The Preparation of 1-Chlorocyclohexyl 4-Dimethylaminophenyl Ketone and 1-Chloro-3,3-dimethylcyclohexyl 4-Dimethylaminophenyl Ketone[1]

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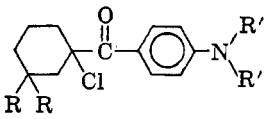
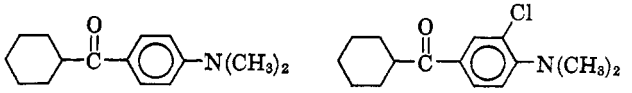
The preparation of 1-chlorocyclohexyl 4-dimethylaminophenyl ketone (Ia) and 1-chloro-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (Ib) by the reaction of the N-phenyl- or N-ethyl-1-chlorocyclohexylimido chlorides VI, XI, and XX with *p*-dimethylaminophenyllithium is discussed.

In order to study further[2,3] the stereochemistry and mechanism of the quasi-Favorskii rearrangement, it was necessary to devise a method for the preparation of the 1-chlorocyclohexyl 4-aminophenyl ketones (I). The synthesis of Ia by halogenation of cyclohexyl 4-



Ia, R = H; R′ = CH_3
b, R = R′ = CH_3

dimethylaminophenyl ketone (II) or the corresponding N-oxide afforded cyclohexyl 3-chloro-4-dimethylaminophenyl ketone (III) in the former case and an inseparable mixture of products in the latter.

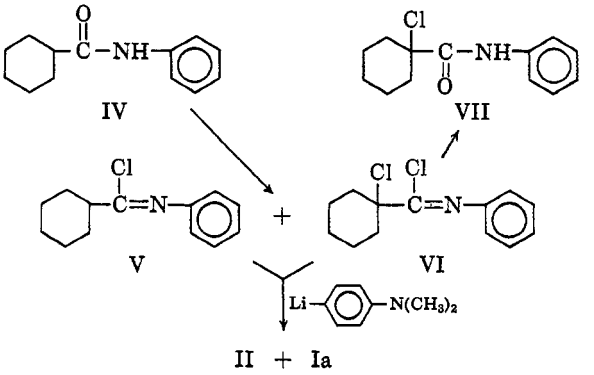


II III

Attempts to acylate N,N-dimethylaniline with α-chlorocyclohexanecarboxylic acid chloride under a variety of Friedel–Crafts conditions failed.

Organometallic compounds have been reported to add 1,2 across carbon–nitrogen double bonds[4-9] of Schiff bases and imido chlorides to produce amines and Schiff bases, respectively. If this reaction is employed to produce a Schiff base, it is reasonable to assume the latter could be decomposed to produce the desired ketone. With this sequence of reactions in mind, N-phenyl-1-chlorocyclohexylimido chloride (VI) was prepared from cyclohexanecarboxanilide (IV) and phosphorus pentachloride (see Chart I) by the method of von Braun, *et al.*[10] The chlorocyclohexylamido chloride VI, owing to its instability, could not be isolated in a form pure enough for elemental analysis but was shown to be present in 20% yield by vapor phase chromatography. The remaining 80% was

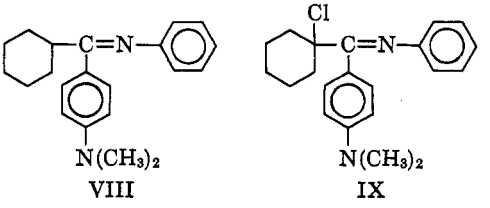
CHART I



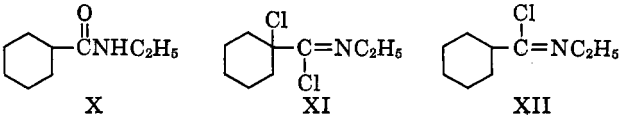
II + Ia

shown to be N-phenylcyclohexylimido chloride (V). 1-Chlorocyclohexanecarboxanilide (VII) was obtained by refluxing the mixture of V and VI with water.

The mixture of the imido chlorides V and VI was allowed to react with *p*-dimethylaminophenyllithium in anticipation of forming 1-chlorocyclohexyl 4-dimethylaminophenyl ketone anil (IX) and cyclohexyl 4-dimethylaminophenyl ketone anil (VIII). However, only 1-chlorocyclohexyl 4-dimethylaminophenyl ketone (Ia) and cyclohexyl 4-dimethylaminophenyl ketone (II) were obtained.



VIII IX



X XI XII

The same reaction sequence was performed with N-ethylcyclohexanecarboxamide (X) to give N-ethyl-1-chlorocyclohexylimido chloride (XI) and N-ethylcyclohexylimido chloride (XII). This mixture when allowed to react with *p*-dimethylaminophenyllithium also produced the amino ketones Ia and II.

A plausible explanation for the failure to isolate the expected anils could be that, on reaction of the imido chlorides with the aryllithium, a stable N-lithio compound XIII was formed which decomposed rapidly during the aqueous acid isolation procedure.

This procedure was next utilized to prepare Ib. Dimedone, 5,5-dimethylcyclohexane-1,3-dione (XIV),

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

(2) E. E. Smissman and G. Hite, *J. Am. Chem. Soc.*, **82**, 3375 (1960).

(3) E. E. Smissman and J. L. Diebold, *J. Org. Chem.*, **30**, 4005 (1965).

(4) M. Busch and M. Fleischman, *Ber.*, **43**, 2553 (1910).

(5) M. Busch and F. Falco, *ibid.*, **43**, 2557 (1910).

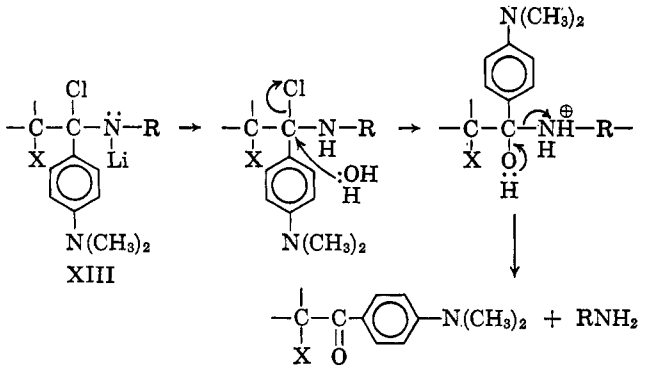
(6) R. C. Fuson, R. J. Lokken, and R. L. Pedrotti, *J. Am. Chem. Soc.*, **78**, 6064 (1956).

(7) E. G. Rochow, D. T. Hurd, and R. N. Lewis, "The Chemistry of Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 276.

(8) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 1062.

(9) H. Gilman and R. G. Jones, *Org. Reactions*, **6**, 339 (1951).

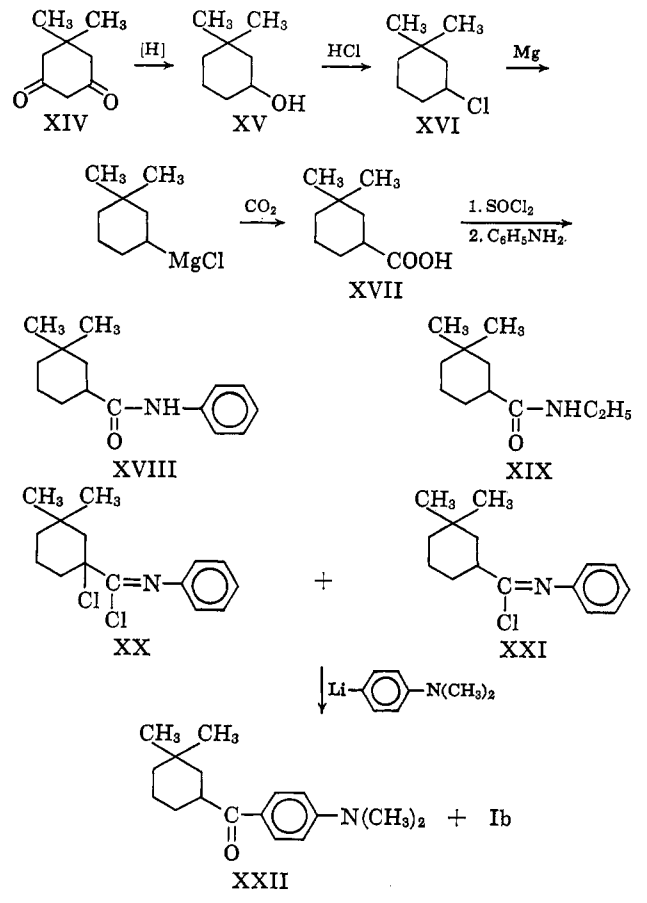
(10) J. von Braun, F. Jostes, and W. Munch, *Ann.*, **453**, 113 (1927).



XIII

was hydrogenated catalytically to yield 3,3-dimethylcyclohexanol (XV) and 3,3-dimethylcyclohexanone (see Chart II) in a 1:1 ratio as indicated by vapor phase chromatography. This mixture was further reduced with lithium aluminum hydride to give the pure alcohol, XV. The alcohol was converted to the corresponding chloride XVI by refluxing with hydrochloric acid and zinc chloride. 3,3-Dimethyl-1-chlorocyclohexane was converted to the Grignard reagent which was then added to powdered, solid carbon dioxide to give 3,3-dimethylcyclohexanecarboxylic acid (XVII). The carboxylic acid was treated with thionyl chloride followed by aniline to give the desired anilide XVIII. The N-ethylamide XIX was prepared in the same manner.

CHART II



When the anilide XVIII was allowed to react with phosphorus pentachloride, a mixture of 20% N-phenyl-1-chloro-3,3-dimethylcyclohexylimido chloride (XX) and 80% 3,3-dimethylcyclohexylimido chloride (XXI) was obtained. Treatment of this imido chloride mixture with a 3:1 mole ratio of 4-dimethylaminophenyllithium produced a 67% yield of 1-chloro-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (Ib) and a 54% yield of 3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (XXII). No unreacted amide was recovered.

Experimental Section[11]

Cyclohexyl 4-Dimethylaminophenyl Ketone (II).—N-Pentamethylenecyclohexanecarboxamide[12] (40.1 g., 0.21 mole), 19.6 ml. (0.21 mole) of phosphoryl chloride, and 82 ml. of chloroform were stirred at room temperature for 12 hr. N,N-Dimethylaniline (55 ml., 0.43 mole) was added and the mixture was refluxed at 110° for 2 hr. To the cold, dark red solution was added 15% sodium hydroxide until it was basic. The two layers were separated and the aqueous layer was extracted with chloroform. The chloroform solution was extracted four times with 20% hydrochloric acid and washed with water until neutral. After being dried over magnesium sulfate, the solvent was removed. The resulting semisolid residue was dissolved in 700 ml. of anhydrous ether, treated with Filtercel and activated charcoal, and filtered, giving a yellow solution. Into this solution was bubbled hydrogen chloride gas, whereupon the amine hydrochloride salt precipitated. The supernatant liquid was decanted and concentrated, and more of the salt was collected. The amine hydrochloride salt was decomposed in a 10% sodium bicarbonate solution giving 30.7 g. (65%) of the amino ketone: m.p. 84–85.5° (lit.[13,14] m.p. 82–84°); λ_{max}^{KBr} 6.05 μ (C=O); λ_{max}^{MeOH} 335 mμ (E 24,900), 240 mμ (E 5600).

Cyclohexyl 3-Chloro-4-dimethylaminophenyl Ketone (III).—To 0.5 g. (0.022 mole) of cyclohexyl 4-dimethylaminophenyl ketone (VII) in 3 ml. of trifluoroacetic acid was slowly added 1.75 ml. (0.021 mole) of sulfuryl chloride. The yellow solution turned brown immediately and was stirred at room temperature for 30 min. After ice was added to decompose the unreacted sulfuryl chloride, 100 ml. of water was added, followed by three extractions with ether. The ether solution was washed with water five times. After being dried over magnesium sulfate, the ether was removed and the oil was distilled to give 0.49 g. of a yellow oil, b.p. 130° (0.15 mm.).

This oil was chromatographed on a silicic acid column utilizing chloroform as the eluent. Recrystallization of the solid obtained from petroleum ether (b.p. 60–68°) gave the chloro ketone: m.p. 85–88°; λ_{max}^{KBr} 6.03 μ (C=O); λ_{max}^{MeOH} 325 mμ (E 13,700), 244 mμ (E 6900).

Anal. Calcd. for $C_{15}H_{20}ClNO$: C, 67.78; H, 7.59; Cl, 13.34; N, 5.27. Found: C, 68.46; H, 7.51; Cl, 13.21; N, 5.30.

Cyclohexyl 4-Dimethylaminophenyl Ketone N-Oxide.—Perbenzoic acid was prepared according to the method of Braun.[15] To 12.0 g. (0.052 mole) of cyclohexyl 4-dimethylaminophenyl ketone (II) in 50 ml. of benzene was added in 15 min. 330 ml. of a benzene solution of perbenzoic acid (8.6 g., 0.062 mole). After stirring at 0° for 1.5 hr., 500 ml. of ether was added; the slurry was cooled in ice before filtration. The solid was washed with 150 ml. of cold ether. It was then dissolved in dichloromethane, extracted with 5% sodium hydroxide, washed with water, and dried over magnesium sulfate. Recrystallization from chloroform and ethyl acetate gave the crystalline

(11) 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, and ultraviolet spectra were recorded on a Bausch and Lomb 505 spectrophotometer. Elemental analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England, and the Huffmann Microanalytical Laboratories, Wheatridge, Colo. All vapor phase chromatography reported herein was performed on an F and M 810 chromatograph utilizing a 4-ft. SE-30 (20%) on Gas Chrom P column. The injection port temperature was 210°; the detector temperature was 230°; and the He flow was maintained at 55 cc./min. The instrument was programmed at 6°/min., range 10².

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(13) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

(14) M. Seefelder, German Patent 1,112,982 (Dec. 17, 1959); *Chem. Abstr.*, **56**, 5810*h* (1962).

(15) G. Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431.

N-oxide: m.p. 153–154° dec.; λ_{max}^{KBr} 6.0 μ (C=O); λ_{max}^{MeOH} 240 mμ (E 11,800), 272 mμ (E 1300).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 72.84; H, 8.55; N, 5.66. Found: C, 73.16; H, 8.28; N, 5.24.

Cyclohexanecarboxanilide (IV).—Cyclohexanecarboxylic acid chloride was prepared using 62 g. (0.48 mole) of cyclohexanecarboxylic acid and 100 ml. (1.38 moles) of thionyl chloride. After removing the excess thionyl chloride, the acid chloride was slowly added to a stirred, cold solution of 134 ml. (1.47 moles) of aniline and 500 ml. of benzene. After stirring overnight, the benzene and 400 ml. of 10% sodium hydroxide and 3 l. of ether were added. The ether layer was extracted with 10% hydrochloric acid and dried over anhydrous sodium sulfate. After partial evaporation of the ether, 2 l. of Skelly A was added, precipitating 83 g. (84%) of the anilide: m.p. 146.5–147.5° (lit.[16] m.p. 141°), λ_{max}^{KBr} 6.02 μ (C=O), λ_{max}^{MeOH} 243 mμ (E 14,100).

N-Phenyl-1-chlorocyclohexylimido Chloride (VI) and N-Phenylcyclohexylimido Chloride (V).—Cyclohexanecarboxanilide (IV, 40 g., 0.20 mole) and 77 g. (0.37 mole) of phosphorus pentachloride in 300 ml. of anhydrous benzene were refluxed for 40 min. and the benzene was removed. Distillation of the yellow oil gave 45.5 g. of liquid, b.p. 143–158° (55–65 mm.).

Vapor phase chromatography showed the liquid to consist of 20% (9.1 g.) of N-phenyl-1-chlorocyclohexylimido chloride and 80% (36.4 g.) of N-phenylcyclohexylimido chloride.

1-Chlorocyclohexyl 4-Dimethylaminophenyl Ketone (Ia) and Cyclohexyl 4-Dimethylaminophenyl Ketone (II). A.—*p*-Dimethylaminophenyllithium was prepared by adding small pieces of lithium metal (0.29 g., 0.041 g.-atom) to 8 ml. of anhydrous ether in a nitrogen system. To this stirred solution was slowly added 4.13 g. (0.021 mole) of *p*-bromo-N,N-dimethylaniline in 10 ml. of ether. Reaction occurred immediately and the mixture was subsequently warmed for 2 hr.

This solution was filtered through glass wool and slowly added over 30 min. to 4.3 g. of the N-ethyl-1-chlorocyclohexylimido chloride (XI, 0.0042 mole) and N-ethylcyclohexylimido chloride (XII, 0.019 mole) mixture in 10 ml. of ether at 0°. The stirred solution was allowed to warm to 25°, and after 1 hr. the yellow slurry was poured into 100 ml. of 10% hydrochloric acid. The solution was extracted three times with petroleum ether and washed until neutral. After drying over sodium sulfate, the solvent was removed and the product was recrystallized from an ethanol–water mixture, giving 0.63 g. (56%) of the α-chloro ketone: m.p. 128–129.5°; λ_{max}^{KBr} 6.07 μ (C=O); λ_{max}^{MeOH} 345 mμ (E 21,800), 243 mμ (E 6400).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 67.78; H, 7.59; Cl, 13.34; N, 5.27. Found: C, 67.58; H, 7.60; Cl, 13.49; N, 5.73.

B.—The synthesis of the α-chloro ketone Ia was performed exactly as described above *via* N-ethyl-1-chlorocyclohexylimido chloride (XI). *p*-Dimethylaminophenyllithium was prepared from 0.70 g. (0.35 mole) of *p*-bromo-N,N-dimethylaniline and 5.1 g. (0.74 g.-atom) of lithium metal in 250 ml. of ether. From the reaction of this lithium compound and 23.4 g. of the N-phenyl-1-chlorocyclohexylimido chloride (VI, 0.019 mole) and N-phenylcyclohexylimido chloride (V, 0.082 mole) mixture in 100 ml. of ether, there was obtained 15.3 g. of solid.

Separation of this solid on a basic alumina chromatographic column in 1:30 ratio with 1:10 of ether–petroleum ether eluent gave 2.26 g. (45%) of 1-chlorocyclohexyl 4-dimethylaminophenyl ketone and 12.2 g. (64%) of cyclohexyl 4-dimethylaminophenyl ketone.

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-Chlorocyclohexanecarboxanilide (VII).—N-Phenyl-1-chlorocyclohexylimido chloride (VI) and N-phenylcyclohexylimido chloride (V) were hydrolyzed in water by refluxing for 30 min. After four recrystallizations from an ethanol–water mixture, the pure α-chloro amide was obtained: m.p. 104–105°, λ_{max}^{KBr} 6.0 μ (C=O), λ_{max}^{MeOH} 245 mμ (E 10,800).

Anal. Calcd. for $C_{13}H_{16}ClNO$: C, 65.58; H, 6.79; Cl, 14.92; N, 5.89. Found: C, 65.19; H, 6.73; Cl, 15.50; N, 6.21.

3,3-Dimethylcyclohexanol (XV).—Dimedone (140.0 g., 1.0 mole) was reduced in a Parr apparatus in the presence of 1.7 g. of platinum oxide at 50 p.s.i. in 100 ml. of glacial acetic acid. The reaction mixture was treated with 100 g. of sodium hydroxide in 500 ml. of water and extracted three times with ether. The ether solution was dried over magnesium sulfate and concentrated to an oil. On distillation 104.7 g. of a mixture of 3,3-dimethylcyclohexanol (XV) and 3,3-dimethylcyclohexanone[17] in a 1:1 ratio (as was shown by vapor phase chromatography) was obtained.

This mixture was reduced to the pure alcohol by addition to 15 g. of lithium aluminum hydride in 250 ml. of ether. After hydrolysis with ice–water, 500 ml. of 10% sulfuric acid was added and the ether layer was separated. This was dried over magnesium sulfate and the ether was removed. Fractional distillation of the oil gave 84.8 g. (66%) of the alcohol, b.p. 93° at 25 mm (lit.[18] b.p. 80–81° at 16 mm.).

3,3-Dimethylcyclohexyl Chloride (XVI).—Zinc chloride 31.6 g., 0.27 mole) was slowly added to a cold stirred solution of 11.4 g. (0.089 mole) of 3,3-dimethylcyclohexanol (XV) and 23 ml. (0.27 mole) of concentrated hydrochloric acid. After being warmed to room temperature, the red solution was refluxed for 1 hr. The two layers were separated and the organic layer was washed with water until neutral. After drying over magnesium sulfate, distillation of the oil gave 9.1 g. (70%) of the chloride, b.p. 64° at 15 mm. (lit.[18] b.p. 70° at 24 mm.).

3,3-Dimethylcyclohexanecarboxylic Acid (XVII).—To 12.4 g. (0.51 g.-atom) of magnesium was added 10 ml. of a solution of 69.5 g. (0.47 mole) of 3,3-dimethylcyclohexyl chloride (XVI) in 275 ml. of anhydrous ether. Ten drops of methyl iodide were added and the mixture was refluxed for 10 min.; 25 ml. of anhydrous ether was added after which the rest of the halide solution was added dropwise. The addition of the halide solution required about 0.5 hr. After refluxing for 0.5 hr., the Grignard reagent was added over 1 hr. to a vigorously stirred slurry of 200 g. of Dry Ice in ether. The resulting mixture was hydrolyzed with dilute hydrochloric acid. The ether layer was separated and the aqueous layer was extracted four times with ether. The combined ether extracts were extracted with four 25-ml. portions of 10% sodium hydroxide. The basic layer was acidified (congo red) with hydrochloric acid and extracted four times with chloroform. After removal of the solvent, the remaining colorless oil (44% yield) was shown to be the pure carboxylic acid by vapor phase chromatography: b.p. 105–110° at 1 mm. (lit.[19] b.p. 103–108° at 0.9 mm).

3,3-Dimethylcyclohexanecarboxanilide (XVIII).—3,3-Dimethylcyclohexanecarboxylic acid chloride was prepared using 64 g. (0.41 mole) of 3,3-dimethylcyclohexanecarboxylic acid and 85.5 ml. (1.19 moles) of thionyl chloride. After removal of the excess thionyl chloride, the acid chloride was slowly added to a stirred, cold solution of 105 ml. (1.15 moles) of aniline and 300 ml. of ether. After 1 hr., 300 ml. of a 10% sodium hydroxide, sodium chloride saturated solution was added. The ether layer was extracted with a 10% hydrochloric acid, sodium chloride saturated solution. After drying over sodium sulfate, the solvent was removed, giving 74 g. (78%) of the anilide, m.p. 122.5–123.5°, when recrystallized from Skelly B: λ_{max}^{KBr} 6.02 μ (C=O), λ_{max}^{MeOH} (E 15,100).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.19; H, 9.14; N, 6.11.

N-Ethyl-3,3-dimethylcyclohexanecarboxamide (XIX).—Using 8.0 g. (0.051 mole) of 3,3-dimethylcyclohexanecarboxylic acid and 11 ml. (0.15 mole) of thionyl chloride, the acid chloride was prepared. The acid chloride was treated with 14 ml. of 70% aqueous ethylamine in 50 ml. of ether. The work-up was followed as in the preparation of the anilide XVIII and gave 7.2 g. (77%) of the desired amide, m.p. 92.5–94°, when recrystallized from an acetonitrile–water mixture: λ_{max}^{KBr} 6.1 μ (C=O).

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.87; H, 11.54; N, 7.18.

N-Phenyl-1-chloro-3,3-dimethylcyclohexylimido Chloride (XX) and N-Phenyl-3,3-dimethylcyclohexylimido Chloride (XXI).—3,3-Dimethylcyclohexanecarboxanilide (XVIII, 60 g., 0.26 mole) and 104 g. (0.50 mole) of phosphorus pentachloride in 350 ml. of anhydrous benzene were refluxed for 40 min. and the solvent was removed. Distillation of the yellow oil gave 68.9 g. of a liquid, b.p. 145–155° at 0.55 mm.

Vapor phase chromatography showed the liquid consisted of 20% (13.8 g.) of N-phenyl-1-chloro-3,3-dimethylcyclohexylimido chloride and 80% (55.1 g.) of N-phenyl-3,3-dimethylcyclohexylimido chloride.

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(17) K. von Auwers and E. Lang, *Ann.*, **401**, 323 (1913).

(18) H. L. Goering and F. H. McCarron, *J. Am. Chem. Soc.*, **78**, 2270 (1956).

(19) H. L. Goering and F. H. McCarron, *ibid.*, **78**, 2287 (1956).

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: λ_{max}^{KBr} 6.03 μ (C=O); λ_{max}^{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: λ_{max}^{KBr} 6.08 μ (C=O); λ_{max}^{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°, λ_{max}^{KBr} 6.0 μ (C=O), λ_{max}^{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.

Acknowledgment.—The authors gratefully acknowledge the support of this project by the National Institutes of Health, Grant NB 02733, and by the Parke-Davis Company.

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

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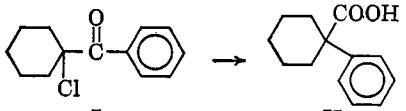
On refluxing a xylene solution of (−)-1-chloro-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (V) with dry, powdered sodium hydroxide, racemic 1-(4-dimethylaminophenyl)-3,3-dimethylcyclohexanecarboxylic acid (VI) and racemic 1-hydroxy-3,3-dimethylcyclohexyl 4-dimethylaminophenyl ketone (VII) were 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.

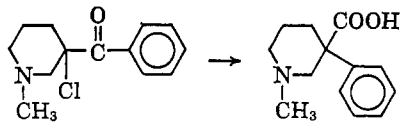
Tchoubar and Sackur,[3] and later Stevens and Farkas,[4] obtained 1-phenylcyclohexanecarboxylic acid (II) from the rearrangement of 1-chlorocyclohexyl phenyl ketone (I). Stevens and Farkas, utilizing powdered sodium



I II

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.

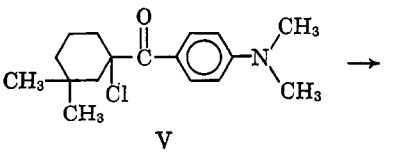
Smissman and Hite,[1] in their study of the rearrangement of (−)-1-methyl-3-benzoyl-3-chloropiperidine (III) to give (±)-1-methyl-3-carboxy-3-phenylpiperidine (IV), proposed an ion-pair mechanism which would appear to refute the semibenzilic mechanism. However, owing to the possibility of neighboring-



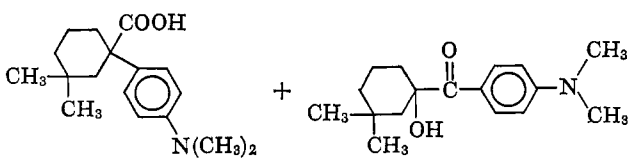
III IV

group participation inherent in the 3-chloropiperidine nucleus, it could be argued that this particular rearrangement does not represent a "classical" quasi-Favorskii rearrangement.

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

(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, *Comp. rend.*, **208**, 1020 (1939).

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