In order that the data could be combined with those of Roberts,[21,22] the following calibration procedure was used. A 3.127×10^{-3} *M* solution of benzoic acid (National Bureau of Standards) in 50% (vol) ethanol–water was half-neutralized and the meter was zeroed to 5.75, the apparent p*K* reported by Roberts.[21] The electrodes were cleaned, dried, and inserted into a 0.02 *N* potassium hydrogen phthalate buffer in 50% (vol) ethanol–water and readings of 5.50 ±0.005 were recorded. In subsequent runs the meter was standardized against this phthalate buffer solution.

All titrations were carried out with a 200-ml, covered beaker maintained at 25.0 ± 0.1° and a buret graduate to 0.01 ml. The base used was 0.06703 *N* sodium hydroxide in 50% (vol) ethanol–water and was prepared from carbonate-free water and base. The solutions were stirred with a magnetic stirring bar under a nitrogen atmosphere. Solutions of the acids (*ca.* 3.1×10^{-3} *M*) in 50% (vol) ethanol–water were prepared, and 50-ml aliquots were titrated. A plot of pH *vs.* volume of base was made for each titration and the p*K* values were determined graphically.

Ethanolysis Procedure (63–83° Range).—All kinetic experiments at 63 and 83° utilized a 12 × 12 in. pyrex bath which contained *ca.* 5 gal of oil (Cities Service, D.C.-915), a Lightnin Model L continuous duty stirrer, a hydrogen-jacketed thermoregulator, and a 500-w continuous heat source which was connected to a Variac. Fine heating was controlled by a 100-w light bulb connected through a relay to the thermoregulator. The entire bath was surrounded by *ca.* 3 in. of polyurethane foam and was covered with a 1-in. styrofoam lid.

The appropriate amount of halide (*ca.* 0.0013 mole) was dissolved in *ca.* 25 ml of water–ethanol (50% by volume at 20.0°) and the solution was distributed among 7–10 ampoules each containing *ca.* 2.3 ml. The ampoules were sealed and placed in the bath (clock started) and at appropriate time intervals ampoules were removed and quenched in ice–water. The necks were scored and snapped off, and an exact aliquot (*ca.* 2 ml) was removed with a pipet calibrated with the same ethanol–water solution. The aliquot was diluted with *ca.* 15 ml of cold distilled water and the acid solution was titrated to a phenolphthalein end point with 0.06307 *N* sodium hydroxide in 50% (vol) ethanol–water which had been standardized against potassium hydrogen phthalate. A 5-ml microburet which could be read directly to 0.01 ml was used. Infinity titers were taken after 10 half-lives.

Rate constants were determined by the method of least squares and the activation parameters were calculated from the Eyring equation.

The data for a typical run are indicated below for the ethanolysis of *p*-ethynylbenzyl chloride (**8**) at 83.00 ± 0.05°. Good first-order kinetics are shown in (Table X) for >69% reaction.

Table X[a]

Time elapsed, min	Titrated (HCl)	−ln (RCl)	Time elapsed, min	Titrated (HCl)	−ln (RCl)
∞	0.04974	. . .	075	0.02251	3.417
015	0.00684	3.027	105	0.02831	3.611
030	0.01121	3.121	135	0.03356	3.827
045	0.01539	3.220	180	0.03859	4.089

[a] Rate constant $(1.085 \pm 0.009) \times 10^{-4}$ sec^{-1}.

Ethanolysis Procedure (20–40° Range).—A constant-temperature bath similar to that previously described was used, except that water was used as the bath liquid and the bath was not insulated. A 10-ft coil of 0.25-in. copper tubing through which cold tap water circulated was utilized for the 20° temperature.

Approximately 240 ml of the ethanol–water solvent (50% by volume at 20.0°) was placed in a 250-ml volumetric flask and allowed to equilibrate for several hours in the bath. A sample of the halide (*ca.* 25 l.) was then quickly added (clock started) and the flask was shaken vigorously for several moments followed by reimmersion in the bath. At appropriate time intervals a sample of *ca.* 25 ml was poured from the flask into a 100-ml beaker (thermostated at the same temperature) equipped with a stirrer and a pair of electrodes.

The apparent pH of the solution was determined potentiometrically by means of a glass electrode (Leeds and Northrup, STD. 1199-30) and a Heath pH recording electrometer (Model EUW-301) with a saturated aqueous potassium chloride, calomel electrode (Leeds and Northrup, STD. 1199-31). A span setting of 5 on the electrometer was used which enabled one to read directly to 0.01 pH unit. The infinity pH was taken after at least 10 half-lives had elapsed.

Rate constants were determined from a plot of elapsed time *vs.* hydrogen ion concentration (calculated from pH reading).

The data for a typical run are indicated (Table XI) for the ethanolysis of *trans*-5-chloro-3-hexen-1-yne (**18**) at 20.00 ± 0.05°.

Table XI[a]

Time elapsed, hr	Titrated (HCl) $\times 10^3$	−ln (RCl)	Time elapsed, hr	Titrated (HCl) $\times 10^3$	−ln (RCl)
	4.170	. . .	2.5	0.646	5.652
1.0	0.0794	5.499	3.0	0.813	5.698
1.5	0.282	5.550	4.0	1.160	5.805
2.0	0.468	5.601	6.0	1.740	6.021

[a] Rate constant $(2.778 \pm 0.009) \times 10^{-5}$ sec^{-1}.

Amino Ketone Rearrangements. VI. Synthesis of 2-Alkylamino-2-phenylcyclohexanones[1a]

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Received March 14, 1966

The utility of the thermal rearrangement of α-amino ketones, α-hydroxy imines, and imine acid salts for the synthesis of a variety of 2-alkylamino-2-phenylcyclohexanones is described. The 2-aminocyclohexanones were reduced and the stereochemistry of four of the resulting amino alcohols determined.

Previous communications in this series have indicated the utility of the amino ketone rearrangement in the syntheses of 2-amino-2-methylcyclohexanones,[2] 2-anilino-2-phenylcyclohexanones,[3] and acyclic amino ketones.[4] Mechanistic aspects have also been discussed.[1,3] In this, and the accompanying communication,[5] the syntheses of a variety of aminocyclohexanones are reported and an evaluation made of the two pyrolytic routes employed. This rearrangement has

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(1) (a) Paper V: C. L. Stevens, H. T. Hanson, and K. G. Taylor, *J. Am. Chem. Soc.*, **88**, 2769 (1966). (b) Abstracted in part from the M.S. thesis of M. D. Pillai.

(2) C. L. Stevens, I. L. Klundt, M. E. Munk, and M. D. Pillai, *J. Org. Chem.*, **30**, 2967 (1965).

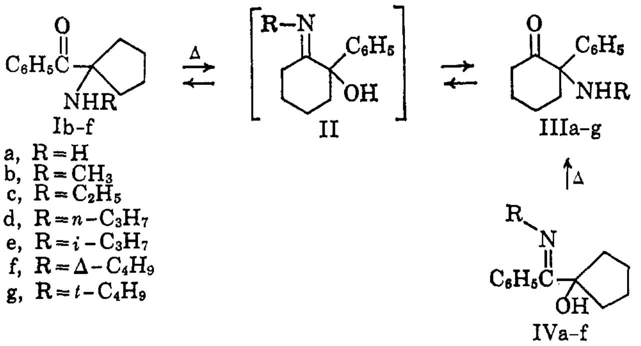
(3) C. L. Stevens, A. Thuillier, and F. A. Daniher, *ibid.*, **30**, 2962 (1965).

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

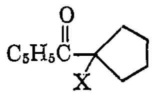
(5) C. L. Stevens, A. Thuillier, K. G. Taylor, F. A. Daniher, J. P. Dickerson, H. T. Hanson, N. A. Nielsen, N. A. Tikotkar, and R. M. Weier, *J. Org. Chem.*, **31**, 2601 (1966).

been found useful for the synthesis of D-homo steroidal amino ketones.[6] Our prime interest in these amino ketones lay in the fact that cyclopentylphenyl ketone carbon skeleton (*cf.* structures I and IV, Scheme I) appeared to give the cleanest rearrangements[3] thus making that system the most desirable one for a kinetic study which would enable an eventual analysis of steric factors and N-substituent bulk effects.

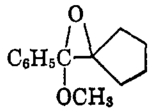
SCHEME I



Syntheses.—The synthesis of the conjugated amino ketones I was accomplished by the reaction of the epoxy ether V with the selected amine.[4,7] Hydroxy imines IV, with the exceptions of IVe and g, could be prepared by the reaction of the appropriate amine with bromo ketone VIa according to the method of Stevens and co-workers.[8] It was generally observed that, while methylamine afforded IVb in a clean reaction, the higher homologs such as n-propyl- and n-butylamine afforded mixtures of products resulting from direct displacement of bromine to give I as well as attack of amine at the carbonyl group. The hydroxy imines IV were always present in predominant amounts and were conveniently separated from the amino ketones by crystallization (at −80° for liquid hydroxy imines).



VIa, X=Br
b, X=OH



V

The reaction of isopropylamine with VIa at and below 0° afforded a mixture of products from which amino ketone Ie was isolated in 25% yield. An infrared spectrum indicated the presence of hydroxy imine IVe in the crude reaction mixture (ν_{CHCl_3} 3.05 and 6.05 μ) but no satisfactory method of isolation could be developed. The reaction of t-butylamine with VIa afforded little basic product and was investigated no further at this time. The reaction of 1-benzoylcyclopentanol, VIb, with isopropylamine at 95° provided a successful alternate synthesis of the desired hydroxy imine IVe.

Rearrangements of Amino Ketones.—Qualitative rearrangement studies were performed on several amino ketones. A kinetic study of the rearrangement of Ib has been reported[1a] wherein the intermediacy of IIb between Ib and IIIb was demonstrated. In this present work, on only one occasion was attempt made to define the intermediacy of such a species in a rearrangement. This is discussed below.

In general, rearrangements were done in hydrocarbon solvents under an inert atmosphere and afforded mixtures of products from which the desired α-aminocyclohexanones III could be isolated in relatively low yields. Fractional crystallization of the amino ketone acid salts was at times satisfactory but often chromatography of the free base mixture was necessary. These results are summarized in Table I.

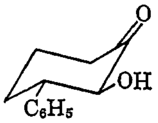
TABLE I

REARRANGEMENTS OF α-AMINO KETONES

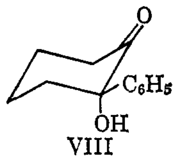
Starting compd	Temp, °C	Time, hr	Solvent	Isolation	Product	Yield, %
Ib	192	48	Decalin	Chromatog[a]	IIIb	30[b]
Ic	192	48	Decalin	Chromatog[a]	IIIc	36[c]
Id	235	14	Tridecane	Crystn[d]	IIId	30
Ie	200	50	Decalin	Crystn[e]	IIIe	29

[a] Florisil was used as adsorbent. [b] Previously rearranged neat in 20% yield (ref 4). [c] Rearranged neat (225°) in 33% yield. [d] Recrystallized from acetone. [e] Recrystallized from ethanol–ether.

The reaction of isopropylamine with epoxide V at 120° afforded, in addition to the expected amino ketone Ie, a 20% yield of 2-hydroxy-3-phenylcyclohexanone,[9] VII. It was established that this neutral product arose during an acidic hydrolysis (100°) of *basic* reaction products thus indicating that its immediate precursor was probably an imine. Control experiments on possible precursors showed that hydroxy imine IVe, hydroxy ketone VIb, and hydroxy ketone VIII *all* afforded VII when subjected to the previously used hydrolysis conditions. The formation of possible precursor IVe in an epoxy ether–aliphatic amine reaction required an abnormal direction of epoxy ether opening,[7,4] thus placing its intermediacy immediately in suspect. Since VII arose from *basic* reaction products, hydroxy ketone VIb or any *neutral* precursor to it were also ruled out as the forebearer of VII. Thus, the precursor that remained in consideration was hydroxy imine IIe, the ketimine of VIII. The following experiments substantiated this conclusion: (1) thermolysis of amino ketone Ie for a time estimated to provide a maximum yield of intermediate IIe was followed by an acid hydrolysis work-up; this indeed yielded VII (15%); (2) repetition of the epoxy ether–isopropylamine reaction was followed by a *room temperature* acid hydrolysis from which hydroxy ketone VIII was isolated as its semicarbazone. The evidence regarding the formation of VII is summarized in Scheme II. The rearrangement of Ie to IIe at 120° as demonstrated above represented the lowest temperature to date at



VII



VIII

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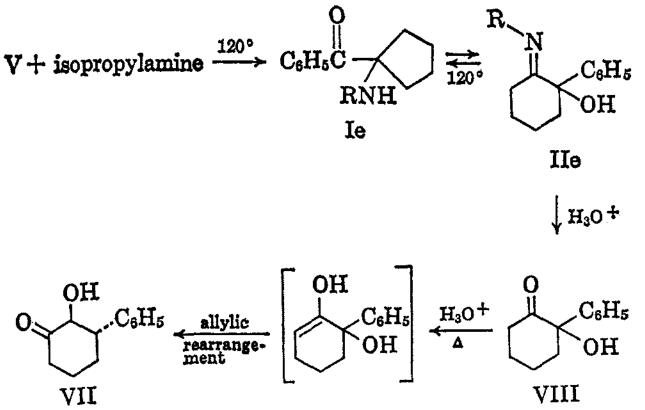
[6] (a) D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 579 (1965). (b) D. F. Morrow, M. E. Brooke, G. W. Moersch, M. E. Butler, C. F. Klein, W. A. Neuklis, and E. C. Huang, *ibid.*, **30**, 212 (1965).

[7] C. L. Stevens, M. E. Munk, C. H. Chang, K. G. Taylor, and A. L. Schy, *ibid.*, **29**, 3146 (1964).

[8] C. L. Stevens, P. Blumbergs, and M. E. Munk, *ibid.*, **28**, 331 (1963).

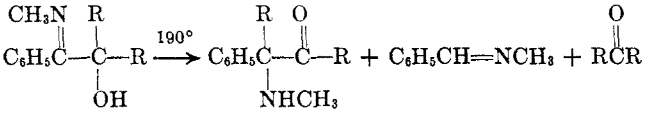
[9] P. Tomboulain and C. A. Bloomquist, *ibid.*, **24**, 1239 (1959).

SCHEME II



which an amino ketone rearrangement of this type has been observed. The hydroxy ketone VII was also isolated (19%) from a preparation of amino ketone Id *via* epoxy ether V.

Rearrangements of α-Hydroxy Imines.—It has been reported[4] that the thermolysis of hydroxy imine IXb afforded amino ketone Xb in only 7% yield. Closer examination of that reaction revealed that the major



$$C_6H_5\overset{CH_3N}{\overset{\|}{C}}-\underset{OH}{\underset{|}{\overset{R}{\overset{|}{C}}}}-R \xrightarrow{190^\circ} C_6H_5\underset{NHCH_3}{\underset{|}{\overset{R}{\overset{|}{C}}}}-\overset{O}{\overset{\|}{C}}-R + C_6H_5CH{=}NCH_3 + R\overset{O}{\overset{\|}{C}}R$$

IXa, R = CH_3 Xa,b
b, R = C_2H_5

pathway was a fragmentation reaction which afforded benzaldehyde N-methylimine and diethyl ketone as products. A similar situation prevailed also for the case of IXa. However, in view of the successful use of hydroxy imines in the synthesis of 2-amino-2-methylcyclohexanones[2] and 2-anilino-2-phenylcyclohexanones,[3] a similar approach was tested here and found to be successful. In general, the rearrangements were conducted in a manner similar to that used for amino ketone rearrangements. A comparison of results (*cf.* Table II) indicates that in every case amino ketones III were prepared in shorter time and in higher yield from the hydroxy imines IV rather than from the amino ketones I. The rearrangement of IVa in decalin solvent afforded no clean basic product perhaps due to partial dimerization of the amino ketone product. Further rearrangements of IVa were conducted on its hydrochloride salt (*vide infra*).

TABLE II

REARRANGEMENT OF α-HYDROXY IMINES

Imine	Temp, °C	Hr	Solvent	Product	Yield, %
IVb	180	2	*o*-Dichlorobenzene	IIIb	70[a,b]
IVc	200	2	Undecane	IIIc	61[b]
IVd	235	0.5	Tridecane	IIId	47[c]
IVe	180	3	*n*-Decane	IIIe	75[c]
IVf	185	3	Decalin	IIIf	51[b]

[a] Reference 1a. [b] Isolated as free base. [c] Isolated as hydrochloride salt.

Since the precursors (Ig and IVg) to the *t*-butylamino ketone IIIg were not readily prepared, another technique, previously successful for other cases,[4,6b] was attempted. The technique involved heating hydroxy ketone VIb with a large excess of *t*-butylamine and an acid catalyst at 145° for an extended period of time. The success of the technique was, of course, dependent upon the *in situ* formation (reversible) and rearrangement (irreversible) of hydroxy imine IVg. The method was successful and aminocyclohexanone IIIg was prepared in 28% yield. The structure of IIIg was indicated by unconjugated carbonyl absorption in its infrared spectrum (ν_{CHCl_3} 5.85 μ) and elemental analysis, but its low yield of formation necessitated a further indication of its structure. This was readily provided by an unexpected reaction. It was noted that the hydrochloride salt of IIIg melted with the evolution of a gas. On raising the temperature the sample resolidified and melted at the higher melting point of amino ketone IIIa. Indeed, when IIIg was treated with constant-boiling hydrobromic acid at reflux it was converted with loss of isobutylene to amino ketone IIIa in 80% yield.

The utility of acid catalysis in hydroxy imine rearrangements has been noted previously.[2,10,11] In this present work, a number of acid salts of the hydroxy imines IV were prepared and subjected to thermal rearrangement. In all cases tested, the imine salts afforded higher rearrangement yields at lower temperatures or shorter reaction times than their corresponding free bases. These results are listed in Table III.

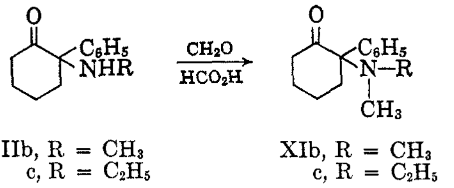
TABLE III

REARRANGEMENTS OF α-HYDROXY IMINE ACID SALTS

Imine (salt)	Temp, °C	Hr	Solvent	Product	Yield, %
IVa (HCl)	160	1	*o*-Dichlorobenzene	IIIa	61[a]
IVb (HCl)	180	0.3	*o*-Dichlorobenzene	IIIb	95[a]
IVd (HOTs)	124	8	*o*-Dichlorobenzene	IIId	80[b]
IVe (HCl)	180	0.1	None	IIIe	95[a]
IVf (HOTs)	130	8	*o*-Dichlorobenzene	IIIf	87[b]
(HBr)	165	2	None	IIIf	70[c]

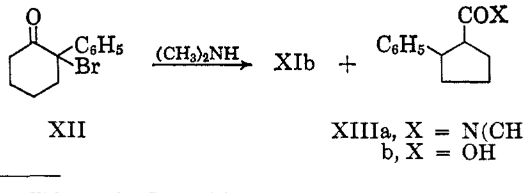
[a] Isolated as hydrochloride salt. [b] Isolated as tosylate salt. [c] Isolated as hydrobromide, but not characterized.

Clark–Eschweiler methylations of the aminocyclohexanones proceeded normally. Thus, IIIb and c were converted to the tertiary amino ketones XI b and c. A previously reported[12] preparation of amino ketone XIb was found to be suspect. It was reported



IIIb, R = CH_3 XIb, R = CH_3
c, R = C_2H_5 c, R = C_2H_5

that treatment of 2-bromo-2-phenylcyclohexanone, XII, with dimethylamine in benzene solvent afforded XIb [lit.[12] bp 138° (0.3 mm), mp 43°] in 73% yield.



XII XIIIa, X = $N(CH_3)_2$
b, X = OH

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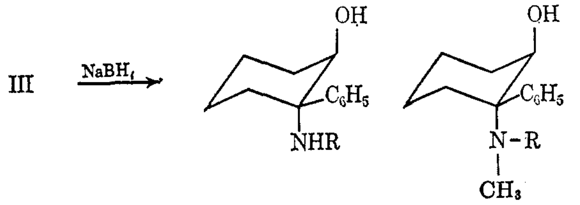
(10) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2188 (1951).

(11) I. Elphimoff-Felkin [*Bull. Soc. Chim. France*, 653 (1962)] reported the synthesis of 2-amino-2-cyclohexylcyclohexanone by thermal ring expansion of the necessary α-hydroxyimine in 96% formic acid.

(12) T. Takahashi, M. Hori, and Y. Hamashima, *Yakugaku Zasshi*, **78**, 6 (1958); see also *Chem. Abstr.*, **52**, 10911c (1958).

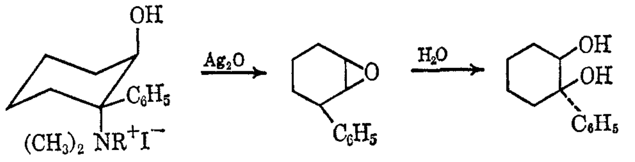
A subsequent lithium aluminum hydride treatment of XIb was further reported to give a reduction product (presumed to be an amino alcohol) with a *lower* boiling, point 90° (3 mm), than the starting ketone XIb. A repetition of the bromo ketone–amine reaction afforded the Favorskii rearrangement product, amide XIIIa, mp 47–48°, as the major product, which was isolated in 30% yield and identified by hydrolysis to the known acid XIIIb.[13] In addition, in our hands pure XIb was a liquid, not a solid, while the hydride reduction of XIb afforded a solid amino alcohol, (*vide infra*). Therefore, we propose that the low melting solid isolated by the Japanese workers was the amide product of Favorskii rearrangement.

Preparation and Stereochemistry of Aminocyclohexanols.—The sodium borohydride reduction of amino ketone IIIb was reported to give a mixture of diastereomers.[4] It has also been reported that subsequent investigation has revealed that this mixture contained at least 80% of the *trans*[14] isomer.[1a] Indeed, sodium borohydride reduction in alcoholic solution of a number of these amino ketones III afforded high yields of sharp melting amino alcohol salts indicating that the reduction, if not stereospecific, was stereoselective. Sodium borohydride reduction results are recorded in Table XI in the Experimental Section. In the cases where the stereochemistry of the amino alcohols has been studied, it has been found to be *trans*. In one approach, the amino alcohol XIVb was converted to its N-methyl homolog XVa by Clarke–Eschweiler methylation. Methyl iodide treatment of XVa afforded the quaternary iodide XVIa. This iodide, on mild treatment with alcoholic silver oxide, afforded 1-phenylcyclohexene oxide as identified by infrared spectral comparison with an authentic sample.[15a] Neutral aqueous opening of the oxide afforded the known *cis*-α-hydroxy-1-phenylcyclohexanol.[15b] Were the amino alcohol of a *cis* configuration, the Hoffman reaction should not have yielded epoxide, but rather products of demethylation and O-methyl ether formation.[16] In a similar manner amino alcohols XIVd and f were subjected to successive Clarke–Eschweiler and methyl iodide methylations (affording XVb and c and XVIb and c respectively). Subsequent Hofmann and hydrolysis reactions indicated a *trans* stereochemistry for both XIVd and f.



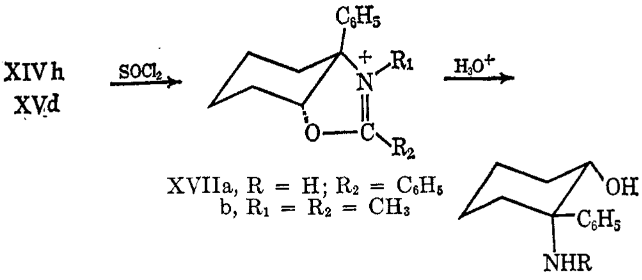
XIVa, R = H
b, R = CH_3
c, R = C_2H_5
d, R = n-C_3H_7
e, R = i-C_3H_7
f, R = n-C_4H_9
g, R = t-C_4H_9
h, R = C_6H_5CO

XVa, R = CH_3
b, R = n-C_3H_7
c, R = n-C_4H_9
d, R = CH_3CO



XVIa, R = CH_3
b, R = n-C_3H_7
c, R = n-C_4H_9

In a second approach amino alcohol XIVa was converted to its N-benzoyl derivative XIVh. Thionyl chloride treatment of benzamide XIVh converted it to a hydroscopic hydrochloride with strong infrared absorption at 6.15 μ ($C{=}N^+$). This hydroscopic salt, presumably oxazoline XVIIa, afforded the *cis* amino alcohol XVIIIa on vigorous acid hydrolysis. N-Benzoylation of the *cis* XVIIIa afforded an amide, XVIIIc, identical with the major product of mild aqueous treatment of oxazoline XVIIa. When both benzamides XIVh and XVIIIc were subjected to alcoholic hydrogen chloride, an infrared analysis indicated that N → O acyl migration took place only in the case of XVIIIa, the amide with the assigned *cis* stereochemistry. In a similar manner, successive thionyl chloride and vigorous acid treatments of acetamide XVd afforded *cis* amino alcohol XVIIIb, *via* the intermediate oxazolinium derivative XVIIb. The two approaches were related when XIVa was converted to XIVd by acylation with propionic anhydride followed by lithium aluminum hydride reduction.



XVIIa, R = H; R_2 = C_6H_5
b, R_1 = R_2 = CH_3

XVIIIa, R = H
b, R = CH_3
c, R = C_6H_5CO

Thus, the *trans* stereochemistry of amino alcohols XIVa, b, d, and f is indicated by their chemical reaction. The *trans* stereochemistry of alcohols XV is indicated by synthesis, and the stereochemistry of XIVc, e, and g is tentatively assigned, by analogy, as *trans*. Definitive assignment, especially in the cases of XIVe and g (bulky N substituents), requires further experiment.

Experimental Section

Melting points are uncorrected and were obtained on a Thomas-Hoover melting point apparatus. Compounds Ib, IIIb, IVb, and related derivatives and reduction products are reported in ref 1a. pK_a' values were obtained in 50% methanol-water on apparatus previously described.[17] Elemental analyses were performed by Midwest Microlab, Inc. Hydrochloride salts, except where noted, were prepared using saturated hydrogen chloride–isopropyl alcohol.

Synthesis of 1-Alkylamino-1-benzoylcyclopentanes, I.—Epoxy ether V[4] was treated with the selected amine by the general procedure previously described.[7] Often, the amino ketone was isolated as its crystalline hydrochloride salt and the free base prepared therefrom. Crude reaction mixtures were initially

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[13] W. Baker and W. G. Leeds, *J. Chem. Soc.*, 974 (1948).

[14] *trans* heteroatom substituents.

[15] (a) Prepared by the procedure of S. Nametkin and N. Iwanoff, *Ber.*, **56B**, 1805 (1923). (b) J. Boeseken, *ibid.*, **56B**, 2409 (1923).

[16] Such is the case with *cis*-2-dimethylaminocyclohexanol methohydroxide: A. C. Cope, E. Ciganek, and J. Lazar, *J. Am. Chem. Soc.*, **84**, 2591 (1962).

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

TABLE IV

1-ALKYLAMINO-1-BENZOYLCYCLOPENTANES, I

Compd	Yield, %[a]	Bp or Mp, °C	Carbon % Calcd	Carbon % Found	Hydrogen % Calcd	Hydrogen % Found	Nitrogen % Calcd	Nitrogen % Found
Ic[b]	76	93 (0.1 mm)	77.38	77.64	8.81	9.03	6.45	6.44
Id[c]	50	82 (0.001 mm)	77.88	78.12	9.15	9.10	6.05	6.33
Ie[d]	53	30–31	77.88	78.01	9.15	9.19	6.05	6.10
If[e]	63	91 (0.06 mm)	78.32	78.58	9.44	9.67	5.72	5.94

[a] Prepared from epoxy ether V and amine. [b] n^{22}_{D} 1.5325. [c] n^{22}_{D} 1.5299; d^{25}_{4} 1.030. [d] Yield 25% from bromo ketone VIa. [e] n^{25}_{D} 1.5254.

TABLE V

DERIVATIVES OF 1-ALKYLAMINO-1-BENZOYLCYCLOPENTANES

Derivative	Mp, °C	Recrystn[a] solvent	$\mathrm{p}K_a'$[b]	Carbon % Calcd	Carbon % Found	Hydrogen % Calcd	Hydrogen % Found	Nitrogen % Calcd	Nitrogen % Found
Ic (HCl)	183–184	A	7.55	66.25	66.11	7.94	7.91	5.52	5.37
Id (HCl)	199–200 (d)	B	7.22	67.26	67.35	8.28	8.36	5.23	5.37
Ie (HCl)	192–193	A	7.20	67.26	66.89	8.28	8.48	5.23	5.22
If (HCl)	146–147	A	7.32	68.18	68.12	8.58	8.69	4.97	5.04

[a] A, ethanol–ether; B, chloroform–ether. [b] In 50% methanol–water.

TABLE VI

1-(α-ALKYLIMINOBENZYL)CYCLOPENTANOLS, IV

Compd	Yield, %	Bp or Mp, °C	Carbon % Calcd	Carbon % Found	Hydrogen % Calcd	Hydrogen % Found	Nitrogen % Calcd	Nitrogen % Found
IVa[a]	57	90–91	76.15	76.16	7.99	7.87	7.40	6.66
IVc[b]	82	93 (0.3 mm)	77.38	77.38	8.81	8.87	6.45	6.31
IVd[c]	80	63 (0.001 mm)	77.88	77.63	9.15	9.19	6.06	5.86
IVe[d]	63	85–6	77.87	77.88	9.15	9.10	6.06	5.87
IVf[e]	50	82 (0.15 mm)	78.32	78.44	9.44	9.30	5.72	5.69

[a] Recrystallized from hexane; very hygroscopic; low N value due to probable hydrolysis. [b] n^{25}_{D} 1.5307; d^{25}_{4} 1.025. [c] n^{25}_{D} 1.5272; d^{25}_{4} 1.016. [d] Prepared from 1-benzoylcyclopentanol; recrystallized from hexane. [e] n^{25}_{D} 1.5190; d^{25}_{4} 1.004.

TABLE VII

SALTS OF 1-(α-ALKYLIMINOBENZYL)CYCLOPENTANOLS, IV

Derivative	Mp, °C	Carbon % Calcd	Carbon % Found	Hydrogen % Calcd	Hydrogen % Found	Nitrogen % Calcd	Nitrogen % Found
IVa (HCl)[a]	130						
IVb (HCl)[b]	174–176	65.12	65.19	7.57	7.61	5.84	5.79
(HOTs)	121–122	63.97	63.69	6.70	6.71	3.73	3.78
IVd (HOTs)[c]	122–124	65.48	65.23	7.24	7.33	3.47	3.35
(HBr)	141–143 dec	57.70	57.53	7.10	7.16	4.49	4.55
IVe (HCl)[d]	160–161	67.26	67.13	8.28	8.46	5.23	5.18
(HOTs)[e]	146–148	65.48	65.64	7.24	7.03	3.47	3.46
IVf (HBr)	142–146	58.99	59.08	7.36	7.51	4.31	4.47
(HOTs)	89–90	66.16	65.92	7.49	7.56	3.36	3.45

[a] Very hygroscopic. [b] $\mathrm{p}K_a'$ 6.65. [c] Could be recrystallized from dried chloroform–ether. [d] Recrystallized from absolute ethanol–ether; $\mathrm{p}K_a'$ 6.47. [c] Recrystallized from chloroform–ether.

subjected to hot, aqueous acid hydrolyses to hydrolyze any α-amino imine[7] that might have formed in the reaction. Amino ketones and their salts are recorded in Tables IV and V.

Synthesis of 1-(α-Alkyliminobenzyl)cyclopentanols, IV.—The preparation of 1-(α-*n*-butyliminobenzyl)cyclopentanol, IVf, is illustrative. Bromo ketone VIa,[4] 23 g (0.09 mole), was cooled (−78°) and cold (−50°) *n*-butylamine was added with stirring. Dissolution was complete on warming to −40°. The reaction was kept at −20° (freezer) for 40 hr. Excess *n*-butylamine was distilled *in vacuo* and the resulting gum was treated with 500 ml dry hexane, whereupon *n*-butylamine hydrobromide crystallized and was removed by filtration. The filtrate was concentrated to 300 ml and then cooled in a Dry Ice–acetone bath, whereupon the hydroxy imine IVf crystallized. The crystals were filtered and washed with hexane at −78° and then distilled *in vacuo*. The fraction with bp 82° (0.15 mm) afforded 11.0 g (50%) of IVf. Hydroxy imine IVf was isolated as its tosylate salt in 60% yield from a similar preparation. Table VI records the hydroxy imines IV.

Preparation of Hydroxy Imine Salts.—Salts of IV were prepared by precipitation from solutions of IV in scrupulously dried ether. For hydrochlorides, dried, gaseous hydrogen chloride of saturated solutions of hydrogen chloride in ether of 2-propanol was added; for hydrobromides, gaseous hydrogen bromide was passed through or over the ethereal solution; for tosylates, a dried (by azeotropy) benzene solution of *p*-toluenesulfonic acid was added. On occasion, the imine salts could be recrystallized from dried solvent pairs. When highly pure reactants and solvents were used, the initially precipitated salt was usually of analytical purity. The salts of IV are recorded in Table VII.

Sodium Borohydride Reductions of I and IV.—The borohydride reductions of certain amino ketones I and hydroxy imines IV were carried out as described below for the 2-alkylamino-2-phenylcyclohexanones III. The results are tabulated in Table VIII.

1-Benzoyl-1-isopropylaminocyclopentane, Ie.—To ice-cold 1.75 g (0.0069 mole) of bromo ketone VIa[4] was added 30 ml of isopropylamine. The mixture was kept at 0° for 3 hr then the temperature was slowly raised to 25° and the excess isopropylamine was distilled *in vacuo*. An infrared spectrum of the residual oily product showed bands at 3.0 (weak), 5.95, 6.08, 6.28 and 7.3 μ indicating a mixture of α-amino ketone, α-hydroxy imine and possibly an elimination product.

This mixture was treated with 3 *N* hydrochloric acid and heated on a steam bath for 2 hr. After cooling it was washed twice with

TABLE VIII

SODIUM BOROHYDRIDE REDUCTIONS OF I AND IV

Compd reduced	Mp, °C, of product (salt)	Recrystn solvent	Carbon %		Hydrogen %		Nitrogen %	
			Calcd	Found	Calcd	Found	Calcd	Found
Ic	65–66[a]	Petroleum ether (bp 30–60°)	76.69	76.71	9.59	9.67	6.39	6.36
	270 (HCl)	Ethanol–ether	65.75	65.63	8.67	8.72	5.47	5.28
Id	269–271 (HCl)	Methanol–acetone	66.78	67.06	8.97	9.20	5.19	5.02
Ie	275–276 (HCl)	Chloroform–ether	66.78	66.88	8.97	9.08	5.19	5.24
IVd	207–209 (HCl)	Methylene chloride–ether	66.78	66.62	8.97	9.15		
IVe	57–58[b]	Petroleum ether (30–60°)	77.25	77.14	9.87	9.74	6.01	5.91

[a] pK_a' 9.50. [b] pK_a' 8.40.

ether to remove neutrals. The aqueous solution was made basic with 10% aqueous sodium hydroxide and extracted four times with ether. The combined ether extracts were dried (sodium sulfate) and the ether distilled yielding a residual brown syrup. After decolorizing with Norit the resulting light yellow syrupy liquid was crystallized from pentane to give 0.4 g (25.4%) of Ie: mp 30–31°; infrared ($CHCl_3$), 5.95, 6.27 (weak) and 7.25 μ; ultraviolet λ_{max} 242, (ϵ 9.38 × 10^3).

1-(α-Isopropyliminobenzyl) cyclopentanol, IVe.—A solution of 6 g (0.0316 mole) of 1-benzoylcyclopentanol[18] (VIb) in 15 ml of isopropylamine in a sealed tube was heated at 95° in an autoclave for 24 hr. The excess amine was distilled *in vacuo* and the residual oil was taken up in pentane and dried (sodium sulfate). The pentane extract was evaporated to one-half its volume, whereupon product IVe began crystallizing. This was collected (mp 78–81°) and was recrystallized from a minimum quantity of dry pentane to yield 4.6 g (63%) of white needles: mp 85–86°; infrared ($CHCl_3$) 3.05 (strong), 6.06 and 6.25 μ (weak).

Isolation of 2-Hydroxy-3-phenylcyclohexanone (VII) from the Preparation of α-Amino Ketone Ie.—In a hard glass tube was taken 4.0 g (0.0196 mole) of epoxy ether V[4] and 10 ml of dry isopropylamine. The tube was sealed and heated in an autoclave at 120° for 20 hr. The tube was opened and the excess isopropylamine was removed *in vacuo*. To the residual brown liquid, 35 ml of 4 *N* hydrochloric acid solution was added and extracted immediately twice with ether to remove neutral products, if any. The clear, aqueous solution was heated on a steam bath for 2 hr. The solution was cooled and extracted three times with ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and the ether distilled *in vacuo*. This gave 1.1 g of light brown solid, mp 110–113°. This, after three crystallizations from benzene–petroleum ether (bp 40–45°), gave constant-melting white solid: 750 mg (20%); mp 121–121.5°; mixture melting point with a sample prepared by the lit.[9] method was undepressed; infrared ($CHCl_3$) 2.88, 5.82 and 6.23 μ; ultraviolet λ_{max} 280 (ϵ 86.1 in absolute ethanol); nmr ($CDCl_3$) τ 2.64–2.84, 5H (multiplet) phenyl, τ 5.8, 1H (doublet, J = 10.4) C-2, τ 6.6, 1H (singlet) OH; τ 7.32–7.65, 2H (multiplet) overlapped C-3, C-6 equatorial, τ 8.0–8.25, 5H (multiplet) C-4, C-5, and C-6.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.80; H, 7.37; O, 16.83. Found: C, 75.73; H, 7.46; O, 17.00.

Alternate Preparations of Hydroxy Ketone VII. A. From Ie.—When Ie was subjected to the acid hydrolysis work-up conditions described above, VII was obtained in 26% yield with mp 118–120°.

B. From VIb.—When 500 mg of VIb was refluxed 2.5 hr with 500 mg of isopropylamine hydrochloride in 20 ml of 4 *N* hydrochloric acid, VII was isolated in 52% yield with mp 119–120°. In the absence of isopropylamine hydrochloride, no VII was isolated. In the absence of 4 *N* hydrochloric acid, no VII was isolated.

C. From VIII.—When 500 mg of VIII[19] and 400 mg of isopropylamine hydrochloride were refluxed 2 hr in 25 ml of 4 *N* hydrochloric acid, 325 mg (65%) of VII was isolated with mp 119–120°. Longer reaction times caused increasing amounts of dehydration from which only small amounts of 2-phenylcyclohex-2-enone could be isolated. Hydrochloric acid, but not isopropylamine hydrochloride, was found necessary for conversion of VIII to VII.

Isolation of VII from Thermolysis of Amino Ketone Ie.—A solution of 1.0 g (0.0037 mole) of amino ketone Ie in 6 ml of distilled decalin was refluxed for 5 hr in an oil bath maintained at 210°. The solution was then divided in half. From one portion decalin was distilled *in vacuo* and the residue taken up in cold 4 *N* hydrochloric acid and extracted once with ether to remove traces of decalin and any other neutral decomposition products. The aqueous solution was heated on the steam bath for 2 hr and subjected to the usual work-up. The resulting gummy solid was crystallized from benzene–petroleum ether (bp 40–45°) to give 80 mg (19.3%) of IV, mp 116–119°. This was recrystallized to give 60 mg of VII, mp 119.5–120.5°. Mixture melting point with an authentic sample was undepressed.

The second portion of the above reaction mixture was used in an unsuccessful attempt to isolate a sodium borohydride reduction product of IIe.

Isolation of Hydroxy Ketone VIII from Epoxy Ether V with Isopropylamine.—A solution of 850 mg (0.0033 mole) of epoxy ether V in 5 ml of isopropylamine in a sealed tube was heated in an autoclave at 135° for 22 hr. The excess isopropylamine was distilled *in vacuo*. The residual light brown oil was treated with 10 ml of 4 *N* hydrochloric acid and was extracted immediately twice with ether to remove any neutrals present. The clear aqueous solution was kept at room temperature for 12 hr. The solution started turning turbid after about 4 hr. It was heated for 10 min on steam bath, cooled, and extracted three times with ether. The combined ether extracts were dried (sodium sulfate) and evaporated to yield about 150 mg of oil. This was immediately converted to its semicarbazone by a standard procedure to yield 130 mg of gummy solid, which after crystallization gave 55 mg of crystalline white solid, mp 193–195°. A mixture melting point with the authentic semicarbazone of VIII[19] was undepressed. The semicarbazone of hydroxy ketone VII melted at 201–02° (lit.[9] 199–201°).

Rearrangement of Amino Ketones I.—The thermal rearrangement of Ic is illustrative. The hydrochloride salt of Ic, 6.03 g, was converted to its corresponding free base which in turn was dissolved in 50 ml of distilled decalin and heated at 192° under a slow helium sweep for 48 hr. The nonhydrolizable basic fraction was subjected to chromatography over Florisil and the products isolated as their corresponding hydrochloride salts. Elution with 5–20% ether–petroleum ether (bp 30–60°) afforded 0.80 g (13%) of recovered Ic hydrochloride. Elution with 20–40% ether–pentane and 25% acetone–pentane afforded 2.2 g (30%) of amino ketone VIc hydrochloride. The yields of other similar rearrangements are recorded in Table I. The physical properties of the rearranged products III were recorded in Tables IX and X.

Thermolysis of 2-(α-Methyliminobenzyl)-propan-2-ol, IXa.—When a solution of 10 g of hydroxy imine IXa[8] in 30 ml of decalin was heated to 190° a low boiling fraction was formed. Collection of this fraction over 6 hr afforded 2 g of liquid identified as acetone by conversion to its 2,4-dinitrophenylhydrazone. The undistilled portion was extracted with 6 *N* hydrochloric acid and the extract (containing *basics*) was heated for 8 hr. Subsequent extraction with ether and distillation afforded 4 g of benzaldehyde identified by conversion to its 2,4-dinitrophenylhydrazone. Further work-up of the acid fraction afforded only 0.25 g of crude amino ketone Xa hydrochloride.[4]

In a similar experiment, thermolysis of hydroxy imine IXb[4] afforded only 8% of amino ketone Xb.[4] The balance of material was accounted for by the isolation diethyl ketone (characterized as its 2,4-dinitrophenylhydrazone) and benzaldehyde-N-methylimine (characterized by hydrolysis to benzaldehyde and oxidation to benzoic acid).

Rearrangement of Hydroxy Imines IV.—The rearrangement of IVf is illustrative. A solution of 11.0 g of IVf in 250 ml of

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(18) I. Elphmoff-Felkin, *Bull. Soc. Chim. France*, 784 (1955).

(19) B. Tchoubar, *Bull. Soc. Chim. France*, 581 (1958).

TABLE IX

2-ALKYLAMINO-2-PHENYLCYCLOHEXANONES, III AND IX

Compd	n^{25}_D	Bp, °C	Carbon % Calcd	Carbon % Found	Hydrogen % Calcd	Hydrogen % Found	Nitrogen % Calcd	Nitrogen % Found
IIIa	1.5541	35 (0.05 mm)	76.15	76.00	7.99	8.05	7.40	7.42
IIIc	1.5373	108 (0.5 mm)	77.38	77.18	8.81	8.79	6.45	6.55
IIId[a]	1.5311	67 (0.001 mm)	77.88	77.66	9.15	9.18	6.06	5.98
IIIe[b]	1.5262	101 (0.04 mm)	77.88	77.71	9.15	9.32	6.06	5.96
IIIf[c]	1.5261	96 (0.05 mm)	78.32	78.37	9.44	9.28	5.72	5.74
XIb[d]	1.5425	83 (0.05 mm)	77.38	77.18	8.81	8.76	6.45	6.41
XIc[e]	1.5372	109 (0.3 mm)	77.88	78.08	9.15	9.14	6.06	5.89

[a] d^{25}_4 1.032. [b] Mp 27–8°. [c] d^{25}_4 1.025. [d] d^{25}_4 1.069. [e] d^{25}_4 1.1114.

TABLE X

2-ALKYLAMINO-2-PHENYLCYCLOHEXANONE SALTS

Compd (salt)	Mp °C	pK_a'	Recrystn solvent[a]	Carbon % Calcd	Carbon % Found	Hydrogen % Calcd	Hydrogen % Found	Nitrogen % Calcd	Nitrogen % Found
IIIa (HCl)	242–243	7.40	. . .	63.86	63.60	7.15	7.17	6.21	6.22
IIIc (HCl)	239–240	8.0	A	66.25	66.56	7.94	8.07	5.52	5.52
IIId (HCl)	209–210	7.80	B	67.26	67.15	8.28	8.36	5.23	5.01
IIIe (HCl)	231–233	7.80	A	67.26	67.29	8.28	8.37	5.23	5.15
IIIf (HCl)	186–189	7.90	A	68.18	68.40	8.59	8.73	4.97	5.10
(HOTs)	167–182	. . .	A	66.16	66.03	7.49	7.58	3.36	3.46
IIIg (HCl)	202–203	8.10	B	68.18	68.35	8.59	8.59	4.97	5.16
XIb (picrate)	199–200	7.80[b]	A	53.81	54.10	4.97	5.26	12.55	12.42
XIc (picrate)	189–190	8.20[b]	A	54.78	54.91	5.25	5.35	12.17	12.11

[a] Solvent A, ethanol–ether; B, acetone. [b] Obtained on free base.

decalin was heated at 185° for 3 hr under helium. The reaction mixture was diluted with 100 ml of ether and the basics extracted with three 100-ml portions of 4 *N* hydrochloric acid. After drying, the ether solution was evaporated and the residue distilled. The fraction boiling at 95–96° (0.05 mm) afforded 5.6 g (51%) of IIIf. The yields of similar rearrangements are recorded in Table II. The properties of the products III are recorded in Tables IX and X.

Rearrangement of Hydroxy Imine IV Salts.—The rearrangement of IVb hydrochloride is illustrative. Dissolution of 0.50 g of IVb hydrochloride in 5 ml of *o*-dichlorobenzene was effected during heating to 180°. The solution was maintained at that temperature for 20 min and then cooled overnight. Filtration of the resulting crystals afforded 475 mg (95%) of IIIb hydrochloride, mp 255–258°, lit.[4] mp 256°; mixture melting point was not depressed.

Similar rearrangements often required one or two recrystallizations to provide analytical material. Yields and conditions of these rearrangements are recorded in Table III; the products are recorded in Tables IX and X.

Synthesis of 2-*t*-Butylamino-2-phenylcyclohexanone, IIIg.—A solution of 10.0 g (0.053 mole) of hydroxy ketone VIb[18] in 30 ml of *t*-butylamine (containing 3 drops of saturated 2-propanol–hydrogen chloride) was heated in a steel autoclave at 145° for 96 hr. The excess amine was distilled and the nonhydrolizable basic fraction was isolated as a dried ethereal solution by employing the usual work-up. After decolorizing with Norit, the hydrochloride salt was prepared. Recrystallization from acetone afforded 3.0 g (28%) of IIIg as white crystals: mp 202–203° (dec); infrared (mull) 3.1 (NH), 5.81 (C=O), and 7.20 (C–CH_3) μ. Other properties are recorded in Table X.

Removal of *t*-Butyl Group from IIIg Hydrochloride.—A solution of 3.0 g (0.010 mole) of IIIg hydrochloride in 500 ml of constant boiling hydrobromic acid was refluxed for 8 hr. The resulting solution was concentrated to 50 ml *in vacuo* and then subjected to the usual work-up. The basic fraction afforded 1.8 g (80%) of IIIa hydrochloride as white crystals, mp 242–243° dec. Recrystallization from methylene chloride–ether did not raise the melting point. A mixture melting point with IIIa hydrochloride prepared by the rearrangement route was undepressed and their infrared spectra were superimposable. Other properties are recorded in Table X.

Derivatives of 2-Alkylamino-2-phenylcyclohexanones, III.—A. **Acetyl derivatives** of IIIb, d and f were prepared by acetylation in pyridine at steam-bath temperatures for 1 hr. Products were isolated by normal procedures, recrystallized from hexane or benzene–hexane mixtures, and showed characteristic infrared absorption at 5.75 and 6.15 μ.

N-Acetyl IIIb had mp 150–151°. *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.58; H, 7.97; N, 5.83.

N-Acetyl IIId had mp 102–103°. *Anal.* Calcd for $C_{17}H_{23}NO_2$: C, 74.73; H, 8.48; N, 5.13. Found: C, 74.99; H, 8.71; N, 5.38.

N-Acetyl IIIf had mp 76–88°. *Anal.* Calcd for $C_{18}H_{25}NO_2$: C, 75.21; H, 8.77; N, 4.87. Found: C, 75.12; H, 8.99; N, 4.85.

B. **Clarke–Eschweiler Derivatives.**—Amino ketones IIIb and c were methylated by heating in formaldehyde–formic acid solution under standard Clarke–Eschweiler conditions. Conventional work-up afforded the ketones XIb and c. These are recorded in Table IX. Salts of XI with halogen acids were too hygroscopic to handle conveniently. Picrates were good derivatives and are recorded in Table X.

The Reaction of 2-Bromo-2-phenylcyclohexanone with Dimethylamine.—A solution of 3.5 g of 2-bromo-2-phenylcyclohexanone, XII,[20] and 1.4 g of anhydrous dimethylamine in benzene was heated in a sealed tube at 60–70° for 3 hr, thus duplicating the conditions of reference 12. The solvents were distilled *in vacuo* leaving a semisolid which was triturated in ether. The triturate was extracted with four portions of 10% hydrochloric acid and the aqueous acid extract neutralized and extracted with ether. This crude ether extract contained some amide as shown by infrared absorption at 6.05 μ and the fact that after neutralization and alumina chromatography 85 mg of amide XIIIa was isolated, mp 45–47°. The ether solution carrying the neutral fraction afforded 1.43 g of crude neutrals with infrared absorption at 6.05 μ.

Separate experiments showed that hydrochloric acid would dissolve the amide as it would a base and prevent its extraction by ether. Thus, at room temperature 10 ml of 10% hydrochloric acid dissolved 76% of a 50-mg sample of XIIIa, 10 ml of 12.5% hydrochloric acid dissolved 91%, and 10 ml of 15% hydrochloric acid dissolved the whole sample. In addition, repeated ether washings of a dissolved sample (15% hydrochloric acid) extracted only 40% of XIIIa.

From the neutral fraction, after treatment with Norit, 810 mg of amide XIIIa was obtained by crystallization from hexane: mp 45–7°; infrared 6.07 μ.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.59; H, 8.72; N, 6.38.

The amide was identified by hydrolysis in 83% yield to the known[13] 2-phenylcyclopentanecarboxylic acid using refluxing

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[20] W. E. Bachmann and L. B. Wick, *J. Am. Chem. Soc.*, **72**, 3388 (1950).

TABLE XI

2-ALKYLAMINO-2-PHENYLCYCLOHEXANOLS AND SALTS

Compd (salt)	Mp, °C	pK_a'	Yield, %	Carbon %		Hydrogen %		Nitrogen %	
				Calcd	Found	Calcd	Found	Calcd	Found
XIVa (HCl)	199–200	8.09	85	63.28	63.15	7.97	8.20		
XIVc (HCl)	205.5–207	8.50	85	65.73	65.65	8.68	8.81		
XIVd (HCl)	221–223	8.05	87	66.78	66.61	8.97	8.90	5.19	5.32
XIVe (HCl)	239–240	8.39	76[a]	66.78	66.90	8.97	9.13	5.19	5.33
XIVf	60–60.5		87	77.68	77.80	10.18	10.18	5.67	5.73
XIVf (HCl)	234–237	8.05		67.70	67.83	9.23	9.04	4.94	4.89
XIVg (HCl)	202–203	8.62	84	67.70	67.97	9.23	9.41		
XIVh[b]	164–165		83	77.26	77.15	7.17	7.27		
XVa	78–80	9.0	67[c,d]	76.66	76.59	9.65	9.71	6.39	6.15
XVb (HCl)	220–221	9.16	64	67.70	67.45	9.23	9.03	4.94	4.70
XVc (HCl)	190–192	8.95	88	68.54	68.76	9.47	9.69	4.70	4.86
XVd[e]	124–126		40	72.84	72.70	8.56	8.62	5.66	5.57
XVIa[e]	144–146		86	49.87	49.94	6.70	6.94	3.88	3.94
XVIb[e]	120–121		85	52.44	52.15	7.25	7.23	3.60	3.66
XVIc[e]	119–121		75	53.60	53.64	7.50	7.58	3.48	3.43
XVIIIa (HCl)[e]	215–216	8.00	48	63.28	63.25	7.97	8.07		
XVIIIb[e]	Gum			76.05	75.80	9.33	9.48	6.82	6.80
XVIIIb (HCl)[e]	203–205	9.1	68	64.58	64.33	8.34	8.23	5.80	5.92

[a] Yield of free base with mp 92.5–94°. [b] Prepared by the method of M. T. Leffler and R. Adams, *J. Am. Chem. Soc.*, **59**, 2252 (1927), and recrystallized from chloroform–hexane. [c] Yield from Clarke–Eschweiler methylation of corresponding secondary amine. [d] By reduction of XIb the yield was 50%. [e] Prepared as separately described in Experimental Section.

hydrobromic acid, mp 85.5–86.5° (lit. 87–88°). The same acid was obtained using monomethylamine with the bromo ketone XII, followed by hydrolysis.

Preparation of *trans*-2-Monoalkylamino-2-phenylcyclohexanols.—The amino ketones III were dissolved in methanol, ethanol, or isopropanol either as the free base or as the hydrochloride salt and treated slowly with solid, excess sodium borohydride. The mixture was then stirred overnight, protected from moisture by a Drierite or potassium hydroxide drying tube. No differences were observed among the three listed solvents nor between the use of the ketone as a free base or as the hydrochloride salt.

The reaction mixture was treated with excess hydrochloric acid and the solvent removed *in vacuo*. The residue was taken up in 2–3 *N* hydrochloric acid, extracted with chloroform, and then raised to pH 12 with solid potassium hydroxide. The basic products were extracted with chloroform which was then dried with anhydrous potassium carbonate and the chloroform removed *in vacuo*. In the cases of free bases, they were crystallized from hexane, ether, or hexane–chloroform. When the hydrochloride salt was isolated, the basic residue was dissolved in anhydrous ethyl ether and treated with 2-propanol–hydrogen chloride solution. These salts usually required recrystallization from acetone or ethanol–ethyl ether. The constants of the resulting *trans*-2-monoalkylamino-2-phenylcyclohexanols and their salts are listed in Table XI.

Preparation of *trans*-2-Dialkylamino-2-phenylcyclohexanol Methiodides, XVI.—The appropriate amino alcohol XIV was subjected to standard Clarke–Eschweiler methylation to afford the amino alcohols XVa, b, and c. Where necessary, the free bases of XV were prepared by neutralization of the described salt. The resulting amino alcohols XV were refluxed in methyl iodide–methanol (3:1) solution for 2 hr. Evaporation of the solvent *in vacuo* and recrystallization from ethanol–ether afforded the methiodides XVI. Both amino alcohols XV and methiodides XVI are described in Table XI.

Hofmann Elimination Reactions.—The example of *trans*-2-dimethylamino-2-phenylcyclohexanol methiodide is illustrative. Sodium hydroxide (0.20 g, 0.005 mole) and silver nitrate (0.25 g, 0.0015 mole) were mixed in 10 ml of distilled water, forming silver oxide as a dark brown precipitate. To this mixture was added methiodide XVIa (0.40 g, 0.0011 mole) in 25 ml of absolute ethanol. This mixture was shaken manually for 20 min. At the end of this time the color of the precipitate had essentially changed from dark brown to yellow. All solids were then removed by filtration; the filtrate was extracted with three 50 ml portions of petroleum ether. The petroleum ether extracts were combined and dried over anhydrous potassium carbonate; petroleum ether was removed *in vacuo* yielding a clear colorless oil (185 mg, 96.8%) of 1-phenylcyclohexene oxide. The infrared spectrum of this oil was superimposable with a spectrum of an authentic sample prepared by the epoxidation of 1-phenylcyclohexene with *m*-chloroperbenzoic acid. Hydrolysis of the oil by refluxing in distilled water overnight yielded 57% of *cis*-1-phenyl-2-hydroxycyclohexanol,[16] as evidenced by melting point and undepressed mixture melting point (all 90–92°) with an authentic sample prepared by similar hydrolysis of independently prepared oxide. This same *cis*-diol could be prepared by the method of Adkins and Roebuck[21] using the olefin with wet performic acid.

***cis*-2-Phenyl-4-(phenyl-4,5-cyclohexaneoxazoline) Hydrochloride, XVIIa.**—A 150-mg (0.51 mmole) sample of the *trans*-benzamide XIVh was cyclized with 10 ml of thionyl chloride according to the procedure of Johnson and Shubert.[22] After the initial reaction had taken place, 50 ml of ether was added and the solution was evaporated to dryness. This yielded an amorphous solid, 87 mg (55%), which was very hygroscopic and could not be recrystallized satisfactorily. The infrared spectrum showed a strong absorption band at 6.15 μ ($N^+{=}C$).

***cis*-2-Phenyl-2-benzoylaminocyclohexanol, XVIIIc.**—To 75 mg of crude oxazoline hydrochloride was added 10 ml of a 1% solution of hydrochloric acid, and the mixture was refluxed for 30 min. After cooling, the solution was made strongly basic, and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated to dryness *in vacuo*. Recrystallization of the residue from chloroform–hexane yielded 33 mg (42%) of the *cis*-hydroxyamide XVIIIc: mp 156–157°; infrared ($CHCl_3$) 6.02 μ. A mixture melting point with the *trans* isomer XIVh was depressed. This amide was not characterized further.

***cis*-2-Phenyl-2-aminocyclohexanol Hydrochloride, XVIIIa.**—To 87 mg of crude *cis*-oxazoline hydrochloride was added 20 ml of a 4% solution of hydrochloric acid, and the resultant mixture was allowed to reflux for 8 hr. After cooling, the solution was made basic with pellets of sodium hydroxide and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and filtered; ether was removed *in vacuo*. The remaining white solid was dissolved in absolute methanol and passed over a 1.2 × 10 cm column of Dowex 50–2X (H^+). The column was first washed with 200 ml of anhydrous methanol, and the basic material was removed by eluting with 50 ml of methanolic ammonia (1.5 ml of concentrated aqueous ammonium hydroxide added to 50 ml of methanol). Upon evaporation of the ammoniacal layer a gum remained which was redissolved in a small

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(21) H. Adkins and A. K. Roebuck, *J. Am. Chem. Soc.*, **70**, 4041 (1948).

(22) W. S. Johnson and E. N. Schubert, *ibid.*, **72**, 2187 (1950).

amount of anhydrous ether. The hydrochloride salt was precipitated as a gelatinous solid. This was dissolved in 100 ml of acetone and concentrated *in vacuo* until the solution became turbid. After cooling, 30 mg (48%), of white solid was collected, mp 212–214°. Two recrystallizations from ethanol–ether yielded analytical material, mp 215–216°. A mixture melting point with the *trans* amino alcohol hydrochloride XIVd was depressed to 175–185°; *cf* also Table XI.

N → O Acyl Migration of *cis*-2-Benzoylamino-2-phenylcyclohexanol, XVIIIc.—To 50 mg of XVIIIc prepared by the N-benzoylation of XVIIIa was added 2 ml of isopropyl alcohol saturated with dry hydrogen chloride. The resultant mixture was allowed to stand at room temperature for 114 hr, and then evaporated to dryness *in vacuo*. An infrared spectrum of the remaining hygroscopic solid showed essentially complete acyl migration as indicated by the strong absorption band at 5.85 μ (ester) and none at 6.02 μ (amide).

Attempted N → O Migration of XIVh.—A solution of 0.1 g of XIVh in isopropyl alcohol saturated with dry hydrogen chloride gas was allowed to stand for 114 hr at room temperature and worked up as above. An infrared spectrum of the reaction mixture at this point showed only the initial amide absorption band at 6.02 μ with no carbonyl absorption in the 5.85-μ region (ester C=O). Further work-up yielded 97% of the starting amide XIVh.

***trans*-2-(N-Methylacetamido)-2-phenylcyclohexanol, XVd.**—Amino alcohol XIVb[1a] (5.22 g, 0.025 mole) was dissolved in 150 ml of freshly distilled triethyl amine and the solution cooled to 0°. One equivalent (2 ml) of acetyl chloride was dissolved in 100 ml of benzene and added very slowly to the amide solution. Throughout the 3-hr addition the temperature was kept at 0° and the reaction mixture stirred magnetically. The mixture was then allowed to come slowly to room temperature and then stirred an additional 2 hr. Ethanol (2 ml) was added; all solvents were removed *in vacuo*. The resulting sludge was washed three times with 100-ml portions of benzene, each washing being filtered. The benzene was removed *in vacuo* and the resulting oil crystallized from chloroform–petroleum ether to give 2.64 g (44%) of XVd, mp 120–5°. Recrystallization afforded white crystals: mp 124–6°; infrared ($CHCl_3$) 2.90 and 6.05 μ. *Cf.* also Table XI.

***cis*-2-Methylamino-2-phenylcyclohexanol, XVIIIb.**—In 50 ml of freshly distilled, colorless thionyl chloride was dissolved XVb (1.6 g, 0.0065 mole). The solution was heated with magnetic stirring at 50 ± 5° for 8 hr and then allowed to stand overnight. The solution was poured on ice and stirred manually until the evolution of hydrogen chloride ceased. The pH of the solution was raised to 12 with potassium hydroxide and all organic material extracted with chloroform. The chloroform was removed *in vacuo* and the residue heated in a steam bath with 50 ml of 6 *N* hydrochloric acid overnight. Neutrals were removed by chloroform extraction; the pH of the solution was raised to 12. The bases were extracted with chloroform; the layer was dried over anhydrous potassium carbonate. The chloroform was then removed *in vacuo* and the residue dissolved in ether. Addition of 2-propanol–hydrogen chloride solution gave no crystals and so all solvents were removed *in vacuo*. Crystals were obtained from a solution of acetone–ethyl ether–petroleum ether (1.085 g, 68%, mp 199–204°). Recrystallization gave XVIIIb (HCl), mp 203–205°.

The free base was obtained in the usual fashion. All attempts to crystallize the compound failed and so the compound was distilled at approximately 100° (0.05 mm) to give a clear gum; *cf.* Table XI.

Conversion of *trans* Alcohol XIVa to *trans* Alcohol XIVd.—Acylation of 75 mg of XIVa was effected with propionic anhydride by standard procedure. The product, an oil, had infrared absorption at 6.02 μ and was not characterized further. The oil was dissolved in 30 ml of ether and refluxed with 40 mg of lithium aluminum hydride for 12 hr. Work-up afforded a basic fraction from which was isolated 60 mg (76%) of XIVd hydrochloride, mp 220–222°. Mixture melting point with a sample prepared by reduction of IIId was not depressed.

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Amino Ketone Rearrangements. VII.[1] Synthesis of 2-Methylamino-2-Substituted Phenylcyclohexanones

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The synthesis of a variety of 2-methylamino-2-substituted phenylcyclohexanones by thermal rearrangement of α-amino ketones, α-hydroxy imines, and imine salts is described. Some chemistry related to those compounds bearing *o*-phenyl substituents is also described.

The preceeding paper describes the synthesis of aminocyclohexanones of type III, by thermal rearrangement of isomers of type I and IV, wherein the nitrogen substituent was varied. This paper reports results of a similar type wherein phenyl substituents were varied. In general, the synthetic techniques described in paper VI were successfully extended to the present series of compounds, but important chemical differences related to the obvious structural differences were noted, and these are emphasized in the discussion following. (See Scheme I.)

Syntheses.—The conjugated amino ketones I were prepared as previously described.[1] Hydroxy imines IV with the exception of IVa were prepared by the method of Stevens and co-workers.[1,3] The *ortho*-phenyl substituents on bromo ketones Va, b, and c afforded varying results on reaction with liquid methylamine. These reactions were, with the exception of Va, synthetically useful for preparation of the desired hydroxy imines IVb and c since these could be isolated by crystallization. Thus, IVb and c were prepared in 66 and 63% yield, respectively. On the other hand, synthesis of hydroxy imine IVa by this route failed, with amino ketone Ia being the only product isolated (67%). Further, the reaction of bromo ketone Va in methylamine at −6° had a half-life of about 2 min and produced no neutral products. By

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[1] Paper VI: see accompanying publication, *J. Org. Chem.*, **31**, 2593 (1966).

[2] (a) NATO Fellow, 1961–1962. (b) Taken in part from the doctoral dissertations of H. T. Hanson and R. M. Weier.

[3] C. L. Stevens, P. Blumbergs, and M. E. Munk, *J. Org. Chem.*, **28**, 331 (1963).