. portions of methylene chloride. The methylene chloride solution was dried over sodium sulfate and filtered, and the solvent was removed. The residue was dissolved in ether and the hydrochloride salt was prepared. The solid was triturated with acetone and filtered

to give 1.5 g. (60% yield) of 2-methyl-2-methylaminocyclohexanone hydrochloride (IIIa), m.p. 189–193°. A mixture melting point with a sample previously prepared was undepressed.

2-Hydroxy-2-methylcyclohexanone (VII).—In a 1-l. three-necked flask equipped with a stirrer, reflux condenser (protected by a calcium chloride drying tube), dropping funnel, and a gas-inlet tube was placed 12.1 g. (0.54 g.-atom) of magnesium. Helium was passed in and the flask was flame dried. The flask was allowed to cool and 100 ml. of dry ether was added. To the flask was added 10 ml. of a methyl iodide solution [76 g. (0.535 mole) of methyl iodide in 150 ml. of ether]. After the reaction had started, an additional 75 ml. of ether was added to the reaction. The remainder of the methyl iodide solution was added over a 2-hr. period. The Grignard reagent was refluxed for 2 hr. and cooled to room temperature, and 20 g. (0.178 mole) of cyclohexane-1,2-dione[8] in 150 ml. of ether was added over a 2-hr. period at such a rate to maintain gentle reflux. The reaction mixture was heated under reflux for 2.5 hr., cooled in an ice bath, and hydrolyzed with 80 ml. of saturated ammonium chloride solution. The ether was decanted from the solid and the solid was washed with 100 ml. of dry ether. The solvent was removed and the residual material was fractionally distilled to give 11.2 g. (49% yield) of a colorless liquid, b.p. 81–83° (13 mm.), $n^{25.5}$D 1.4642, n.m.r. ($CDCl_3$) τ 8.66 [lit.[19] b.p. 86–87° (16 mm.), $n^{20.4}$D 1.4669].

2-Hydroxy-2-methylcyclohexanone N-Methylimine (IIa).—In a pressure bottle was placed 7.6 g. (0.059 mole) of 2-hydroxy-2-methylcyclohexanone and 15 ml. of methylamine. After standing at 25° for 6 days, the reaction mixture was dissolved in ether and all of the solvent and the excess methylamine was removed. The residue was taken up in ether, dried over sodium sulfate, and filtered, and the ether was removed. The residue was treated with 15 ml. of methylamine for 48 hr. and worked up as described above. The reaction was treated three additional times (48 hr. each) with methylamine. After each treatment with methylamine, an infrared spectrum was obtained. The treatments with methylamine were repeated until the carbonyl peak in the infrared spectrum was absent. In a subsequent preparation, the use of sodium hydroxide as desiccant shortened the necessary reaction time down to about 1 week. Distillation produced 2.5 g. (30% yield) of a pale yellow oil, b.p. 41.5–42° (1 mm.), n^{25}D 1.4733, d^{20}_4 0.9822, λ_{max} 305 mμ (ε 162), n.m.r. ($CDCl_3$) τ 8.69.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.88; H, 10.63; N, 9.89.

2-Methyl-2-hydroxy-N-methylcyclohexylamine Hydrochloride (VIIIa).—A solution containing 10 ml. of methanol, 132 mg. (3.5 mmoles) of sodium borohydride, and 480 mg. (3.4 mmoles) of IIa was allowed to stand at room temperature for 3 days. The reaction mixture was diluted with 50 ml. of water and continuously extracted with ether for 36 hr. The ether was dried over sodium sulfate and filtered, and all of the solvent was removed. The residue was dissolved in 30 ml. of dry ether, and dry hydrogen chloride in isopropyl alcohol was added. The solid was filtered and recrystallized from alcohol–ether to give 200 mg. (33% yield) of a white solid, m.p. 203–204°, pK_a' = 9.65 (50% methanol).

Anal. Calcd. for $C_8H_{18}ClNO$: C, 53.47; H, 10.10; Cl, 19.73. Found: C, 53.63; H, 10.10; Cl, 20.06.

Pyrolysis of the N-Methylimine of 2-Hydroxy-2-methylcyclohexanone (IIa).—In a sealed tube was placed 3.0 g. (0.021 mole) of the N-methylimine of 2-hydroxy-2-methylcyclohexanone. The imine was heated at 170° for 10 hr. The tube was cooled and opened, and the contents was dissolved in 40 ml. of 4 *N* hydrochloric acid. The aqueous acid was heated on a steam bath for 0.5 hr. and allowed to stand at room temperature for 13 hr. It was extracted with ether to remove any neutral material and made basic with sodium hydroxide. The basic solution was extracted with ether to remove the amino ketone. The ether solution was dried over sodium sulfate and filtered, and the solvent was removed. The residue was dissolved in dry ether and a hydrochloride salt was prepared. The solvent was evaporated to dryness and the residue was azeotroped twice with benzene. The residue was triturated with acetone and the solid was filtered to give 580 mg. (15% yield) of IIIa as its hydrochloride salt as identified by melting point and mixture melting point.

(19) L. W. Butz, B. L. Davis, and A. M. Gaddis, *J. Org. Chem.*, **12**, 122 (1947).

α-Anilinocyclopentyl Methyl Ketone (Ib).—The procedure described by Julian[6] was employed. In a 100-ml. flask equipped with a reflux condenser and heating mantle were placed 11.0 g. (0.06 mole) of α-bromocyclopentyl methyl ketone, 7 g. of aniline, 8.4 g. of sodium bicarbonate, and 50 ml. of absolute alcohol. The reaction was then heated to reflux and stirred with a magnetic stirrer for 5 hr. The reaction was filtered to remove the inorganic salts, poured into 300 ml. of water, and extracted with 200 ml. of ether. The ether layer was dried over anhydrous sodium sulfate and filtered, and the solvent was removed. The resulting dirty brown solid was taken up in hot petroleum ether and filtered to remove a black insoluble tar. On concentrating and cooling the petroleum ether solution, 4.01 g. (34.1%) of pale yellow crystals were obtained, m.p. 81–83°. Chromatography over alumina and elution with pentane gave white crystals, m.p. 82–83°, λ_{max} 293 mμ (ε 2050) and 248 mμ (ε 14,400), n.m.r. (CCl_4), τ 7.85, pK_a' = 2.65 (50% methanol).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.90. Found: C, 76.55; H, 8.47; N, 6.75.

1-(1-Anilinocyclopentyl)ethanol (VIb).—In a 50-ml. flask were placed 0.8 g. (4.0 mmoles) of Ib, 8 ml. of 95% ethanol, and 0.4 g. (10 mmoles) of sodium borohydride. The reaction was allowed to stand at room temperature for 24 hr. and was then treated with 15 ml. of 2 *N* hydrochloric acid and 50 ml. of water. The acid solution was made basic by the addition of solid potassium hydroxide and the basic solution was extracted with ether. The ether solution was dried, filtered, and taken to dryness with a stream of cold air and the solid was recrystallized from alcohol–water to yield 650 mg. (80%) of crystalline VIb, m.p. 78–79°, pK_a' = 5.10 (50% methanol).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.84; H, 9.30; N, 7.07.

Sodium Periodate Cleavage of VIb.—In a 50-ml. flask were placed 0.32 g. (1.6 mmoles) of VIb, 16 ml. of methanol, 16 ml. of 0.1 *N* hydrochloric acid, and 16 ml. of 0.2 *M* sodium periodate. The reaction was allowed to stand at room temperature for 24 hr. It was diluted with 50 ml. of saturated sodium chloride solution and extracted with three 50-ml. portions of ether. The ether solution was concentrated by boiling on a steam bath. The residue was poured into a 2,4-dinitrophenylhydrazine solution and the remaining ether was boiled off. The solid which formed was recrystallized three times from ethanol–water to give 170 mg. (40%) of cyclopentanone 2,4-dinitrophenylhydrazone, m.p. 142–143°. A mixture melting point with an authentic sample was undepressed.

Pyrolysis of α-Anilinocyclopentyl Methyl Ketone (Ib).—In a sealed tube was placed 2.95 g. (0.015 mole) of Ib. The tube was placed inside a steel bomb and heated at 184° for 10 hr. The bomb was cooled and opened, and the tube was removed and opened. The reaction mixture was taken up in 60 ml. of 6 *N* hydrochloric acid and extracted with ether. The aqueous layer was made basic by the addition of solid potassium hydroxide and extracted with ether. Both ether fractions, one containing the neutral material and the other containing the basic material, were dried over anhydrous sodium sulfate. After filtration and removal of the solvent 0.42 g. of neutral material was isolated. The ether solution containing the basic material was filtered, and the solvent was removed. A dark solid was obtained which was taken up in a minimum amount of acetone and placed on an alumina column. After elution with 5% acetone–petroleum ether, 2.09 g. (71%) of the starting Ib was isolated, m.p. 82–83°.

N-Phenylimine of 1-Acetylcyclopentanol (IVb).—In a 100-ml. flask equipped with a Dean–Stark trap were placed 400 ml. of benzene, 10 ml. of aniline, and a trace of *p*-toluenesulfonic acid. The reaction was azeotroped dry and 12.8 g. (0.1 mole) of 1-acetylcyclopentanol was added. The reaction was heated under reflux for 14 hr. The solvent was removed and the residue was fractionally distilled twice to give 5.2 g. (25% yield) of a colorless liquid, b.p. 81–83° (0.1 mm.), n^{25}D 1.5469, d^{25}_4 1.064, λ_{max} 274 mμ (ε 2040), n.m.r. (CCl_4) τ 8.23.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.90. Found: C, 76.74; H, 8.46; N, 6.93.

1-(2-Anilinoethyl)cyclopentanol Hydrochloride (XIb).—In a 125-ml. flask were placed 1 g. (5 mmoles) of the N-phenylimine of 1-acetylcyclopentanol, 50 ml. of anhydrous methanol, and 1 g. (0.03 mole) of sodium borohydride. This was heated under reflux for 1 hr., poured into 150 ml. of water, and extracted continuously with ether for 20 hr. The ether was dried and filtered, and the solvent was removed. The residue was taken up in dry

ether and 2-propanol saturated with dry hydrogen chloride was added. The solid hydrochloride was recrystallized from alcohol–ether to give 0.8 g. (66% yield) of a white solid, m.p. 136°. Recrystallization from acetone gave an analytical sample, m.p. 139–140°, pK_a' = 4.37 (50% methanol).

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34; Cl, 14.66. Found: C, 64.67; H, 8.48; Cl, 14.79.

2-Anilino-2-methylcyclohexanone (IIIb).—To 25 ml. of decalin was added 2 g. (9.8 mmoles) of IVb. This was heated under reflux (about 190°) for 4 hr. The decalin solution was extracted with four 25-ml. portions of 6 *N* hydrochloric acid. The acid layer was made basic with potassium hydroxide and extracted with chloroform. The chloroform was dried and filtered, and the solvent was removed. Addition of pentane to the residue caused the oil to solidify. Recrystallization from hexane gave 0.88 g. (44% yield) of white solid, m.p. 92–93°, with infrared analysis showing a carbonyl at 5.83 μ and an N–H at 2.96 μ, λ_{max} 294 mμ (ϵ 2480) and 248 mμ (ϵ 16,500), n.m.r. ($CDCl_3$) τ 8.65, pK_a' = 4.55 (50% methanol).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.90. Found: C, 76.91; H, 8.62; N, 7.07.

N-Phenylimine of 2-Hydroxy-2-methylcyclohexanone (IIb).—In a 100-ml. flask equipped with a Dean–Stark trap and a reflux condenser was placed 50 ml. of benzene, 12 ml. of aniline, and a trace of *p*-toluenesulfonic acid. The reaction mixture was azeotroped dry and then 11 g. (0.086 mole) of 2-hydroxy-2-methylcyclohexanone (VII) was added. The reaction was refluxed for 17 hr. The amount of water collected was approximately 1.3 ml. (84% yield). The solvents were removed under reduced pressure and the residual material was fractionally distilled to give 15.03 g. (85%) of a colorless liquid, b.p. 90–93° (0.2 mm.), $n^{26.5}D$ 1.5461. Redistillation gave an analytical sample, b.p. 74–74.5° (0.08 mm.), $n^{25}D$ 1.5465, d^{25}_4 1.053, λ_{max} 276 mμ (ϵ 1910), n.m.r. ($CDCl_3$) τ 8.63.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.90. Found: C, 76.53; H, 8.47; N, 6.81.

1-Anilino-2-hydroxy-2-methylcyclohexane Hydrochloride (VIIIb).—In a 125-ml. flask were placed 2.0 g. (9.75 mmoles) of IIb and 50 ml. of methanol. To this was added 1.5 g. (0.04 mole) of sodium borohydride and the reaction was allowed to stand at room temperature for 30 min. About 25 ml. of the methanol was removed *in vacuo*, and the reaction mixture was diluted with 50 ml. of water and continuously extracted with ether for 18 hr. The ether was dried and filtered and the solvent was removed. Dry ether was added to the residue and a hydrochloride salt was prepared as described above. The solid was recrystallized from a mixture of acetone–ether to yield 1.89 g. (93.5%), m.p. 138–148°. Two recrystallizations from acetone gave a white solid, m.p. 103–158°, pK_a' = 4.38 (50% methanol).

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34; Cl, 14.66. Found: C, 64.50; H, 8.56; Cl, 14.37.

Rearrangement of the N-Phenylimine of 2-Hydroxy-2-methylcyclohexanone (IIb).—In 25 ml. of dry decalin was placed 2.0 g. (9.8 mmoles) of IIb. This was heated under reflux for a total of 45 hr. The reaction mixture was extracted with four 25-ml. portions of 6 *N* hydrochloric acid. The acid extract was heated on a steam bath for 1 hr., cooled, extracted with ether, and made basic with potassium hydroxide. The basic aqueous solution was extracted with chloroform, the chloroform extract was dried and filtered, and the solvent was removed. The residue was taken up in hexane and passed through an alumina column. Removal of the solvent under reduced pressure caused a solid to form. Filtration of the remaining solution gave 850 mg. (42% yield) of white solid, m.p. 76–79°. Recrystallization from pentane gave white plates, m.p. 80.5–82°. A mixture melting point with amino ketone Ib gave no depression, m.p. 80.5–82°.

Rearrangement of Hydroxy Imines with Acid Catalysis.—Yields of products and solvents used are recorded in Table III. A representative procedure is outlined below.

To 300 mg. of hydroxy imine IIb was added 35 ml. of freshly distilled decalin and 5 drops of glacial acetic acid. The mixture was heated under reflux for 23 hr. Solvent was then removed *in vacuo*. The residual sirupy liquid was treated with 25 ml. of 3 *N* aqueous hydrochloric acid, heated on a steam bath for 1 hr., cooled, and extracted with ether twice to remove the neutral products. The aqueous solution was then made basic with 10% potassium hydroxide solution and extracted with ether four times. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered, and the ether was removed *in vacuo*. The residual, brown semisolid material was treated with Norit and then crystallized from pentane to give 180 mg. (60%) of amino ketone Ib, m.p., 78–79.5°. Mixture melting point with a previously prepared sample was undepressed.

Thermal Stability of α-Amino Ketones IIIa and b.—A neat sample of 2.6 g. of amino ketone IIIa was heated in a sealed tube at 190° for 18 hr. An infrared spectrum ($CHCl_3$) of the crude reaction product indicated fairly extensive decomposition with broad absorptions at ~3.0, 5.8, and 6.0 μ. The neutral fraction consisted mainly of an ether-insoluble black tar. The ether-soluble fraction afforded 200 mg. of a dark oil which yielded 100 mg. of 2-methylcyclohex-2-en-1-one 3,5-dinitrophenylhydrazone, m.p. 201–203°, identified by comparison with the dinitrophenylhydrazone prepared from hydroxy ketone VII (lit.[20] m.p. 198–199°). The basic fraction, 440 mg. of a black oil, could not be purified further.

A solid sample of amino ketone IIIb was heated at 180° in a sealed tube. One reaction, stopped after 4 hr., had turned dark brown but had an infrared spectrum ($CHCl_3$) almost identical with starting material. The great predominance of IIIb was confirmed by thin layer chromatography. After 24 hr. at 180°, infrared analysis of the dark brown oil indicated ~50% loss of starting IIIb. Thin layer chromatography showed a major spot corresponding to IIIb, a dark brown spot at the origin, and two very minor spots running slower than IIIb.

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(20) A. J. Birch, *J. Chem. Soc.*, 593 (1946).