red-orange sirup was 9.5 to 10 g. This sirup was dissolved in 100 ml. of benzene and the resultant solution was extracted 20 times with 100-ml. portions (total 2 liters) of distilled water. The water extracts were then extracted with 10 portions of 100 ml. each of chloroform (total 1 liter) and these extracts dried over anhydrous sodium sulfate. The average yield of 1,3,4,6-D-fructofuranose tetraacetate as a light-colored sirup was 6.5 to 7.0 g. after removal of solvent.

An amount of 6.94 g. of 1,3,4,6-D-fructofuranose tetraacetate and 6.94 g. of 2,3,4,6-D-glucopyranose tetraacetate was dissolved in 200 ml. of dry benzene. About 0.5 g. of phosphoric anhydride was added and the reactants were shaken vigorously for forty-eight hours. The benzene solution was decanted carefully and extracted with ten 200-ml. portions (total 2 liters) of water. A yield of 2.0 g. of amber-colored sirup was obtained after solvent removal at 40° under reduced pressure. An ether solution of this sirup yielded 0.2 g. of crystals; m. p. 131–132°, mixed melting point with an authentic specimen of isosucrose octaacetate[6] was 131–132°; $[\alpha]^{27}D + 20.4°$ (*c* 4.9, chloroform). Irvine, Oldham and Skinner[7] cite for isosucrose octaacetate the constants: m. p. 131–132°, $[\alpha]D + 20°$ (*c* 3.8, chloroform).

An amount of 1.0 g. of the above sirup was dissolved in 15 ml. of benzene. This solution was added at the top of a column (43 mm. in diameter by 200 mm. in length) of a mixture of 5 parts (by wt.) of Magnesol[8] and 1 part of Celite[9] previously wetted with 35 ml. of benzene. The chromatogram was developed with 750 ml. of 100–1: benzene–ethanol[10] (volume ratio). The column was extruded and streaked with the alkaline permanganate indicator.[2] The third zone, 42–65 mm. from the top of the column, was eluted from the adsorbent with acetone (yield, 209 mg.), and 26 mg. of crystal isosucrose octaacetate separated from ethanolic solution; m. p. 131–132°, mixed melting point with isosucrose octaacetate, 131–132°. An amount of 100 mg. of material from this zone was deacetylated with 10 ml. of 0.2 *N* sodium hydroxide and on the addition of freshly prepared diazo-uracil gave a negative color test[5] for sucrose.

An amount of 5 mg. each of sucrose and isosucrose octaacetates in 1 ml. of benzene was added at the top of a column (19 mm. in diameter by 120 mm. in length) of a mixture of 5 parts (by wt.) of Silene EF[11] and 1 part of Celite (previously wetted with 10 ml. of benzene). The chromatogram was developed with 150 ml. of 250–1: benzene–ethanol (volume ratio). After extruding the column and streaking it with the alkaline permanganate indicator, two zones were detected and isolated by elution with acetone. Zone 1 was 59–79 mm. from the top; zone 2 was 85–97 mm. An ethanolic solution of the material from zone 1 gave crystals, m. p. 84–85°, mixed melting point with sucrose octaacetate 84–85°; a similar treatment of the material from zone 2 gave crystals, m. p. 131–132°, mixed melting point with isosucrose octaacetate 131–132°. An amount of 10 mg. of material from the previously described third zone of the Magnesol chromatogram was adsorbed on Silene EF exactly as described above. Only one zone, 91–101 mm. from the top of the column, was detected and isolated. An ethanolic solution of this zone material yielded crystals; m. p. 131–132°, mixed melting point with isosucrose octaacetate 131–132°.

(6) Kindly supplied by Dr. E. T. Stiller.

(7) J. C. Irvine, J. W. H. Oldham and A. F. Skinner, THIS JOURNAL, **51**, 1279 (1929).

(8) Westvaco Chlorine Products Co., South Charleston, West Virginia.

(9) No. 535, Johns–Manville Co., New York, N. Y.

(10) All ethanol used in the chromatographic work was absolute; all benzene was thiophene-free.

(11) Columbia Chemical Division, Pittsburgh Plate Glass Co., Barberton, Ohio.

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Summary

1. New directions are cited for the preparation of 1,3,4,6-D-fructose tetraacetate from inulin.

2. An investigation, by chromatographic brush techniques, of the condensation products of 1,3,-4,6-D-fructose tetraacetate and 2,3,4,6-D-glucose tetraacetate yielded only isosucrose octaacetate.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE LAKESIDE LABORATORIES, INC.]

The Preparation of β-Tetralone by the Catalytic Reduction of β-Naphthol

BY GILBERT STORK AND E. LEON FOREMAN

In spite of its very interesting and sometimes unexpected properties, β-tetralone has been a comparatively unavailable compound. It is true that a number of methods have been devised for its preparation but they either give very low yields or involve a great number of steps.

Bamberger and Lodter,[1] who first prepared this compound, used the reaction of 2-hydroxy-3-chloro-1,2,3,4-tetrahydronaphthalene with quinoline and obtained a poor yield of β-tetralone. Almost simultaneously, Einhorn and Lumsden prepared the ketone by the dry distillation of the calcium salt of the dicarboxylic acid obtained by the reduction of either 2-hydroxy-1-naphthoic acid or of 2-hydroxy-3-naphthoic acid with sodium and alcohol.[2] The isomerization of the oxide of 3,4-dihydronaphthalene under the influence of anhydrous hydrogen chloride was used by Straus and Rohrbacher,[3] while more recently Tchoubar performed this isomerization with the help of magnesium bromide.[4]

Another approach to the problem was that of v. Braun and his collaborators who isolated good yields of β-tetralone from the pyrolysis of the methiodide of 1-dimethylamino-2-hydroxy-1,2,3,-4-tetrahydronaphthalene. Unfortunately, the method of preparation of the last mentioned compound required numerous steps from *ac*-tetrahydro-β-naphthol.[5] Crowley and Robinson devised a method starting with γ-phenylbutyric acid which consisted essentially of the Curtius degradation of ethyl 3,4-dihydro-β-naphthoate.[6] In spite of the considerable theoretical interest which some of these methods present, they are ill-suited

(1) Bamberger and Lodter, *Ber.*, **26**, 1833 (1893).

(2) Einhorn and Lumsden, *Ann.*, **286**, 257 (1895).

(3) Straus and Rohrbacher, *Ber.*, **54**, 40 (1921).

(4) Tchoubar, *Compt. rend.*, **214**, 117 (1942).

(5) v. Braun, Braunsdorf and Kirschbaum, *Ber.*, **55**, 3648 (1922).

(6) Crowley and Robinson, *J. Chem. Soc.*, 2001 (1938).

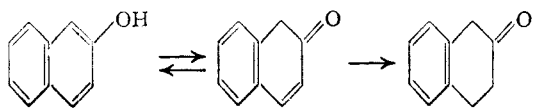
to the laboratory preparation of β-tetralone. In fact, it is only within the last few years that methods have been proposed which offer a convenient route to the desired compound. The first of these, devised by Cornforth, Cornforth and Robinson,[7] uses the sodium and alcohol reduction of β-naphthol methyl ether to the enol ether of β-tetralone which is then hydrolyzed to the ketone.

The second method, recently proposed by Birch, involves the direct reduction of β-naphthol to β-tetralone by means of sodium in liquid ammonia, *t*-amyl alcohol being used as the source of hydrogen.[8] Yields as high as 65% of the theoretical have been claimed for this procedure.

While both of these methods are quite useful and relatively easy to carry out on a small scale, the difficulties involved in handling lange quantities of sodium and the troublesome use of liquid ammonia were thought to constitute serious drawbacks if one wanted to prepare sizable quantities of β-tetralone.

It seemed that it might be possible to effect the conversion of β-naphthol to β-tetralone by some process of catalytic hydrogenation rather than by chemical reduction. It was thought that such a process might be successful, as the catalytic hydrogenation of phenols to ketones has been reported in certain selected cases. For example, appreciable quantities of cyclohexanone have been obtained from the catalytic reduction of phenol with platinum black.[9] In spite of this, a previous attempt to obtain β-tetralone from the catalytic reduction of β-naphthol, using nickel as the catalyst, was fruitless.[10] We have confirmed this finding, although it is certain that small amounts of β-tetralone were formed during this reduction, as evidenced by the blue coloration obtained when the reduction mixture was treated with an alcoholic solution of sodium hydroxide.[7]

If the reduction of β-naphthol should proceed by way of the α,β-unsaturated ketone tautomer, it might be possible to stop the hydrogenation at the β-tetralone stage with a catalyst which would show less tendency to reduce the carbonyl group than is exhibited by Raney nickel. It was thought



that palladium-on-charcoal might be such a catalyst.

When this catalyst was used at room temperature and pressure no hydrogenation took place, and it was therefore decided to try high pressure hydrogenation at elevated temperature. At an initial hydrogen pressure of about 2,000 pounds, it was necessary to raise the temperature to about 180° before an appreciable rate of reduction was obtained, and even then the absorption of hydrogen was extremely slow. The mixture of reduction products gave a dark blue coloration when treated with alcoholic sodium hydroxide solution, and it was in fact possible to isolate a small amount of β-tetralone, as the bisulfite addition compound. The yield was very low, but the experiment showed that the reduction of β-naphthol to β-tetralone by catalytic hydrogenation was possible.

It was though that a base might promote the reduction to the ketone stage, possibly by favoring the shift toward the ketonic tautomer of β-naphthol, and in that expectation small quantities of the readily available N-ethyl morpholine were used in the reaction. This seemed to promote the reduction considerably, as the absorption of one mole of hydrogen was completed in ten to fifteen hours. Distillation of the reaction products gave essentially two fractions; the lower boiling one was liquid, while the other solidified and consisted of recovered β-naphthol. From the first fraction β-tetralone could readily be isolated through its bisulfite addition compound. In this manner, we obtained yields up to 40% of the theoretical (65% yield based on the β-napthol not recovered).

The mechanism of the reaction by which β-tetralone is formed is by no means certain, although the hypothesis that the keto form of β-naphthol undergoes reduction is attractive. The reduction of β-naphthol through its keto form has been postulated by Musser and Adkins[11] to explain the fact that β-naphthol is reduced over copper chromite while its ethyl ether is not. Heretofore, however, such a mechanism was conjectural since no β-tetralone, which would be the first reduction product expected from the ketonic tautomer, had ever been isolated from a catalytic hydrogenation of β-naphthol. The data presented here support the view that the ketonic tautomer is an intermediate in the reduction, although we are aware of the fact that other explanations are possible.

Experimental

Formation of β-Tetralone in the Absence of Base.—A solution of 144 g. of β-naphthol in 240 ml. of absolute alcohol was reduced in the presence of 10 g. of a palladium charcoal catalyst containing about 5% palladium. The hydrogenation bomb was charged with hydrogen at an initial pressure of 2000 pounds. The bomb was heated to 180° and shaken until one mole of hydrogen had been absorbed. This required forty-eight hours. After cooling the reaction vessel and filtering the catalyst, the alcohol was removed and the residue was distilled under reduced pressure to give a fraction boiling up to 166° at 25 mm., consisting of a mixture of β-tetralone and tetrahydronaphthol. This was treated with saturated sodium bisulfite solution, the solid bisulfite addition compound of β-tetralone was filtered, washed with ether and dried. The material thus obtained weighed 15 g. and β-tetralone could easily be recovered from it by warming with 10% sulfuric acid.

Formation of β-Tetralone in the Presence of N-Ethylmorpholine.—A solution of 72 g. of β-naphthol in alcohol

(7) Cornforth, Cornforth and Robinson, *J. Chem. Soc.*, 890 (1942).
(8) Birch, *J. Chem. Soc.*, 430 (1944).
(9) Vavon and Detrie, *Compt. rend.*, **172**, 1231 (1921).
(10) Schroeter, *Ann.*, **426**, 89 (1921).
(11) Musser and Adkins, THIS JOURNAL, **60**, 664 (1938).

containing 25 ml. of N-ethylmorpholine (total volume was 250 ml.) and 5 g. of a palladium charcoal catalyst containing 5% palladium were treated as above under an initial hydrogen pressure of 2500 pounds. Reduction was carried out at 175°, and the absorption of one mole of hydrogen required between ten and fifteen hours. After removing the catalyst by filtration, ether was added to the solution which was then extracted with dilute hydrochloric acid to remove the N-ethylmorpholine. If this were not done, the solution turned dark because of the effect of the base on β-tetralone. The clear, orange-yellow solution was washed with water, dried over anhydrous sodium sulfate and distilled under reduced pressure. Fifty grams of a fraction b. p. 116–135° at 5 mm. was obtained, and on shaking with a saturated sodium bisulfite solution gave 50 g. (40%) of the bisulfite addition compound of β-tetralone. The β-tetralone recovered from several experiments was identified as its semicarbazone m. p. 193–194° (reported m. p. 193°).[8]

Summary

The preparation of β-tetralone by the high pressure catalytic hydrogenation of β-naphthol with a palladium catalyst is described.

The mechanism of this reaction is briefly considered.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON AND CO.]

Analgesics. I. N-Alkylated-1,2-diphenylethylamines Prepared by the Leuckart Reaction

BY L. H. GOODSON, C. J. W. WIEGAND[1] AND JANET S. SPLITTER[2]

The preparation of amines from aldehydes and ketones by their reaction with excess ammonium formate has come to be known as the Leuckart reaction. In a recent paper by F. S. Crossley and M. L. Moore[3] the bibliography for the work on this reaction is given along with some of their own results and views on the reaction mechanism.

In the present investigation the Leuckart reaction has been utilized in the preparation of N-alkylated-1,2-diphenylethylamines. Two other amines not belonging to this series are included for purposes of comparison. The primary amines and formic acid were mixed and used in the reaction with ketones without isolating the intermediate ammonium salts or formamides. As may be seen from the summary of the results (Table I), the yields of N-alkylated-1,2-diphenylethylamine varied from 5 to 36%. At first glance it would appear that these low yields are due to the activating influence of the phenyl groups and the ease with which the resulting amines cleave to give stilbene derivatives and aliphatic amines. That this explanation is not sufficient is shown by the reaction of formamide on desoxyanisoin where a yield of 75% of 1,2-di-*p*-methoxyphenylethylamine was obtained (Table I). Neither should the low yields be attributed solely to the presence of the alkyl group on the formamide since Novelli,[4] in his experiments on the Leuckart reaction, employed the formamides prepared from methyl, ethyl and butyl amines on *p*-chloroacetophenone and obtained yields of 70–80% of the corresponding secondary amines.

When sufficient quantities of the amines for pharmacological testing had been obtained, there was usually no attempt to work out the optimum conditions. However, the time, temperature and catalyst were varied somewhat in an attempt to improve the yield of N-methyl-1,2-di-*p*-methoxyphenylethylamine. In each of these cases approximately four moles of methyl formamide was treated with one mole of desoxyanisoin. It appeared that the addition of a few grams of acetic acid or sodium acetate had little or no effect in promoting the reaction whether it be added at the beginning or in small portions throughout the reaction. Temperatures of 140° or below gave no appreciable reaction and the starting materials were recovered unchanged. In another experiment the mixture was heated to 225° for six hours; this gave none of the desired product and the starting ketone could not be recovered. In this particular experiment the neutral fraction was crystallized from acetic acid to give a little di-*p*-methoxystilbene, m.p. 210–211°, which gave no depression of its melting point on mixing with an authentic sample. This derivative was presumably formed by the pyrolysis of the formyl derivative of the N-methyl-1,2-di-*p*-methoxyphenylethylamine. Of the conditions tried, those listed in the table for this compound appear to be the best.

It is particularly interesting to note that β-diethylaminoethylamine and ethanolamine may be used in the Leuckart reaction to give secondary amines possessing the β-diethylaminoethyl- or β-hydroxyethyl groups, respectively.

The salts of these compounds, if soluble to the extent of 1% or more in water, were tested for their analgesic action on mice by Professor Harald Holck of the School of Pharmacy, University of Nebraska. Whereas detailed pharmacology on these compounds will be published at a later date, preliminary results indicate that N-methyl-1,2-di-*p*-methoxyphenylethylamine and N-methyl-1-*p*-methoxyphenyl-2-phenylethylamine do possess some analgesic activity but are less active than isonipecaine.

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(2) Present address: 5585 Waterman, St. Louis, Mo.

(3) F. S. Crossley and M. L. Moore, *J. Org. Chem.*, **9**, 529 (1944).

(4) A. Novelli, THIS JOURNAL, **61**, 520 (1939).