[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

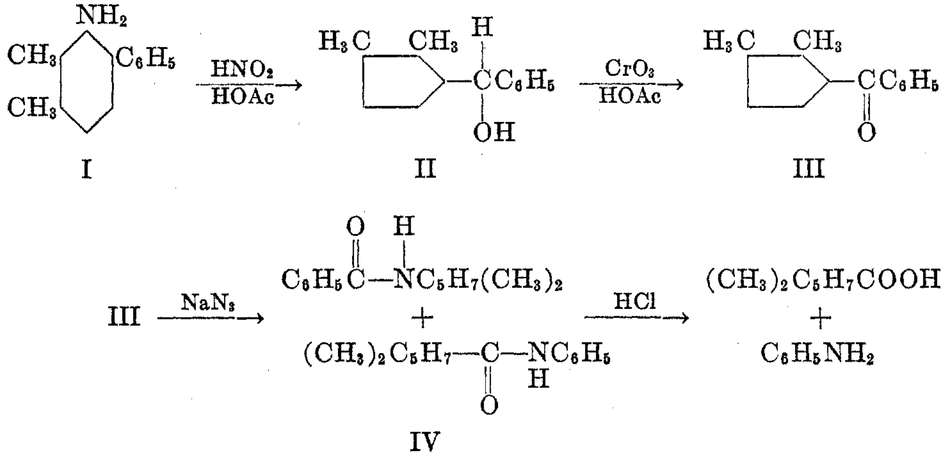
THE ACTION OF NITROUS ACID ON SOME ALICYCLIC AMINES[1]

DOROTHY V. NIGHTINGALE, JACK D. KERR, JAMES A. GALLAGHER, AND MILLARD MAIENTHAL

Received March 24, 1952

In a previous publication (1) it was established that *trans*-2-phenylcyclohexylamine reacted with nitrous acid to form cyclopentylphenylcarbinol. Qualitative evidence indicated that a dimethylcyclopentylphenylcarbinol (II) was the principal product from the reaction of 2-phenyl-4,5-dimethylcyclohexylamine (I) and nitrous acid. The carbinol II did not form the usual derivatives.

The structure of II has now been established as follows:



The aniline obtained by the hydrolysis of the crude amide IV was identified by its benzoyl derivative. The odor of the amine from one experiment and the fact that the melting point of its benzanilide was five degrees low indicated the presence of a small amount of dimethylcyclopentylamine in the hydrolysis product. The crude dimethylcyclopentanecarboxylic acid was reconverted to its anilide for purification. The two methyl groups may be in the 2,3-positions on the cyclopentane nucleus. The synthesis of II by reactions analogous to those used by Maienthal (1) was not feasible.

The fact that these two substituted cyclohexylamines yielded ring-contracted products suggested the study of the action of nitrous acid on other similar mono 2-substituted cyclohexylamines and the corresponding 4-isomers. In the reactions of nitrous acid with alicylcic amines described in the literature, an alkyl group was *alpha* to the amino group.

The *trans* forms of 2-cyclohexylcyclohexylamine, 4-phenylcyclohexylamine,

---

[1] Abstracted from the Ph. D. theses of J. D. Kerr (1951) and Millard Maienthal (1949) and the Master's thesis of J. A. Gallagher (1951).

4-cyclohexylcyclohexylamine, and 4-*tert*-butylcyclohexylamine were prepared by the reduction of the corresponding cyclohexanone oximes with sodium and alcohol. It is generally agreed that monosubstituted cyclohexylamines prepared in this manner have the *trans* configuration (2), although the reduction of 3-methylcyclohexanone oxime is reported to yield both *cis*- and *trans*-3-methylcyclohexylamine (3).

All efforts to obtain the *cis* isomers of the above amines by reduction of the oximes with hydrogen and platinum in glacial acetic acid (4), with hydrogen and Raney nickel (5), or with hydrogen and palladium on charcoal (6) were fruitless. The only pure compounds isolated from these reductions were the *trans* forms of the amines, but it is possible that small amounts of the *cis* isomers were formed, both in the catalytic reductions and in the reductions with sodium and alcohol. Thus, the *trans*-2-phenylcyclohexylamine obtained by reduction of the oxime melted two degrees lower than the same amine from *trans*-1-nitro-2-phenyl-4-cyclohexene. Two of the other amines melted over a two degree range after repeated recrystallizations.

The *trans* form of the 4-phenyl-, 4-cyclohexyl-, 4-*tert*-butyl-, and 4-methylcyclohexylamine reacted with nitrous acid to form the corresponding *trans*-cyclohexanols in yields of 49–60%. The 4-*tert*-butylcyclohexanol melted slightly lower than the authentic sample and depressed slightly the melting point of the authentic sample. It is possible that a small amount of the *cis* isomer was present. The liquid *trans*-4-methylcyclohexanol was characterized by its solid *p*-nitrobenzoyl ester.

The 2-cyclohexylcyclohexanol obtained from *trans*-2-cyclohexylcyclohexylamine melted at 47–48° and formed a phenylurethan, m.p. 126–128°, which did not depress the melting point of an authentic sample. On the basis of the published melting point diagrams for mixtures of pure *cis*- and *trans*-2-cyclohexylcyclohexanol and of their phenylurethans (7), these values correspond to a mixture of approximately 87% of the *trans* isomer and 13% of the *cis* isomer.

The data obtained from these experiments would indicate that a phenyl radical *alpha* to the amino group of the cyclohexylamines facilitates ring contraction when the amines react with nitrous acid.

EXPERIMENTAL[2]

The *2-phenyl-4,5-dimethylcyclohexylamine* was prepared as previously described (8).

4-Phenylcyclohexanol was obtained from 4-hydroxybiphenyl by catalytic hydrogenation. The other cyclohexanols were purchased from the Dow Chemical Company. The *cyclohexanones* were prepared by oxidation of the cyclohexanols with sodium dichromate in acetic acid and sulfuric acid (9). To obtain the pure ketones in solid form, it was sometimes necessary to convert the ketone to the oxime, purify the oxime by crystallization, and hydrolyze it with 10% sulfuric acid. The oximes were obtained from the cyclohexanones and hydrazine sulfate by the usual procedures.

The *trans*-cyclohexanols used for reference compounds were prepared from the pure

---

[2] The carbon and hydrogen analyses of the compounds obtained from 2-phenyl-4,5-dimethylcyclohexylamine were made by J. A. Gallagher and J. S. Finney. The others were made by J. D. Kerr and P. D. Strickler.

cyclohexanones by reduction with sodium and alcohol. The 2-cyclohexylcyclohexanol was a liquid mixture of the *cis* and *trans* isomers which was not separated. It formed a phenylurethan, m.p. 127–128°, which corresponds to a mixture of 87% of the *trans* isomer and 13% of the *cis* isomer (7).

The preparation of *trans*-4-phenylcyclohexylamine is typical. A solution of 37.8 g. (0.2 mole) of 4-phenylcyclohexanone oxime in 400 ml. of absolute alcohol was heated to boiling in a 2-l. round-bottom flask fitted with a reflux condenser. The heating was stopped and the refluxing was maintained by adding 50 g. of sodium in strips through the top of the condenser. The solution was refluxed for 30 minutes after all of the sodium had been added. Water (500 ml.) was added cautiously while the solution was still warm. Conc'd hydrochloric acid was added until the solution was acid to Congo paper, plus an additional 10-ml. portion of the acid. The solution was concentrated under reduced pressure until the amine hydrochloride began to crystallize.

Sodium hydroxide (40% aqueous solution) was added to *p*H 11 or more as indicated by Hydrion *p*H paper. The solution was extracted with ether and the ether extract was washed with water. The ether was evaporated and the *trans*-4-phenylcyclohexylamine was distilled at 106–108° (3 mm.). The amine solidified in the receiver and melted at 87–88° after recrystallation; yield 24 g. (65%).

Anal. Calc'd for $C_{12}H_{17}N$: C, 82.22; H, 9.78.
Found: C, 81.99; H, 9.85.

The *benzoyl* derivative of *trans*-4-phenylcyclohexylamine melted at 213.5–214.5°.

Anal. Calc'd for $C_{19}H_{21}NO$: C, 81.70; H, 7.58.
Found: C, 81.52; H, 7.69.

trans-4-Cyclohexylcyclohexylamine distilled at 105–115° (1 mm.) and melted at 92–94°; yield, 50%.

Anal. Calc'd for $C_{12}H_{23}N$: C, 79.43; H, 12.78.
Found: C, 79.71; H, 12.65.

The *benzoyl* derivative of this amine melted at 215–216°.

Anal. Calc'd for $C_{19}H_{27}NO$: C, 79.95; H, 9.54.
Found: C, 79.71; H, 9.72.

trans-4-*tert*-Butylcyclohexylamine distilled at 142–145° (19 mm.) and melted at 81–83° after recrystallization; yield, 52%.

Anal. Calc'd for $C_{10}H_{21}N$: C, 77.34; H, 13.63.
Found: C, 77.18; H, 13.48.

The *benzoyl* derivative of this amine melted at 178–179°.

Anal. Calc'd for $C_{17}H_{25}NO$: C, 78.71; H, 9.72.
Found: C, 78.58; H, 9.85.

trans-2-Cyclohexylcyclohexylamine (10) and *trans*-4-methylcyclohexylamine (11) were known compounds and also were originally obtained by the reduction of the corresponding cyclohexanone oximes with sodium and alcohol.

trans-2-Phenylcyclohexylamine prepared by the reduction of the oxime with sodium and alcohol melted at 55–56° and formed a *benzoyl* derivative, m.p. 179–180°, which did not depress the melting point of the benzoyl derivative, m.p. 180–181°, of 2-phenylcyclohexylamine (m.p. 57–58°) obtained by the reduction of 1-nitro-2-phenyl-4-cyclohexene with hydrogen and Raney nickel (1).

Reduction of 4-phenylcyclohexanone oxime with hydrogen and Raney nickel. The nickel (6.5 g.) was added to 19 g. (0.1 mole) of the oxime in 75 ml. of ethanol in the copper liner of the conventional high pressure reduction apparatus. The initial pressure was 1500 p.s.i. and reduction took place at 75°. The catalyst was removed, the solvent was distilled, and the residue was dissolved in benzene. The benzene solution was extracted with 5% aqueous hydrochloric acid from which the amine was isolated as described above; yield, 8.5 g. (40%). The *benzoyl* derivative of the amine melted at 213.5–214.5° and did not depress the melting point of an authentic sample of the benzoyl derivative of *trans*-4-phenylcyclohexylamine described above.

The action of nitrous acid on 2-phenyl-4,5-dimethylcyclohexylamine. The procedure was essentially that of Hückel (12). A saturated aqueous solution of 13.5 g. (0.19 mole) of sodium nitrite was added slowly with stirring to a solution of 28 g. (0.13 mole) of amine in 115 cc. of 10% acetic acid. The mixture was heated and stirred at 80-90° for two hours. The oily layer was extracted with ether, washed with 10% hydrochloric acid, 10% sodium carbonate, and water, and the ether solution was dried over Drierite. Distillation of the product at 1 mm. yielded three fractions: (a) 7 g., b.p. 90–101°, n_D^{25} 1.5228; (b) 7 g., b.p. 101–107°, n_D^{25} 1.5234; (c) 12 g., b.p. 107–115°, n_D^{25} 1.5232. Attempts to purify these fractions by distillation through a micro column resulted in partial decomposition of the carbinol. A center cut of fraction c was used for the analytical sample of II.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.30; H, 9.86.

Found: C, 81.98; H, 9.76.

Fractions a and b were largely II; a sample of fraction b liberated one mole of methane from methylmagnesium iodide in the Grignard machine. Fractions of similar refractive indices were obtained from several reactions.

Oxidation of dimethylcyclopentylphenylcarbinol (II). To a stirred solution of 7 g. of II dissolved in 12 cc. of glacial acetic acid was added dropwise 7 g. of chromic oxide in 13 cc. of 80% acetic acid at such a rate that the temperature did not rise above 50°. After standing 24 hours at room temperature, the reaction mixture was poured into 60 cc. of water and extracted with benzene. The benzene extract was washed with 5% sodium carbonate solution and then with water, dried over Drierite, and distilled. The crude ketone distilled at 140–147° (5 mm.); n_D^{25} 1.5180. Purification of this crude ketone with Girard's "T" reagent yielded pure III, b.p. 110–112° (5 mm.); n_D^{20} 1.5138. Fractions a and b also yielded the ketone III.

Anal. Calc'd for $C_{14}H_{18}O$: C, 83.12; H, 8.97.

Found: C, 83.33; H, 9.08.

The *2,4-dinitrophenylhydrazone* of III melted at 115–116°.

Anal. Calc'd for $C_{20}H_{22}N_4O_4$: C, 62.82; H, 5.79.

Found: C, 62.29; H, 5.76.

Schmidt reaction with III (13). The dimethylcyclopentylphenyl ketone III (3 g., 0.015 mole) was dissolved in 20 ml. of 90% sulfuric acid in a three-necked flask and cooled to 0°. The flask was fitted with a reflux condenser and a stirrer. Sodium azide (1.43 g., 0.02 mole) was added through the third neck. The mixture was allowed to stand for six hours at 0° and was stirred intermittently. The thick liquid was then poured onto ice and the solution was neutralized with 10% sodium hydroxide and extracted with benzene. The benzene extracts were combined and concentrated to yield the amide IV as a gummy solid which could not be crystallized.

This crude amide was hydrolyzed with hydrochloric acid in alcohol solution to yield aniline and dimethylcyclopentanecarboxylic acid, the latter as a mushy solid of no definite melting point. The crude acid was dissolved in benzene, traces of water were removed by azeotropic distillation, and the benzene was evaporated to a small volume. Thionyl chloride (10 ml.) was added to the acid and the solution was refluxed for 30 minutes. The benzene and excess thionyl chloride were removed at reduced pressure and aniline was added to the crude acid chloride. Recrystallization of this anilide IV, first from alcohol and finally from petroleum ether (60–70%), yielded pure IV, m.p. 110–111°.

Anal. Calc'd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81.

Found: C, 77.78; H, 8.81.

The amine from this particular hydrolysis had a slight odor characteristic of cyclopentylamine, and on benzoylation yielded an amide, m.p. 154–155°, which did not depress the melting point of an authentic sample of benzanilide. Benzoylation of the aniline from the hydrolysis of another sample of IV yielded benzanilide, m.p. and mixture m.p. with an authentic sample 161–162°.

trans-4-Phenylcyclohexylamine and nitrous acid. The procedure, based on Demjanow's method (14), is typical and is described in detail. Solid sodium nitrite (5 g.) was ground with 10 g. (0.05 mole) of *trans*-4-phenylcyclohexylamine hydrochloride. The mixture was placed in a 500-ml. three-necked flask equipped with a reflux condenser and a stirrer. Water (100 ml.) was added and the mixture was stirred and refluxed for 12 hours.

The cooled solution was extracted with ether and the ether was washed with 10% aqueous hydrochloric acid, 10% sodium carbonate, and water. A total of 3 g. of amine hydrochloride was recovered from the acid washings. The ether solution was dried over Drierite and the solvent was removed by distillation to yield 4 g. of crude product. Recrystallization from benzene yielded 3 g. (53% based on the amine which reacted), of pure carbinol, m.p. 117–118°, recorded value 117.2–118.5° (9). The melting point of a mixture of this compound and authentic *trans*-4-phenylcyclohexanol was 116.5–118°.

trans-4-Cyclohexylcyclohexylamine yielded *trans*-4-cyclohexylcyclohexanol (49%), m.p. 102.5–104°, which did not depress the melting point (103–104°) of an authentic sample of carbinol.

trans-4-*tert*-Butylcyclohexylamine yielded *trans*-4-*tert*-butylcyclohexanol (55%), m.p. 78–79°, recorded value 80–80.5° (15). A mixture of this carbinol and an authentic sample (m.p. 79–80°) melted at 77–79°.

trans-4-Methylcyclohexylamine yielded *trans*-4-methylcyclohexanol (60%) which formed a *p*-nitrobenzoyl ester, m.p. 64–64.5°. A mixture of this ester and an authentic sample of the ester (m.p. 66–67°) was 64–66°.

trans-2-Cyclohexylcyclohexylamine (16 g.) yielded a liquid which was collected in two fractions: (a) 7 g., b.p. 86–100° (1 mm.), n_D^{19} 1.4960; (b) 4.5 g., b.p. 110–118° (1 mm.), n_D^{19} 1.4980.

Fraction a reacted with sodium but it would not form a solid derivative, and oxidation yielded no identifiable product.

Fraction b partially solidified on standing at room temperature. The solid 2-cyclohexylcyclohexanol melted at 47–48° and recrystallization from petroleum ether (28–38°) did not change the melting point. It formed a *phenylurethan*, m.p. 126–128°. These values both correspond to a mixture of approximately 13% of the *cis* isomer and 87% of the *trans* isomer (7). The recorded value for *trans*-2-cyclohexylcyclohexanol is 52° and for its phenylurethan 136° (7). The phenylurethan, m.p. 126–128°, did not depress the melting point of the same derivative of the 2-cyclohexylcyclohexanol obtained by reduction of 2-cyclohexylcyclohexanone.

When 32 g. of *trans*-2-cyclohexylcyclohexylamine was reacted with nitrous acid by the procedure which Maienthal used for *trans*-2-phenylcyclohexylamine (1), 12 g. of amine was recovered. The reaction product was distilled at 4 mm. and collected in four fractions: (a) 4 g., b.p. 88–95°, n_D^{20} 1.4905; (b) 3 g., b.p. 97–105°, n_D^{20} 1.4928; (c) 4 g., b.p. 105–121°, n_D^{20} 1.4956; (d) 5 g., b.p. 124–125°, n_D^{20} 1.4975. A tarry residue remained in the flask.

Carbon and hydrogen analyses of fractions a and b indicated that they contained 40–50% olefin.

Fractions c and d did not solidify, but they both formed a *phenylurethan*, m.p. 126–127° which did not depress the melting point of the phenylurethan of 2-cyclohexylcyclohexanol m.p. 127–128°.

SUMMARY

2-Phenyl-4,5-dimethylcyclohexylamine reacted with nitrous acid to form dimethylcyclopentylphenylcarbinol.

The *trans* forms of 4-phenyl-, 4-cyclohexyl-, 4-*tert*-butyl-, and 4-methylcyclohexylamine yielded the corresponding *trans*-4-R-cyclohexanols.

trans-2-Cyclohexylcyclohexylamine yielded a mixture of *cis*- and *trans*-2-cyclohexylcyclohexanol.

Columbia, Missouri

REFERENCES

(1) Nightingale and Maienthal, *J. Am. Chem. Soc.*, **72**, 4823 (1950).
(2) Skita, *Ber.*, **56**, 1014 (1923).
(3) Cauquil, Guizard, and Calas, *Bull. soc. chim.*, [5] **9**, 252 (1942).
(4) Anziani and Cornubert, *Compt. rend.*, **221**, 103 (1945).
(5) Mousseron, Froger, Granger, and Winternitz, *Bull. soc. chim.*, 843 (1947).
(6) King, Barltrop, and Walley, *J. Chem. Soc.*, 277 (1945).
(7) Hückel, Nuenhoeffer, Gercke, and Frank, *Ann.*, **477**, 99 (1929).
(8) Nightingale and Tweedie, *J. Am. Chem. Soc.*, **66**, 1969 (1944).
(9) Ungnade, *J. Org. Chem.*, **13**, 361 (1948).
(10) Hückel and Doll, *Ann.*, **526**, 103 (1936).
(11) Skita and Hauber, *Angew. Chem.*, **34**, 230 (1921).
(12) Hückel, *Ann.*, **533**, 9 (1937).
(13) Dice and Smith, *J. Org. Chem.*, **14**, 179 (1949).
(14) Demjanow, *Ber.*, **40**, 4393 (1907).
(15) Vavon and Barbier, *Bull. soc. chim.*, [4] **49**, 567 (1931).