1-Chloro-3,3-dimethylcyclohexyl 4-Dimethylaminophenyl Ketone (Ib) and 3,3-Dimethylcyclohexyl 4-Dimethylaminophenyl Ketone (XXII).—The synthesis of the α-chloro ketone Ib was performed as described for the preparation of 1-chlorocyclohexyl 4-dimethylaminophenyl ketone (Ia). *p*-Dimethylaminophenyllithium was prepared from 3.76 g. (0.019 mole) of *p*-bromo-N,N-dimethylaniline and 0.28 g. (0.04 g.-atom) of lithium metal in 30 ml. of ether. From the reaction of this lithium compound and 1.78 g. of the N-phenyl-1-chloro-3,3-dimethylcyclohexylimido chloride (XX, 0.0012 mole) and N-phenyl-3,3-dimethylcyclohexylimido chloride (XXI, 0.0057 mole) mixture in 10 ml. of ether, there was obtained 1.39 g. of solid.

Separation of this solid on a basic alumina chromatographic column in a 1:30 ratio with a 1:10 ratio of ether-petroleum ether eluent gave 0.24 g. (67%) of 1-chloro-3,3-dimethylcyclohexyl-4-dimethylaminophenyl ketone, m.p. 121.5–122.5°, when treated with charcoal and recrystallized from Skelly B: $\lambda_{\max}^{\mathrm{KBr}}$ 6.03 μ (C=O); $\lambda_{\max}^{\mathrm{MeOH}}$ 345 mμ (*E* 22,200), 242 mμ (*E* 6200).

Anal. Calcd. for $C_{17}H_{24}ClNO$: C, 69.49; H, 8.23; Cl, 12.07; N, 4.77. Found: C, 69.54; H, 8.40; Cl, 12.30; N, 4.77.

The other eluted product consisted of 0.80 g. (54%) of 3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone, m.p. 89.5–90.5°, when treated with charcoal and recrystallized from a methanol–water mixture: $\lambda_{\max}^{\mathrm{KBr}}$ 6.08 μ (C=O); $\lambda_{\max}^{\mathrm{MeOH}}$ 335 mμ (*E* 26,200), 240 mμ (*E* 5900).

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.72; H, 9.72; N, 5.40. Found: C, 78.70; H, 9.73; N, 5.47.

1-Chloro-3,3-dimethylcyclohexanecarboxanilide.—The procedure for the synthesis of the α-chloro ketone Ib using a 1:1.5 mole ratio of N-phenyl-1-chloro-3,3-dimethylcyclohexylimido chloride (XX) and N-phenyl-3,3-dimethylcyclohexylimido chloride (XXI) to *p*-dimethylaminophenyllithium was performed as described above.

Separation of the solid produced on a basic alumina chromatographic column gave the α-chloro amide XIX which was recrystallized from an ethanol–water mixture: m.p. 104–104.5°, $\lambda_{\max}^{\mathrm{KBr}}$ 6.0 μ (C=O), $\lambda_{\max}^{\mathrm{MeOH}}$ 245 mμ (*E* 10,800).

Anal. Calcd. for $C_{15}H_{20}ClNO$: C, 67.78; H, 7.58; Cl, 13.34; N, 5.27. Found: C, 67.60; H, 7.62; Cl, 14.10; N, 5.44.

This material was not obtained when a 1:3 instead of a 1:1.5 mole ratio was used.

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The Quasi-Favorskii Rearrangement. III.[1] Rearrangement of (−)-1-Chloro-3,3-dimethylcyclohexyl 4-Dimethylaminophenyl Ketone

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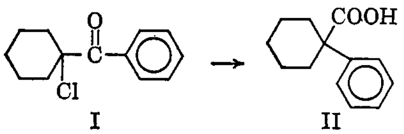
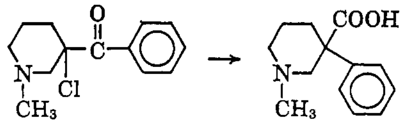
On refluxing a xylene solution of (−)-1-chloro-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (V) with dry, powdered sodium hydroxide, racemic 1-(4-dimethylaminophenyl)-3,3-dimethylcyclohexanecarboxylic acid (VI) and racemic 1-hydroxy-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (VII) were obtained. Under these conditions neither V nor 1-chlorocyclohexyl 4-dimethylaminophenyl ketone (VIII) gave any dehydrohalogenation product. A discussion of an ion-pair mechanism for this reaction is given.

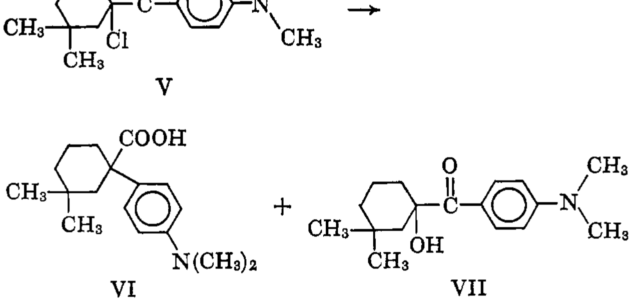
Tchoubar and Sackur,[3] and later Stevens and Farkas,[4] obtained 1-phenylcyclohexanecarboxylic acid (II) from the rearrangement of 1-chlorocyclohexyl phenyl ketone (I). Stevens and Farkas, utilizing powdered sodium hydroxide in refluxing xylene to effect the rearrangement, suggested a surface-catalyzed reaction in which the anionoid transition state is formed by initial nucleophilic attack of a hydroxide ion at the carbonyl carbon of the α-halogenated ketone I. This semibenzilic rearrangement implies that inversion at the reaction terminus should occur affording a stereospecific reaction.


I II

Smissman and Hite,[1] in their study of the rearrangement of (−)-1-methyl-3-benzoyl-3-chloropiperidine (III) to give (±)-1-methyl-3-carboxy-3-phenylpiperidine (IV), proposed an ion-pair mechanism which would appear to refute the semibenzilic mechanism. However, owing to the possibility of neighboring-group participation inherent in the 3-chloropiperidine nucleus, it could be argued that this particular rearrangement does not represent a "classical" quasi-Favorskii rearrangement.


III IV

A more suitable compound for the study of this rearrangement, (−)-1-chloro-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (V), was selected. The ketone was rearranged utilizing dry, powdered sodium hydroxide to give (±)-1-(4-dimethylaminophenyl)-3,3-dimethylcyclohexanecarboxylic acid (VI) in 45% yield and (±)-1-hydroxy-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (VIII) in 41% yield.


V VI VII

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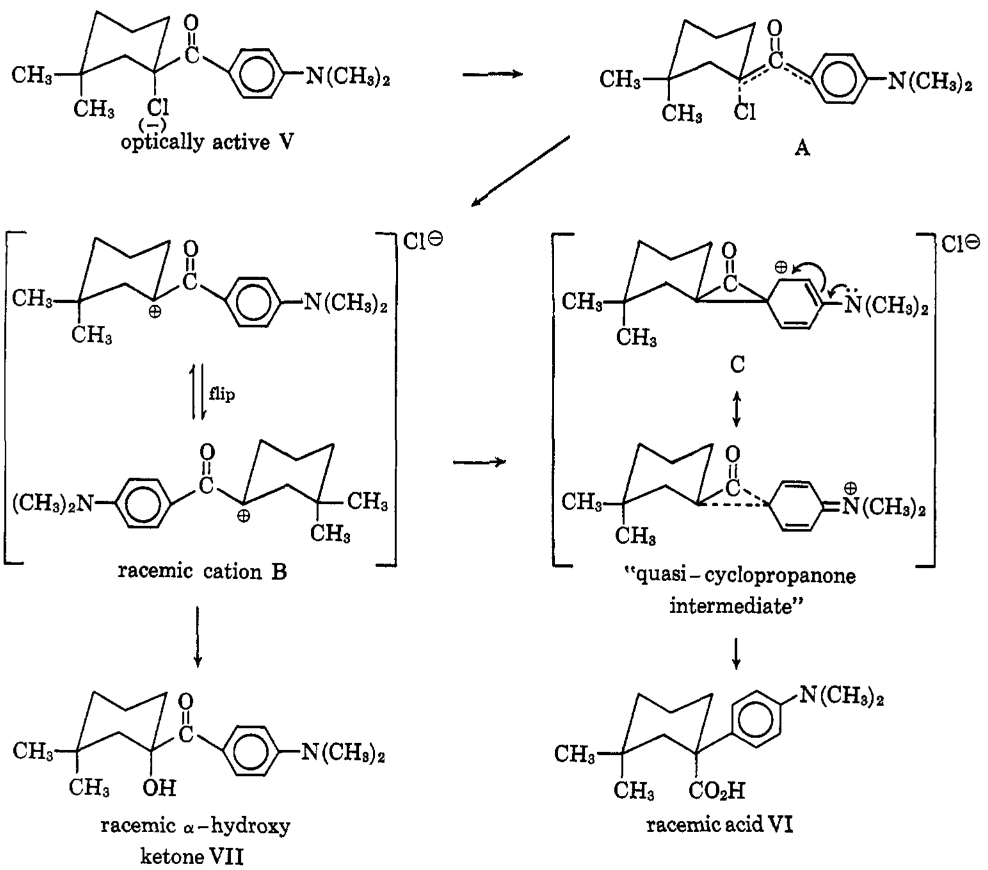
[1] For the second paper in this series, see E. E. Smissman and G. Hite, *J. Am. Chem. Soc.*, **82**, 3375 (1960).

[2] Taken from the dissertation presented by J. L. Diebold, June 1964, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy degree.

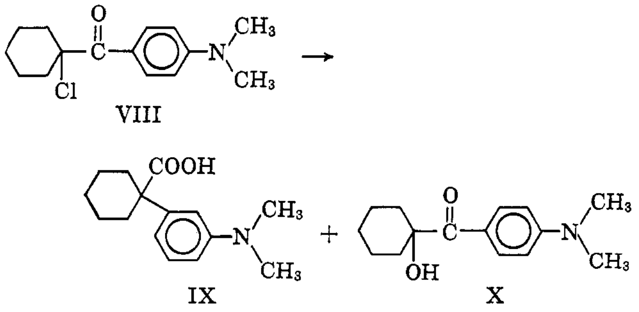
[3] B. Tchoubar and O. Sackur, *Compt. rend.*, **208**, 1020 (1939).

[4] C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 5352 (1952).

SCHEME I



A model compound, 1-chlorocyclohexyl 4-dimethylaminophenyl ketone (VIII), on treatment with dry, powdered sodium hydroxide in refluxing xylene yielded 1-(4-dimethylaminophenyl)cyclohexanecarboxylic acid (IX) and 1-hydroxycyclohexyl 4-dimethylaminophenyl ketone (X) in 68 and 18% yields, respectively. The rearrangement of the α-chloro ketone VIII was found to be sensitive to the particle size and the amount of sodium hydroxide used in the system. This is in agreement with the earlier finding and the postulation by Smissman and Hite that the reaction occurs at the sodium hydroxide ionic surface.



In the rearrangement of the α-chloro ketones V and VIII, the exclusion of oxygen was found to be necessary to prevent decomposition during the course of the reaction to afford *p*-dimethylaminobenzoic acid. No dehydrohalogenated product could be detected in the rearrangement of either α-chloro ketone, V or VIII. The optically active ketone V was stable in refluxing xylene.

From the results obtained, the rearrangement mechanism can be postulated to proceed by several different pathways. One plausible mechanism would involve an initial ionization of the (−)-α-halogenated ketone (V → A) at the catalyst surface with assistance from the adjacent benzoyl π-orbital system to give a solvent-separated external ion pair, B (see Scheme I). This racemic cation ultimately recombines with a hydroxide ion after participation of the phenyl group through a phenonium ion intermediate (quasi-cyclopropanone intermediate) C. This racemic rearrangement acid, VI, is obtained upon collapse of the quasi-cyclopropanone intermediate C, while the racemic α-hydroxy ketone, VII, is formed by collapse of the racemic external ion pair, B, with bond formation occurring α to the carbonyl group.

The racemic acid VI, obtained from the rearrangement of the optically active α-chloro ketone, V, under nonpolar, heterogeneous quasi-Favorskii conditions, supports the ion-pair mechanism proposed in paper II of this series.

The greater yield of rearranged acid in the nonpiperidine system can be explained by the absence of the nitrogen-stabilized carbonium ion and greater stabilization of the quasi-cyclopropanone intermediate by the dimethylamino group in the *para* position of the aryl function.

The validity of this mechanism is dependent on the racemization of the rearrangement acid, VI, and the α-hydroxy ketone, VII, as shown by optical rotatory dispersion (O.R.D.). Determination of the optical activity of (−)-α-chloro ketone, V, was obtained by O.R.D. which gave a negative Cotton effect curve (Figure 1). Essentially no rotation was found at the D line of sodium for this compound, and compounds VI and VII exhibited no O.R.D. curves.

The case presented could also be considered as a special example of the quasi-Favorskii rearrangement in that ionization of the chloride ion could be assisted by the *p*-dimethylamino group. The ionic form so generated could then return to racemic chloro ketone V. This appears to be improbable, since on performing the reaction for a much shorter period optically active chloro ketone was recovered. The optical stability of the compound V in refluxing xylene would also tend to eliminate this as a possibility.

Experimental Section[5]

Rearrangement of 1-Chlorocyclohexyl 4-Dimethylaminophenyl Ketone (VIII) with Sodium Hydroxide in Xylene.—A mixture of 1.0 g. (0.0038 mole) of 1-chlorocyclohexyl 4-dimethylaminophenyl ketone[6] (VIII), 1.52 g. (0.038 mole) of finely powdered, dried (150–160° at 0.01 mm., 12 hr.) sodium hydroxide, and 35 ml. of anhydrous xylene was stirred and refluxed under a nitrogen atmosphere for 30 hr.

The aqueous extract from the mixture was acidified to pH 7.0 with hydrochloric acid. The solid was collected on sintered glass, washed with water, and dried, giving 0.67 g. of a solid. Chromatography of this solid on an acid-washed alumina column gave 0.026 g. of a compound that was *p*-dimethylaminobenzoic acid as indicated by its ultraviolet spectra and 0.64 g. (68%) of 1-(4-dimethylaminophenyl)cyclohexanecarboxylic acid (IX). Treatment with charcoal and recrystallization from ethyl acetate gave the pure acid: m.p. 179.5–182.5° dec.; $\lambda_{\max}^{\text{KBr}}$ 5.95 μ (C=O); $\lambda_{\max}^{\text{MeOH}}$ 262 mμ (*E* 16,200), 300 mμ (*E* 2200).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.55; N, 5.66. Found: C, 73.15; H, 8.59; N, 5.42.

The remaining xylene solution was extracted with concentrated hydrochloric acid. Sodium hydroxide was slowly added to the extract until the solution was neutral, and 0.17 g. (18%) of 1-hydroxycyclohexyl 4-dimethylaminophenyl ketone (X) was collected on sintered glass. Treatment with charcoal and recrystallization from benzene gave the pure α-hydroxy ketone X: m.p. 140–140.5°; $\lambda_{\max}^{\text{KBr}}$ 6.09 μ (C=O); $\lambda_{\max}^{\text{MeOH}}$ 339 mμ (*E* 25,800), 242 mμ (*E* 5800).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.55; N, 5.66. Found: C, 72.54; H, 8.40; N, 5.91.

Rearrangement of (±)-1-Chloro-3,3-Dimethylcyclohexyl 4-Dimethylaminophenyl Ketone[6] (V) with Sodium Hydroxide in Xylene.—The rearrangement of this compound was performed as described for the rearrangement of VIII.

From 1.00 g. (0.0034 mole) of (±)-α-chloro ketone V and 1.36 g. (0.0034 mole) of sodium hydroxide in 70 ml. of xylene, there was obtained 0.43 g. (45%) of 1-(4-dimethylaminophenyl)-3,3-dimethylcyclohexanecarboxylic acid (VI), m.p. 158.5–160° dec., when treated with charcoal and recrystallized from an ethanol–water mixture: $\lambda_{\max}^{\text{KBr}}$ 5.95 μ (C=O); $\lambda_{\max}^{\text{MeOH}}$ 263 mμ (*E* 16,900), 300 mμ (*E* 2400).

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 73.99; H, 8.80.

From the xylene solution there was obtained 0.042 g. (45%) of(±)-1-hydroxy-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (VI), m.p. 122–123°, when treated with charcoal and recrystallized from petroleum ether (b.p. 63–68°): $\lambda_{\max}^{\text{KBr}}$ 6.1 μ (C=O); $\lambda_{\max}^{\text{MeOH}}$ 337 mμ (*E* 24,200), 242 mμ (*E* 6200).

Resolution of (±)-1-Chloro-3,3-dimethylcyclohexyl 4-Dimethylaminophenyl Ketone (V).—The racemic α-chloro ketone V (3.39 g., 0.012 mole) and 2.68 g. (0.012 mole) of (+)-10-camphorsulfonic acid were each dissolved in 40 ml. of hot ethyl acetate and then mixed. After failing to obtain crystals by cooling or seeding, the solvent was evaporated, leaving an oil. Trituration of this oil with ether gave a solid.

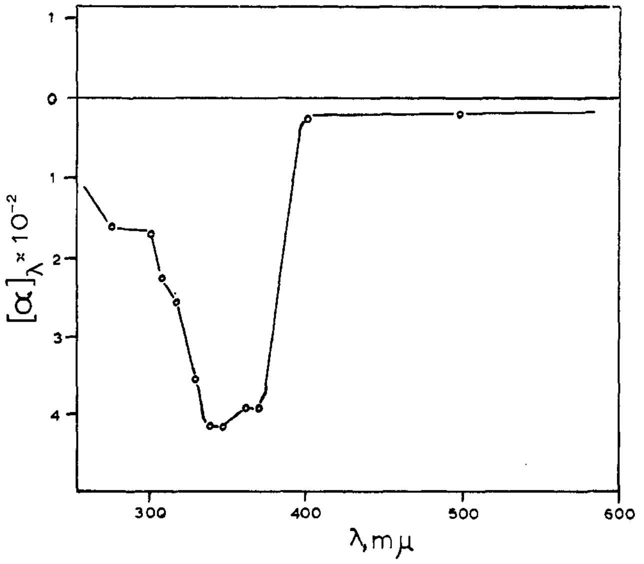


Figure 1.—The optical rotatory dispersion curve of (−)-1-chloro-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone in acetonitrile solvent.

Four recrystallizations from ethyl acetate gave 0.91 g. of the pure (+)-10-camphorsulfonate salt of (−)-1-chloro-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (V), m.p. 101–102°, $[\alpha]^{25}\text{D}$ +28.22° (*c* 4.1, absolute ethanol). This salt was dissolved in water, treated with an excess of sodium bicarbonate, and extracted with petroleum ether. After drying over sodium sulfate, the solution was concentrated and the crystalline product was collected: 0.36 g.; m.p. 119.5–120.5°; $[\alpha]^{25}\text{D}$ 0° (*c* 14.5, chloroform). O.R.D. (Figure 1) in acetonitrile (*c* 0.0764) gave a negative Cotton effect curve: $[\alpha]_{589}$ −21°, $[\alpha]_{500}$ −21°, $[\alpha]_{400}$ −21°; (*c* 0.00764) $[\alpha]_{370}$ −398°, $[\alpha]_{360}$ −398°, $[\alpha]_{350}$ −419°, $[\alpha]_{340}$ −419°, $[\alpha]_{330}$ −356°, $[\alpha]_{320}$ −259°, $[\alpha]_{310}$ −230°, $[\alpha]_{300}$ −168°, $[\alpha]_{280}$ −168°, $[\alpha]_{260}$ −118°.

Rearrangement of (−)-1-Chloro-3,3-dimethylcyclohexyl 4-Dimethylaminophenyl Ketone (V) with Sodium Hydroxide in Xylene.—The rearrangement of this compound was performed as described for the rearrangement of 1-chlorocyclohexyl 4-dimethylaminophenyl ketone (VIII).

From 0.328 g. (0.0011 mole) of (−)-α-chloro ketone V and 0.45 g. (0.011 mole) of sodium hydroxide in 20 ml. of xylene, there was obtained 0.136 g. (45%) of (±)-1(4-dimethylaminophenyl)-3,3-dimethylcyclohexanecarboxylic acid (VI), m.p. 153.5–156° dec., when treated with charcoal and recrystallized from an ethanol–water mixture, $[\alpha]^{25}\text{D}$ 0° (*c* 4.6, chloroform). An acetonitrile solution of this compound showed no optical activity by O.R.D.

From the xylene solution there was obtained 0.125 g. (41%) of (±)-1-hydroxy-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (VII), m.p. 122–123°, when treated with charcoal and recrystallized from petroleum ether. An acetonitrile solution of this compound showed no optical activity by O.R.D.

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(5) Melting points were obtained on a Kofler micro hot stage and are corrected. Infrared data were recorded on Beckman IR-5 and IR-8 spectrophotometers. Ultraviolet spectra were recorded on a Bausch and Lomb 505 spectrophotometer. A Zeiss polarimeter was used to determine specific rotations. Elemental analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England, and the Huffman Microanalytical Laboratories, Wheatridge, Colo.

(6) E. E. Smissman and J. L. Diebold, *J. Org. Chem.*, **30**, 4002 (1965).