

hours. Removal of the methanol, acidification and continuous extraction afforded 27 g. (77%) of crude III. Two crystallizations from benzene-isopropyl ether gave 23 g. (67%) of III, m.p. 76–79° (reported¹⁶ 78–79°).

Anal. Calcd. for C₇H₁₂O₃: neut. equiv., 88.1. Found: neut. equiv., 87.

Resolution of III.—Cinchonidine, when mixed with III in the molar proportions of two-to-one gave a salt which crystallized readily from water, m.p. 181–182° dec.

Anal. Calcd. for C₄₅H₅₆O₇N₄: C, 70.65; H, 7.38; N, 7.32. Found: C, 70.42; H, 7.27; N, 7.50.

After several crystallizations, the α -methoxyadipic acid regenerated from the head fractions had m.p. 80–85°, [α]_D²³ –6.85° (*c* 2 in ethyl acetate). Crystallization from methanol-ethyl acetate was also feasible, and using this solvent pair, resolution proceeded somewhat further. From 200 g. of salt there was obtained after fractional crystallization 4.5 g. of (–) α -methoxyadipic acid from the head fraction of the salt, m.p. 90–97°, which when further purified by partition chromatography on silicic acid⁶ had m.p. 94.5–97°, [α]_D^{22.5} –50.6° (*c* 2 in ethyl acetate), neut. equiv., 88.0. This material showed an infrared spectrum identical with that obtained by Noyce and Denney.⁶ From the second fraction there was obtained 2.2 g. of (–)III, m.p. 84–95°, [α]_D²⁰ –47.8° (*c* 2 in ethyl acetate).

From the appropriate mother liquors there was obtained 16.7 g. of partially resolved (+)-III, m.p. 76–81°, [α]_D²⁰ +4.75°.

Reduction of III.—*dl*- α -Methoxyadipic acid, 10 g. (0.057 mole), esterified with diazomethane, was reduced with a slurry of 4.5 g. of lithium aluminum hydride in 200 ml. of ether. The mixture was allowed to reflux overnight. Water (20 ml.) was added cautiously to destroy excess reducing agent, and the mixture was acidified with 6 *N* sulfuric acid. The 2-methoxy-1,6-hexanediol was recovered by continuous ether extraction for 36 hours. It was necessary to add methanol to the ether after extraction to obtain an homogeneous solution. After drying and removal of the volatile solvents, distillation afforded 4.5 g. (53%) of 2-methoxy-1,6-hexanediol, b.p. 125° (0.5 mm.), as a very viscous sirup.

The bis-*p*-nitrobenzoate was prepared in the usual fashion and crystallized from ethanol, m.p. 73.0–74.2°.

Anal. Calcd. for C₂₁H₂₂N₂O₉: C, 56.60; H, 4.97; N, 6.28. Found: C, 56.68; H, 4.85; N, 6.37.

In a similar manner 1.5 g. of (–)III ([α]_D –50.6°) was reduced *via* the ester to give 0.5 g. (40%) of (–)2-methoxy-

1,6-hexanediol, b.p. 122–124° (0.5 mm.), [α]_D¹⁷ –3.0° (*c* 2 in methanol).

Likewise, 15.0 g. of (+)-III, [α]_D +4.75°, was reduced with lithium aluminum hydride to give 5.5 g. (44%) of (+)VIII, b.p. 120–123°, [α]_D^{21.5} 0.28° (*c* 5 in methanol). The bis-*p*-nitrobenzoate, crystallized from ethanol, m.p. 69.6–71.0°, but had no observable rotation.

Anal. Found: C, 56.44; H, 5.00; N, 6.06.

Formation of the Bis-*p*-toluenesulfonate of VIII.—To a cooled solution of VII in 20 ml. of pyridine, 5.7 g. of *p*-toluenesulfonyl chloride was added. The mixture was stirred at room temperature for five hours, added to water, and acidified with 6 *N* sulfuric acid. The aqueous solution was extracted with benzene, and the benzene extract dried and the benzene removed by distillation. There was obtained 2 g. (32%) of an oil which slowly crystallized. Crystallization from ether-pentane afforded the bis-*p*-toluenesulfonate of VIII, m.p. 63.0–64.4°.

Anal. Calcd. for C₂₁H₂₈O₇S₂: C, 55.24; H, 6.18; S, 14.04. Found: C, 55.27; H, 6.28; S, 14.19.

In a similar fashion the bis-*p*-toluenesulfonate of (+)-VII was obtained as an oil which was used immediately before crystallization occurred.

Reduction of the Bis-*p*-toluenesulfonate of VIII: Formation of 2-Methoxyhexane (IX).—A solution of 1.7 g. of crude bis-*p*-toluenesulfonate of VIII in benzene was added to a slurry of 2.0 g. of lithium aluminum hydride in 50 ml. of di-*n*-propyl ether. The mixture was heated under reflux for 3 days. At the end of this time, the excess lithium aluminum hydride was decomposed with 10 ml. of water, and acidified with 6 *N* sulfuric acid. The ether layer was separated, washed with dilute sodium hydroxide solution, dried and fractionated through a two-foot modified Podbielniak column. There was obtained 0.10 g. of *dl*-2-methoxyhexane (22%), b.p. 115°. The infrared spectrum of this material was indistinguishable from the infrared spectrum of 2-methoxyhexane obtained from 2-hexanol, by methylation with methyl iodide.

In a similar manner, 5.0 g. of the crude bis-*p*-toluenesulfonate of (+)-VIII was reduced to afford after distillation through a modified Lecky-Ewell column, 0.55 g. of (+)2-methoxyhexane, b.p. 114–115°, [α]_D^{18.5} +0.37° (homog., 11) which was characterized by infrared spectrum. The infrared spectrum of the (+)2-methoxyhexane was essentially identical with the spectrum of the material obtained above, except for the presence of two weak bands characteristic of toluene at 728 and 694 cm.⁻¹.

(15) W. Meyer and M. B. Neymeyr, *Ann.*, **572**, 212 (1951).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Synthetic Routes to *trans*-2-Decalone

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Various possible routes to *trans*-2-decalone from readily available starting materials have been investigated. Several reported transformations of certain $\Delta^{1,9}$ -2-octalones to *trans*-2-decalone involving catalytic hydrogenations have been shown to yield instead *cis*-2-decalone. Two new methods for the production of the *trans*-isomer from the octalone have been developed: (1) catalytic hydrogenation of the enol ethyl ether followed by hydrolysis of the resulting dihydro derivative or, preferably, (2) reduction with excess lithium in liquid ammonia and subsequent chromic acid oxidation of the unisolated intermediate decalol.

In connection with the prosecution of certain research programs in this Laboratory^{1a} as well as in others,^{1b} the need for *trans*-2-decalone (I) encouraged us to develop a convenient preparative method for this substance. The purpose of this report is to describe such a method and also to present our experimental evaluations of other possible routes to the same compound—both those at-

tempted for the first time in this Laboratory as well as those described in the previous literature.

Although the 105°-melting *cis*-2-decalol, convertible to *cis*-2-decalone (II) by chromic acid oxidation, can be readily obtained from 2-naphthol by

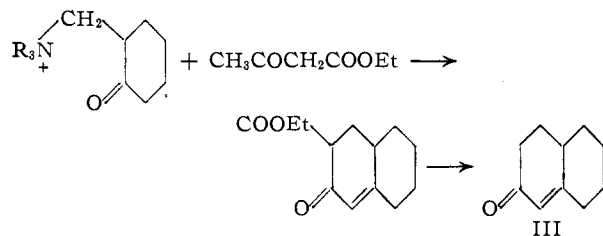


(1) (a) E. E. van Tamen and M. Shamma, *THIS JOURNAL*, **76**, 950 (1954); (b) *e.g.* A. R. Pinder and R. Robinson, *J. Chem. Soc.*, 1221 (1952).

catalytic hydrogenation,² the utilization of the naphthol in the preparation of the *trans* ketone does not appear to be nearly as satisfactory. Hückel³ has published a procedure for isolating the small percentage of *trans*-2-decalol of melting point 75° present in the mixture obtained by various catalytic hydrogenation procedures⁴; the use of Hückel's method is, however, far from practical on a laboratory scale when sizable amounts of the *trans*-ketone are required.

An apparent exception to the rule of preponderant *cis*-decalol formation in such hydrogenation techniques is the report of Baker and Schuetz⁵ that platinum-catalyzed hydrogenation of 2-naphthol in glacial acetic acid at room temperature and under high pressure afforded an 89% yield of the 75°-*trans*-decalol. Numerous attempts on our part to reproduce this result have been fruitless; only the 105°-*cis*-decalol (average yield 84%) could be isolated.⁶ In spite of the shortcomings of the 2-naphthol hydrogenation, it apparently has been the route most commonly used^{1b,3,6} for the preparation of I.

Another promising pathway to the *trans* series involves the reduction of $\Delta^{1,9}$ -2-octalone (III) or a related substance. Since the octalone is readily available by cyclization and decarbomethoxylation of the product obtained by condensing ethyl acetoacetate and a quaternary salt of a Mannich base⁷ derived from cyclohexanone,⁸ is not surprising that



accounts of such reductions have already appeared in the literature. For example, Mannich^{9a} claimed that hydrogenation in methanol over a palladium-on-charcoal catalyst yielded the *trans*-decalone, while Robinson^{9b} in the same year reported the preparation of the *cis* ketone by hydrogenation over palladium-on-strontium carbonate in neutral medium. The experimental directions given by Mannich were carefully repeated several times and yet each time the only material isolated was *cis*-2-decalone, which was identified by its boiling point and refractive index as well as by the preparation of a semicarbazone and a dinitrophenylhydrazone.

(2) F. Radt, "Elsevier's Encyclopedia of Organic Chemistry," Vol. 12B, Elsevier Publishing Co., Inc., New York, N. Y., 1950, pp. 1364-1365.

(3) W. Hückel, *Ann.*, **451**, 109 (1927).

(4) Reference 2, p. 1370.

(5) R. H. Baker and R. D. Schuetz, *THIS JOURNAL*, **69**, 1250 (1947).

(6) W. H. Dauben, E. Hoerger and N. K. Freeman, *ibid.*, **74**, 5208 (1952), have reported similar findings.

(7) C. Mannich and P. Braun, *Ber.*, **53**, 1874 (1920).

(8) Dr. R. Pappo and Mr. W. Tsatsos have developed in this Laboratory a convenient synthesis of $\Delta^{1,9}$ -2-octalone in which cyclohexanone is condensed with methyl vinyl ketone in the presence of Triton B; cyclization of the addition product affords III in about 30% over-all yield.

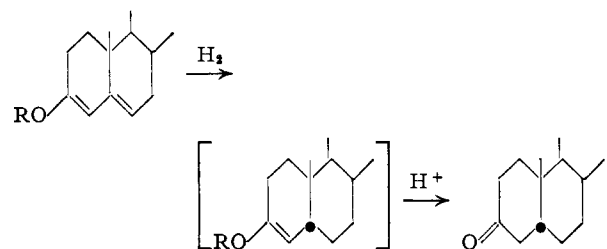
(9a) C. Mannich, W. Koch and F. Borkowsky, *Ber.*, **70**, 355 (1937).

(9b) E. C. Du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, **53** (1937)

In the reported hydrogenation of $\Delta^{1,9}$ -3-carboxy-2-octalone to the *trans*-locked ketone^{9a} we again encounter a claim at variance with our own experimental findings. Mannich stated that decarboxylation of the hydrogenated keto acid affords *trans*-decalone; we find that his directions are reliable in every respect except for the identification of the final product, which is not *trans*, but *cis*-2-decalone, identified in the manner just described.

In the hope that variations of the hydrogenation technique might alter the stereochemical course, we attempted the reduction of III with different solvents and catalyst combinations or with small amounts of either strong acid or base added; in each case, however, the *cis*-ketone was the preponderant, if not the sole, product.

We then sought to apply to this simple problem some of the recently developed techniques for more complex octalone \rightarrow *trans*-decalone transformations. One of these is the catalytic hydrogenation of the enol ether¹⁰ of the octalone followed by hydrolytic cleavage, a procedure frequently successful in the steroid field. The operations involved in the application of this scheme to the parent octa-



lone III proved to be, however, decidedly capricious. The preparation of the enol ether by treatment of III with ethyl orthoformate was not reliably reproducible in that the refractive indices as well as ethoxyl and carbon-hydrogen determinations were erratic; moreover the product foamed badly during distillation. The hydrogenation tended to be most nearly reproducible when the enol ether was used *immediately* after preparation. By adhering rigidly to a procedure ultimately developed and by using scrupulously dried and purified solvents at all necessary points, over-all yields approximating 20-40% of product consisting of 70-88% *trans* ketone, could be obtained.

The last and most successful approach attempted was the direct chemical reduction of III. After carrying out a number of trial runs in which the proportion of reducing agent to ketone was varied, we found that reduction with a 250% excess of lithium metal in liquid ammonia¹¹ afforded a product—presumably mostly *trans*-decalol—which, without isolation, was oxidized by chromic acid to give a 65-66% over-all yield of ketonic material, which refractive index analysis indicated to be 90% *trans*-2-decalone. The identity of the product was confirmed by the preparation of an oxime and a dinitrophenylhydrazone as well as by nitric acid oxidation to *trans*-cyclohexane-1,2-diacetic acid.

(10) A. Serini and H. Köster, *Ber.*, **71**, 1766 (1938).

(11) A. L. Wilds and N. A. Nelson, *THIS JOURNAL*, **75**, 5360, 5366 (1953).

Experimental¹²

Hydrogenation of $\Delta^{1,9}$ -2-Octalone.— $\Delta^{1,9}$ -2-Octalone⁷ was hydrogenated in absolute methanol over 5% palladium-on-charcoal at room temperature and at an initial pressure of 40 lb. per sq. in.⁹ The product, which was worked up in the usual fashion, boiled at 120° (19 mm.), n_D^{25} 1.4915; the corresponding constants for authentic *cis*-2-decalone are 119° (16 mm.)¹³ and n_D^{20} 1.4935.¹⁴ The melting points of the semicarbazone (184°) and the dinitrophenylhydrazone (154–156°) compared favorably with those of the corresponding authentic derivatives (182–183°¹⁵; 185–186°¹³ and 155–156°¹⁰ respectively). No depressions in appropriate mixed melting points were observed.

Reduction of 3-Carboxy- $\Delta^{1,9}$ -2-octalone.—Mannich's directions⁹ for the hydrogenation and subsequent decarboxylation of 3-carboxy- $\Delta^{1,9}$ -2-octalone were followed as closely as possible. After decarboxylation of the intermediate carboxydecalone, a practically quantitative yield of *cis*-2-decalone resulted, n_D^{25} 1.4916. The melting point (182–183°) of a semicarbazone was not depressed on admixture with authentic *cis*-2-decalone semicarbazone.

Ethyl Enol Ether of $\Delta^{1,9}$ -2-Octalone.—Five grams (0.033 mole) of the octalone, 13.2 g. (0.09 mole) of freshly distilled ethyl orthoformate, 0.7 ml. of absolute ethyl alcohol, 70 ml. of anhydrous¹⁶ dioxane and 3.6 ml. of dioxane containing 0.18 ml. of concentrated sulfuric acid were mixed in a 125-ml. erlenmeyer flask. During the 18 minutes the reaction was allowed to stand, it changed from colorless to light chartreuse and finally to dark green. The reaction was then stopped by the addition of 2 ml. of pyridine, upon which the color changed to a clear yellow-orange. Excess solvents and reactants were removed by distillation *in vacuo* (water aspirator). Fractionation of the residue, which is accompanied by foaming, yielded 45–70% of $\Delta^{1,9}$ -2-octalone ethyl enol ether, b.p. 88–89° (0.5 mm.). In successful runs the refractive indices lay in the range 1.5180–1.5190 (n_D^{25}). Material of the highest refractive index was analyzed within a day after preparation; runs which gave n values below 1.5100 or which were allowed to stand for some days, gave carbon analyses 2–4% lower than calculated.

Anal. Calcd.: C, 80.89; H, 10.17. Found: C, 80.56; H, 10.21.

Hydrogenation of $\Delta^{1,9}$ -2-Octalone Ethyl Enol Ether.—In a typical run, 19 g. of freshly prepared enol ether, dissolved in 100 ml. of pure ethyl acetate, was hydrogenated over 0.8 g. of 5% palladium-on-charcoal in a low pressure shaker. After about 10 hours the uptake of hydrogen had stopped (often the reduction did not proceed entirely to completion, as evidenced by the hydrogen uptake). After removal of the catalyst by filtration, the ethyl acetate was evaporated on the steam-bath. The residue was taken up in 30 ml. of glacial acetic acid, and then an amount of water just sufficient to maintain homogeneity of the hot solution was added. To ensure complete hydrolysis of the enol ether linkage, the resulting solution was heated on the steam-bath for 30 minutes. The cooled mixture was nearly neutralized with aqueous sodium hydroxide, after which the decalone was removed by four extractions with 50-ml. portions of ether. After being washed successively with water, saturated sodium bicarbonate and saturated sodium chloride solution, the combined ether extracts were concentrated on the steam-bath. Distillation of the residue afforded 45–60% of decalone, b.p. 120–121° (19 mm.). The refractive indices varied from 1.4825 to 1.4843, indicating (see below) the presence of 70–88% of the *trans* isomer; preparation of a semicarbazone, m.p. 194–195° dec. (lit. 192–193°¹⁵) and a dinitrophenylhydrazone confirmed the presence of this product.

(12) Melting points are corrected; boiling points are uncorrected.

(13) K. A. N. Rao, *J. Chem. Soc.*, 1954 (1929).

(14) R. P. Linstead and K. D. A. Michaelis, *ibid.*, 1134 (1940).

(15) J. W. Barret, A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 1065 (1935).

(16) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 368.

Lithium-Ammonium Reduction of $\Delta^{1,9}$ -2-Octalone.—The following operations should be carried out in a hood.

A one-liter three-necked flask fitted with a mercury-sealed stirrer, a 10-inch drying tube filled with soda-lime, and an inlet that can be closed to the atmosphere, was heated briefly with a free flame. Dry nitrogen gas was swept through the system while heating and for 30 additional minutes. After introducing 20 g. (0.133 mole) of $\Delta^{1,9}$ -2-octalone dissolved in 100 ml. of commercial anhydrous ether, the anhydrous ammonia source was connected to the flask, and 500 ml. of liquid ammonia was run in. The ammonia inlet tube was closed and stirring cautiously begun. Then, with vigorous stirring, 5 g. (0.7 mole) of lithium wire cut into small pieces was added over a 3-minute period. After the initial vigorous evolution of ammonia had ceased, the solution was stirred for ten minutes; excess ammonium chloride was then added cautiously over a 30-minute period. After the medium turned white and pasty, 100 ml. of water was added to dissolve the salts. Heating the resulting mixture for one hour on the steam-bath served to expel most of the ammonia. The reaction mixture was subsequently extracted with six 50-ml. portions of ether; the combined extracts were washed twice with water, then with 100 ml. of 5% hydrochloric acid, again with water and finally twice with saturated sodium chloride solution. After removal of the ether on the steam-bath, the brown residue was taken up in 45 ml. of glacial acetic acid. Oxidation of the decalol was effected by adding carefully and with cooling so as to maintain the temperature below 30°, a solution of 7.8 g. of chromic anhydride dissolved in the minimum amount of water. After the exothermic reaction had definitely subsided, the oxidation mixture was allowed to stand for two days. The dark green solution was then heated for two hours on the steam-bath and, with cooling, treated with a solution of 15 g. of sodium hydroxide in 60 ml. of water. After extraction with five 30-ml. portions of ether and subsequent washing of the extracts with water and saturated salt solution, the decalone was isolated and purified by vacuum distillation of the concentrated ether extract. The entire distillate boiled over about a two-degree range (e.g., 112–114° (13 mm.)), n_D^{25} 1.4823–1.4824. By combining, at the first ether extraction stage, the products of three or four separate runs, the over-all yields of 65–66% could be obtained.

Portions of the ketonic product were converted to the semicarbazone, m.p. 192–192.5° dec., and also to *trans*-cyclohexane-1,2-diacetic acid, m.p. 166–167° (lit. 167°¹⁵) in good yield by nitric acid oxidation. In our hands, the dinitrophenylhydrazone¹⁸ was not altogether satisfactory as a derivative in that the melting point was not reliably reproducible; material melting at about 147° dec. could be obtained from samples of ketone produced by both reduction procedures described above, whereas a derivative melting at 162–162.5° dec. was formed on other occasions from the product of the lithium-ammonia method. Both samples gave correct analyses and depressed the melting of the corresponding derivative from the *cis*-ketone. Whether the derivative exhibits polymorphism or is difficultly purified and possesses a melting behavior greatly influenced by the presence of isomeric (or nearly isomeric) impurities, was not determined.

Anal. Calcd.: C, 57.81; H, 6.06; N, 16.85. Found (material of m.p. 147°): C, 58.21; H, 6.29; N, 16.90. Found (material of m.p. 162–162.5°): C, 57.82; H, 6.21.

Careful fractionation of the *trans*-decalone gave a quantity of material which melted at 5.5–6.5° (lit. 6°¹⁵), n_D^{25} 1.4814, and was considered to be essentially pure. This sample and one of *cis*-2-decalone of highest purity were used to make up an empirical composition–refractive index graph; the relationship was approximately linear. By this means, the ketonic product from the lithium-ammonia method was shown to be 90% *trans*, assuming *cis*-2-decalone to be the only other component present.

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(17) A. Kandiah, *J. Chem. Soc.*, 922 (1931).

(18) A mixture of *cis*- and *trans*-2-decalone DNP¹⁸'s is reported to melt at 137° (ref. 10).