4,500) (one month later); infrared bands (in chloroform) at 1745, 1660 and 1573 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}O_{10}$: C, 56.59; H, 5.70. Found: C, 51.94, 52.45, 52.61; H, 6.24, 6.18, 6.31.

Potentiometric titration of 20 cc. of a $1.17 \times 10^{-2}M$ aqueous solution of I (0.493 g. of I in 100 cc. of water) with 0.0262 *N* aqueous sodium hydroxide free from carbonate (quinhydrone electrode-saturated calomel electrode, 25 ± 0.1°) gave a potentiometric titration curve, from which the ionization constant of I was obtained; pK_{a_1} 2.13 (25 ± 0.1°).

Sodium salt Ia was formed when an ether solution of I was shaken vigorously with aqueous sodium sulfate or aqueous sodium chloride, or when compound I was added to sodium ethoxide solution.

Potassium Salt of I.—(i) When to an ether solution of free compound I, prepared from sodium salt Ia (5 g.), anhydrous potassium carbonate (about 10 g.) was added for drying purposes, the granular potassium carbonate was transformed into a fine orange powder with vigorous emission of gas. When the ether solution was evaporated 0.7 g. of I was recovered. The solid was collected on a filter, and washed with water to remove potassium carbonate, yielding 2.5 g. of potassium salt of a reddish-orange solid. Recrystallization from ethanol gave reddish-orange long plates, m.p. 246–249° dec., ferric chloride test in ethanol blood-red; λ_{max} 342 (ϵ 50,700), 258 (ϵ 10,200) mμ; infrared bands at 1745, 1720, 1690 and 1544 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}O_{10}K$: C, 51.92; H, 5.01. Found: C, 51.58; H, 5.08.

(ii) An ether solution of I prepared from Ia (2 g.) was vigorously shaken with aqueous potassium iodide, yielding a reddish-brown solid. Recrystallization from ethanol gave a pure compound which was identical with the potassium salt of I, m.p. 246–249° dec., prepared above; yield 1.8 g.

Copper Derivative of I (With Miss A. Yoshizawa).—(i) An ether solution of I prepared from Ia (3 g.) was vigorously shaken with aq. copper acetate (1.4 g.) in a separatory funnel, yielding a dark gray solid. Recrystallization from acetone, then from aq. methanol, gave the copper derivative of I as pale greenish-yellow square plates, m.p. 231–233° dec., yield 1.6 g. (52%), ferric chloride test in ethanol, dark red, λ_{max} 332 mμ (ϵ 273,000).

Anal. Calcd. for $C_{20}H_{23}O_{10}\cdot{}^1/_2Cu$: C, 52.77; H, 5.09. Found: C, 51.99; H, 5.07.

(ii) To an ether solution of I (0.2 g.) was added satd. aq. copper acetate (0.1 g.), and the whole was shaken vigorously and slightly warmed in a water-bath, yielding the copper derivative almost quantitatively; yield 0.21 g. (95%).

Ethyl Bicyclo[3.3.0]octene-2-one-5-ol-1,3,4,6-tetracarboxylate (VI).—When catalytic reduction of 0.5 g. of the sodium salt Ia in 30 cc. of acetic acid containing 10% water (catalyst was 0.2 g. of platinum black) was carried out, 25.1 cc. (0.92 mole) of hydrogen was absorbed in 30 min. at which time hydrogen uptake ceased. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure below 40°. Ether was added to the residue, which then was washed with water, dried, and the ether evaporated, leaving 0.4 g. of crystals. Recrystallization from aq. methanol gave almost colorless (slightly pink) square plates, m.p. 106.5–108°, ferric chloride test in ethanol reddish purple, λ_{max} 247 mμ (ϵ 13,000), infrared bands at 3312, 1742, 1692, 1672 and 1647 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{26}O_{10}$: C, 56.33; H, 6.15. Found: C, 56.58; H, 6.15.

BUNKYO-KU, TOKYO, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

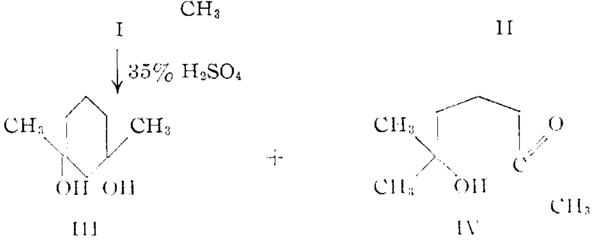
The Synthesis and Acid-catalyzed Cyclization of α-Methylheptenone

BY JERROLD MEINWALD AND JOHN A. YANKEELOV, JR.

RECEIVED APRIL 12, 1958

α-Methylheptenone (V) has been prepared from β-methylheptenone (I) by a reaction sequence consisting of hydration, acetylation and pyrolysis. Compound V cyclizes in 10% sulfuric acid to give a mixture of the *cis* and *trans* forms of 1,3-dimethylcyclohexan-1,3-diol; in 20% sulfuric acid only the *cis*-diol (IIIb) is formed. Compound I yields no carbocyclic products under comparable conditions. The mechanistic implications of these results are discussed, and the relationship to some other cyclization reactions noted.

Introduction.—The early claim that β-methylheptenone (I) gives rise to a dihydro-*m*-xylene (II) on vigorous acid treatment[1] recently has been shown to be substantially correct.[2a] It also has been found that a 1,3-dimethylcyclohexan-1,3-diol (III) is formed in small amounts, along with the ketol 6-methylheptan-6-ol-2-one (IV) when I is subjected to less strongly acidic conditions. These cyclizations of I to II and III are of interest since they seem at first sight to represent a novel type of reaction leading to carbocyclic systems.



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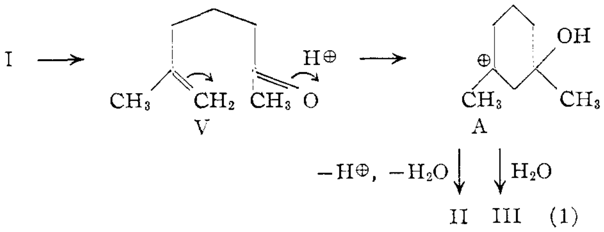
(1) A. Varley, *Bull. soc. chim. Paris*, [3] **17**, 175 (1897); *cf.* O. Wallach, *Ann.*, **395**, 74 (1913); **396**, 264 (1913).

(2) (a) J. Meinwald and R. F. Grossman, THIS JOURNAL, **78**, 992 (1956). (b) α-Methylheptenone has been the subject of a fair amount of controversy in the earlier chemical literature. Thus, Grignard and Verley debated about the content of α-methylheptenone in various samples of natural and synthetic "methylheptenone," but were unable to reach any agreement (see, for example, V. Grignard, J. Doeuvre and R. Escourou, *Compt. rend.*, **117**, 669 (1923); A. Verley, *Bull. soc. chim.*, **35**, 1653 (1924)). A considerable clarification of the situation was brought about by the infrared spectral studies of D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, 915 (1950). These authors studied methylheptenone from a variety of sources and found *no detectable amounts of the α-isomer*. These observations have been confirmed by infrared examination of the β-methylheptenone used in the present work.

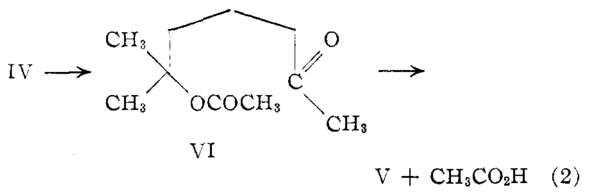
One synthesis of α-methylheptenone has been reported recently (C. J. Albisetti, Jr., U. S. Patent 2,628,252 (1953); *C. A.*, **48**, 1423 (1954)), using a high-temperature, high-pressure reaction between isobutylene and methyl vinyl ketone. The properties of the product were not given in sufficient detail to allow a good comparison with the product obtained in the present investigation.

The first well-documented synthesis of α-methylheptenone (V) was carried out by H. Kappeler, D. Stauffacher, A. Eschenmoser and H. Schinz, *Helv. Chim. Acta*, **37**, 957 (1954). These authors prepared V by the action of methyllithium on the appropriate unsaturated acid. The properties of the product prepared by the new route described in the present work are in good agreement with those reported by the Swiss workers.

Direct cyclization of the ε-methyl group of I with the carbonyl group appears intrinsically unlikely, since there is no adequate activation for the methyl hydrogens. It has therefore been suggested that a migration of the double bond of I to give V (α-methylheptenone) might occur prior to ring closure.[2a] The formation of II and III from V would then follow straightforwardly as an internal Prins reaction. [The reaction is portrayed in a stepwise fashion (equation 1) at this point for the sake of clarity.] In order to test the hypothesis that I isomerizes to V before cyclization, V has been synthesized and subjected to a variety of acidic conditions as described below.

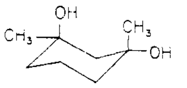


Synthesis of α-Methylheptenone.[2b]—The simplest route to V was considered to be pyrolysis of the ketol acetate VI, derived from the readily available IV (equation 2). Precedent for the preferential formation of a *terminal* olefin by the pyrolysis of a tertiary acetate was provided by work of Schinz[3] as well as more recent work of Bailey.[4] Although in the latter work the chief evidence for structure assignments seems to consist of refractive indices and boiling points, the general conclusion that ester pyrolysis tends to produce the least substituted olefin appears justified. After several unsuccessful attempts to acetylate IV, treatment with ketene in the presence of *p*-toluenesulfonic acid was found to bring about the esterification smoothly.[5] Pyrolysis of VI at 450° gave rise to a mixture of V and acetic acid in excellent yield. α-Methylheptenone prepared in this way showed sharp new infrared absorption bands at 3.28, 6.05 and 11.25 μ, indicative of the newly-introduced terminal methylene group. A semicarbazone and a 2,4-dinitrophenylhydrazone were obtained in good yield, and were different from the corresponding derivatives of β-methylheptenone.[6]

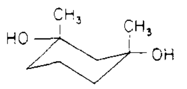


Cyclization Studies.—Of a large number of cyclization experiments carried out with both α- and β-methylheptenones, probably the most significant results were obtained by comparing the behavior of these two unsaturated ketones in the presence of 10% aqueous sulfuric acid. Under these conditions, β-methylheptenone is recovered largely unchanged, and forms no carbocyclic products. α-Methylheptenone, on the other hand, is converted in 50% yield into a mixture of approximately equal amounts of two isomeric 1,3-dimethylcyclohexan-1,3-diols. The facile cyclization of V is, of course, compatible with the suggestion represented in equation 1.

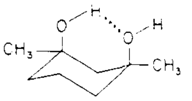
The stereochemistry of the cyclic diols is of interest because it casts some additional light on their genesis. It is appropriate to consider the probable conformations for each of these stereoisomers before discussing the assignment of configuration. The *trans* isomer has only one conformation available to it, shown below as VII. The *cis* form, on the other hand, may have the two methyl groups axial and the hydroxyls equatorial (IIIa), or *vice versa* (IIIb). There are two obvious factors which favor the latter conformation. One is the relative size of the two substituents ($CH_3 >$ OH),[7] and the other is the opportunity for the stabilization of the diaxial diol *via* an internal hydrogen bond. The choice of IIIb as the more populated of the two states is thus clear. As summarized in the Experimental section, the isomer of m.p. 95° gave no infrared spectral evidence of internal hydrogen bonding, while the isomer of m.p. 92° appeared to have an internal hydrogen bond. Furthermore, the 95° isomer had a much lower solubility in carbon tetrachloride and in cyclohexane. Both these factors speak for the assignment: 95° isomer is *trans*, 92° isomer is *cis*. As a confirmation of this point, the relative stability of the *cis* and *trans* forms was considered. On grounds similar to those discussed above, one would expect IIIb to be more stable than VII. In accord with this expectation, the 95° isomer was found to be convertible into the 92° isomer (probably *via* their common carbonium ion A) in good yield by treatment with 20% aqueous sulfuric acid.



VII

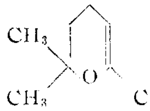


IIIa



IIIb

With this last result in hand, it is appropriate to consider the cyclization experiments carried out using 20% sulfuric acid. Once more, compound I failed to give rise to any carbocyclic product, although small amounts of 2,2,6-trimethyl-2,3-dihydropyran (VIII) and the ketol IV were obtained; V, however, gave the expected *cis*-diol IIIb in about 20% yield, along with I, IV and VIII. In view of



VIII

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[3] A. Brenner and H. Schinz, *Helv. Chim. Acta*, **35**, 1333 (1952); A. Brenner, U. Steiner and H. Schinz, *ibid.*, **35**, 1336 (1952).

[4] W. J. Bailey, J. J. Hewitt and C. King, This Journal, **77**, 357 (1955).

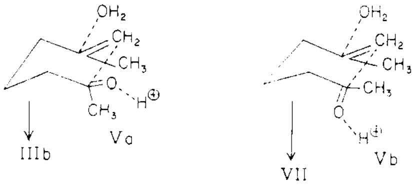
[5] C. D. Hurd and A. S. Roe, *ibid.*, **61**, 3355 (1939).

[6] The possibility that the α-methylheptenone prepared in this investigation contains small amounts of the β-isomer is not excluded by any of these findings. The β-isomer has practically no characteristic infrared absorption by which it could be identified in a mixture. Vapor-phase chromatography was of no help in this case, since authentic mixtures of the α- and β-isomers failed to separate under a variety of conditions. It should be noted, however, that even if there were small amounts of β-isomer present in the α-methylheptenone, the significance of the subsequent results would not be changed.

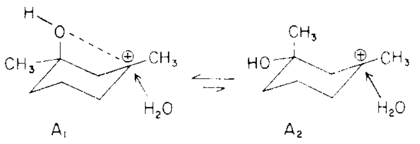
[7] For an excellent, recent discussion of similar nature see E. L. Eliel and C. A. Lukach, This Journal, **79**, 5986 (1957).

the known ability of the *trans*-diol VII to isomerize to IIIb under the conditions used in this experiment, the failure to obtain both isomers is not especially significant.

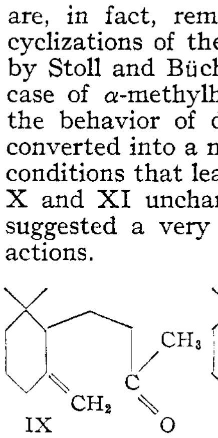
It follows from the above results that the approximately equimolar mixture of *cis*- and *trans*-diols obtained from the 10% sulfuric acid cyclization represents the kinetically controlled rather than the equilibrium product. Considering the conformations of V which should be appropriate for reaction, the two most attractive arrangements are those shown as Va and Vb below. If it is presumed that the new carbon-to-carbon bond is formed in a *concerted anti-planar* addition of the protonated carbonyl group and water across the terminal methylene double bond, it may be seen that Va would yield the *cis*-diol while Vb would yield the *trans*.[8] The obtention of essentially equimolar amounts of IIIb and VII implies that reactions taking place through Va and Vb are about equally likely, a conclusion which appears reasonable from an examination of molecular models.



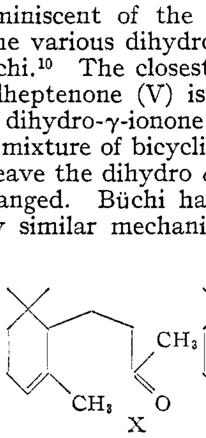
A *non-concerted* cyclization mechanism would appear less attractive, for the following reasons. A stepwise process, as shown in equation 1, would give rise to the ion A. It has been shown already that in 10% sulfuric acid, the products were kinetically controlled. This would therefore imply that A must suffer attack by water with equal facility from either side. Considering the two conformations open to A shown below, it would seem that A_1 should be preferable to A_2 (both because CH_3 is larger than OH, and because of the possibility of distributing the charge in A_1). Addition of water from the less hindered side of A_1 would give *trans*-diol, while similar addition to A_2 would give the *cis* isomer.[9] On the basis of this analysis, predominantly *trans*-diol would be expected to arise as the kinetically preferred product derived from the ion A, and the concerted mechanism discussed above is therefore favored.



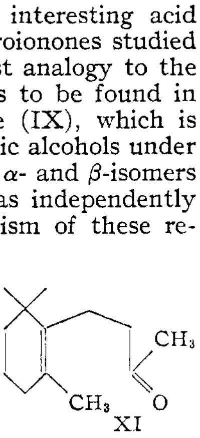
As has been stated above, the facile cyclization of V under conditions where I itself is unreactive is in accord with the necessity of a prior double bond migration, as originally suggested. These results are, in fact, reminiscent of the interesting acid cyclizations of the various dihydroionones studied by Stoll and Büchi.[10] The closest analogy to the case of α-methylheptenone (V) is to be found in the behavior of dihydro-γ-ionone (IX), which is converted into a mixture of bicyclic alcohols under conditions that leave the dihydro α- and β-isomers X and XI unchanged. Büchi has independently suggested a very similar mechanism of these reactions.



IX

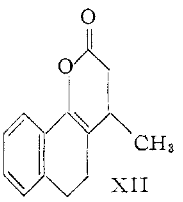


X

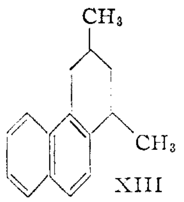


XI

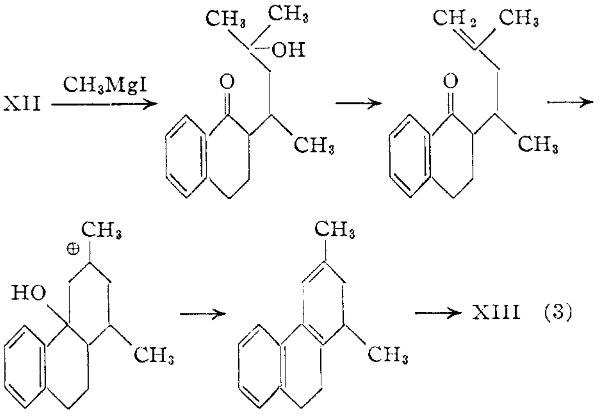
Another interesting example of an unexpected cyclization which undoubtedly is closely related to the β-methylheptenone case was encountered by Belleau,[11] who found that treatment of the enol lactone XII with methylmagnesium iodide and then an acid hydrolysis, gave rise to 1,3-dimethyl-1,2,3,4-tetrahydrophenanthrene (XIII) in 30% yield. One possible reaction sequence which would provide a simple rationalization of this observation is shown in equation 3.



XII



XIII



(3)

In conclusion, it may be noted that all of the above cyclizations lose their novelty with the realization that they involve simply a combination of well known steps. It is to be anticipated that many analogous transformations will come to light.[12]

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[8] A fine review of the theory of similar cyclization processes is given by L. Ruzicka in "Perspectives in Organic Chemistry," edited by A. Todd, Interscience Publishers, Inc., New York, N. Y., 1956, pp. 265–314. See also P. A. Stadler, A. Nechvatal, A. J. Frey and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957); E. Romann, A. J. Frey, P. A. Stadler and A. Eschenmoser, *ibid.*, **40**, 1900 (1957).

[9] This argument is similar to that used by Zimmerman in the explanation of the stereochemical course of ketonization. See, for example, H. E. Zimmerman, THIS JOURNAL, **79**, 6554 (1957).

[10] M. Stoll and M. Hinder, *Helv. Chim. Acta*, **38**, 1593 (1955); M. Stoll, C. F. Seidel, B. Willhalm and M. Hinder, *ibid.*, **39**, 183 (1956); G. Büchi, K. Biemann, B. Vittimberga and M. Stoll, THIS JOURNAL, **78**, 2622 (1956).

[11] B. Belleau, *ibid.*, **73**, 5441 (1951). The authors are indebted to Dr. Belleau for calling this interesting transformation to their attention.

[12] Another reaction which is somewhat related to the ones discussed above is the classical cyclodehydration of α- or β-ionone (i or ii)

Acknowledgment.—The partial support of the work reported herein by a Research Grant from the National Science Foundation is gratefully acknowledged.

Experimental

Acetylation of 6-Methylheptan-6-ol-2-one (IV → VI).—A 27.0-g. portion of ketol IV[13] was placed in a sintered glass bubbler, and 0.02 g. of *p*-toluenesulfonic acid was added. The apparatus was cooled in an ice-bath and a stream of ketene was allowed to pass through the sample for 105 minutes.[5] Small additional portions of catalyst were added at half-hour intervals.

The reaction product was washed twice with 25 ml. of 6 *N* sodium hydroxide solution and twice with 25-ml. portions of water. The combined aqueous layers were extracted with 50 ml. of ether, which was then washed with water and combined with the main organic product. After drying over magnesium sulfate, the ether was evaporated. Crude ketol acetate VI (28.0 g.), showing only very weak hydroxyl absorption in the infrared, remained.

A total of 150.5 g. of IV (in three runs) was treated in the above manner. After two distillations of the product, 117.5 g. of ketol acetate (61%) was collected at 108–109° (8.0 mm.), $n^{25}\mathrm{D}$ 1.4313, d^{25} 0.9652; $M\mathrm{D}$ calcd. 50.04, found 49.94.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.70; H, 9.60.

A semicarbazone, m.p. 132–133°, was prepared in the usual manner.

Anal. Calcd. for $C_{11}H_{21}O_3N_3$: C, 54.08; H, 8.66; N, 17.20. Found: C, 54.44; H, 8.62; N, 17.50.

Treatment with Brady reagent gave a 2,4-dinitrophenylhydrazone, m.p. 110–111°.

Anal. Calcd. for $C_{16}H_{22}N_4O_6$: C, 52.50; H, 6.05; N, 15.28. Found: C, 52.84; H, 5.80; N, 15.28.

Pyrolysis of 6-Methylheptan-6-ol-2-one Acetate (VI → V).—A 1-cm. diameter Pyrex condenser tube was packed with 30 cm. of carborundum chips. The tube was placed in a vertical oven and heated to 450° (as measured by a calibrated thermocouple placed half-way along the outside of the column) while being flushed with a slow stream of dry nitrogen. The ketol acetate VI (105 g.) was pyrolyzed at the rate of 16 drops per minute. The product was collected in a receiver cooled with an ice–salt-bath. The total pyrolysate was diluted with 100 ml. of 30–60° petroleum ether and washed with two 50-ml. portions of water, then with two 50-ml. portions of 10% sodium bicarbonate. The combined aqueous washings were made alkaline with 6 *N* sodium hydroxide and extracted with three 50-ml. portions of 30–60° petroleum ether. The organic layers were washed once with 20 ml. of water, and then dried over magnesium sulfate. The crude product, after removal of the solvent, weighed 67.0 g. Distillation at reduced pressure gave 62.8 g. (87%) of V, b.p. 75° (26 mm.), $n^{25}\mathrm{D}$ 1.4337, d^{25} 0.8475; $M\mathrm{D}$ calcd. 38.69, found 38.74. The infrared spectrum of this product was very similar to that of β-methylheptenone, with additional characteristic bands at 3.28, 6.05 and 11.25 μ.

Anal. Calcd. for $C_8H_{14}O$: C, 76.13; H, 11.17. Found: C, 75.89; H, 10.79.

The semicarbazone of V, after recrystallization from ethanol, showed m.p. 124–125°.

Anal. Calcd. for $C_9H_{17}N_3O$: C, 58.98; H, 9.35; N, 22.92. Found: C, 59.13; H, 9.16; N, 23.08.

In a single experiment, reductive ozonolysis of V gave a 10% yield of formaldehyde, identified as its dimedone derivative (mixture m.p. with an authentic sample, 189.5–190.5°).

Cyclization of α-Methylheptenone (V) in 10% Sulfuric Acid.—An 8.7-g. portion of V was shaken with 100 ml. of 10% sulfuric acid for 24 hours. The reaction mixture was then neutralized by dropwise addition of 20% aqueous sodium hydroxide, keeping the temperature below 15°. Ether extraction yielded 5.1 g. of crude product.

The aqueous portion was evaporated to a volume of 80 ml. and re-extracted with ether, to yield an additional 1.6 g. of partly crystalline product. Further evaporation to *ca.* 50 ml. resulted in crystallization of inorganic salts. Ether extraction of these remaining solid and liquid residues gave another 0.8 g. of crystalline material.

The combined organic extracts, after removal of ether, were taken up in cyclohexane and allowed to crystallize slowly. A 2.0-g. yield of *trans*-diol VII was obtained in this way. Recrystallization from ether gave VII as hard, colorless prisms, m.p. 95.0–95.3°.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.48; H, 11.24.

Compound VII showed no uptake of bromine in carbon tetrachloride, and failed to react with 5% neutral potassium permanganate. It gave a positive Lucas test in 30 sec. with concentrated hydrochloric acid.

The cyclohexane mother liquor was concentrated and the low boiling components (chiefly β-methylheptenone) removed by distillation. A faintly yellow 2.1-g. residue of crude *cis*-diol IIIb was obtained. It could be induced to crystallize by seeding with a sample of authentic material. Its infrared spectrum indicated the presence of *ca.* 10–15% of ketol IV. Recrystallization from cyclohexane gave the authentic *cis*-diol, m.p. 92°, previously described.[2a] The total weight of combined diols corresponded to about 50% of the 7.6 g. of recovered product.

Conversion of VII to IIIb in 20% Sulfuric Acid.—A 0.52-g. sample of pure *trans*-diol VII was treated with 18 ml. of chilled 20% sulfuric acid and allowed to stand at room temperature for one day. The solution was neutralized in the cold and worked up in the usual way. The recovered product consisted of 0.45 g. of *cis*-diol IIIb, identified by direct comparison with an authentic sample.

Treatment of VII with 10% Sulfuric Acid.—In an experiment identical to that described above, except for the use of 10% sulfuric acid, VII was recovered unchanged.

Cyclization of α-Methylheptenone in 20% Sulfuric Acid.—A 5.4-g. sample of V was treated with 37 ml. of 20% sulfuric acid and neutralized as described above. Ether extraction gave 4.9 g. of crude product. This material was subjected to a vacuum distillation which was stopped when the column temperature reached 107° (10 mm.). The residue crystallized spontaneously, and was shown to consist of the *cis*-diol IIIb by infrared comparison with an authentic sample. The weight of IIIb corresponded to a 20% yield. Infrared examination of the distillate showed the presence of small amounts of 2,2,6-trimethyl-2,3-dihydropyran (VIII) (5.95 μ), and considerable amounts of I and IV. The absence of absorption at 11.25 μ precluded the presence of any unchanged V.

Infrared Spectra of *cis*- and *trans*-Diols IIIb and VII.—In chloroform solution, both diols show a doublet in the hydroxyl region. At comparable concentrations, however, IIIb has a much stronger associated OH peak (2.90 μ, strong and broad) than VII (2.92 μ, medium and broad). At the same time IIIb shows weaker unassociated OH (2.77 μ, medium and sharp) than VII (2.79 μ, strong and sharp).

In carbon tetrachloride,[14] IIIb showed behavior typical of an internally hydrogen-bonded diol. Thus, with increasing dilution, a 3.0 μ band (intermolecularly bonded OH) virtually vanishes while the remaining 2.86 μ (internally bonded OH) and 2.79 (free OH) decrease in roughly constant ratio. (In high dilution, the 2.86 μ band is the predominant one.) Compound VII was much less soluble in carbon tetrachlo-

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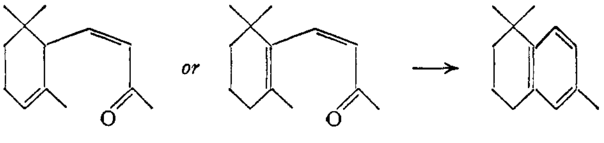
with iodine or with phosphorus and hydriodic acid to give ionene (iii)



[F. Tiemann and P. Krüger, *Ber.*, **26**, 2693 (1893); M. T. Bogert and V. G. Fourman, THIS JOURNAL, **55**, 4670 (1933); M. T. Bogert, D. Davidson and P. M. Apfelbaum, *ibid.*, **56**, 959 (1934)].

The authors are grateful to the Referee of this manuscript for calling their attention to the contents of a number of papers, all of which bear some relation to the present work: A. Caliezi and H. Schinz, *Helv. Chim. Acta*, **35**, 1637 (1952); **35**, 1649 (1952); H. Kappeler, H. Grütter and H. Schinz, *ibid.*, **36**, 1862 (1953); H. Grüssner, J. Hellerbach, A. Brossi and O. Schnider, *ibid.*, **39**, 1371 (1956).

(13) See footnote 2a for references to the preparation of IV.

(14) F. A. Smith and E. C. Creitz, *J. Research Natl. Bur. Standards*, **46**, 145 (1951).

ride, but in saturated solution shows only a single sharp 2.79 μ band, characteristic of unassociated OH.

Treatment of β-Methylheptenone (I) with 10% Sulfuric Acid.—A 7.0-g. sample of I was shaken with 10% sulfuric acid for 24 hours. Working up in the usual way gave 5.3 g. of material, the infrared spectrum of which showed the absence of characteristic bands for both IIIb and VII. Evaporation of the aqueous phase followed by further extraction gave 0.3 g. of an oil whose infrared spectrum excluded the presence of significant amounts of either diol. No crystalline product could be isolated from this oil.

Treatment of β-Methylheptenone (I) with 20% Sulfuric Acid.—In an experiment carried out exactly as described above for cyclization of V, 21.3 g. of I was treated with 200 ml. of 20% sulfuric acid. After working up in the usual way, 19.3 g. of crude product was obtained. Distillation gave rise to a small amount of 2,2,6-trimethyl-2,3-dihydropyran (VIII) and roughly equal amounts of I and IV. No diol was found either in the distilled IV or in the residue from the distillation.

ITHACA, N. Y.

[CONTRIBUTION FROM ABBOTT LABORATORIES]

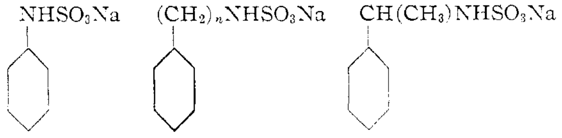
Reductions with Ruthenium Catalysts. I. Preparation of Some Cyclohexylalkylamines[1]

BY MORRIS FREIFELDER AND GEORGE R. STONE

RECEIVED MARCH 26, 1958

Low pressure hydrogenation of phenylalkylamines to cyclohexylalkylamines with noble metal catalysts is often slow and requires high catalyst ratios to obtain complete reduction. In high pressure hydrogenation of β-phenylalkylamines with Raney nickel, temperature conditions high enough for reduction also cause cracking. Reduction of these aralkylamines in this work with ruthenium gave excellent yields of ring hydrogenated products.

The interest of this Laboratory in sweetening agents led us to prepare some cyclohexylalkylamines as intermediates in the preparation of salts of cyclohexylsulfamic acid[2] (A) homologs. Our purpose was to observe the change in sweetness when alkylene groups were placed between the nitrogen atom and the saturated ring.

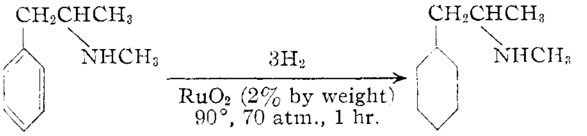


A n = 1 or 2

Even though the homologs lacked sweet taste, the unusual results of hydrogenation of the aralkylamines with ruthenium led us to expand the series to cover preparation of β-cyclohexylalkylamines.

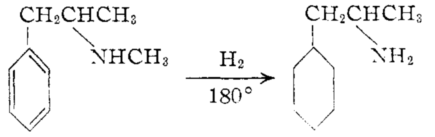
The difficulty in hydrogenating β-phenylalkylamines ($C_6H_5CH_2CHRNHR'$ where R and R′ = H or alkyl) has been reported by other investigators. Metayer[3] points out that in hydrogenations of phenylalkylamines when the amino group is beta to the aromatic ring, incidental hydrolysis and cracking occur. Zenitz and co-workers[4] in their study with platinum oxide at low pressure often found it necessary to make additions of catalyst to induce complete hydrogenation. Kindler,[5] in low pressure hydrogenations with palladium black, used excessively high catalyst ratios (25% by weight of compound) to obtain complete uptake of hydrogen.

In contrast, in this work when ruthenium was used in the hydrogenation of these difficultly reducible β-phenylalkylamines, most reductions were complete within one hour at 90° and 70 atmospheres.

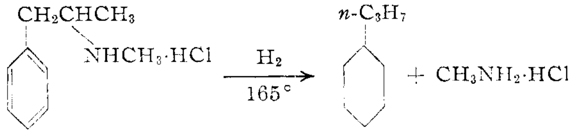


B VI 90%

The effect of higher temperature on hydrogenation also was investigated. When the reduction of B was carried out at 120-130°, the yield of VI remained at the same high level. At 150°, however, it dropped to 50% and at 180° demethylation accompanied ring reduction.



The hydrochloride of B was also reduced. When the hydrogenation in water or alcohol was carried out under the same conditions described for the base, a comparable yield was obtained. In water, however, when the temperature was raised to 165°, deamination occurred and propylcyclohexane was obtained.



In the reduction of β-phenylalkylamines, the effect of a branched substituent on the ring was noted when the hydrogenation of β-(p-isopropylphenyl)-ethylamine was carried out. The time for complete uptake was ten to twelve hours in contrast to the shorter time needed for hydrogenation of the unsubstituted aralkylamines.

l-Ephedrine was hydrogenated to the corresponding cyclohexyl compound without hydrogenolysis of

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[1] Presented at the San Francisco Meeting of the American Chemical Society, April, 1958.

[2] Manufactured and sold by Abbott Laboratories under the trade name of Sucaryl Sodium and Sucaryl Calcium.

[3] M. Metayer, *Bull. soc. chim.*, [5] **19**, 276 (1952).

[4] B. L. Zenitz, E. B. Macks and M. L. Moore, THIS JOURNAL, **69**, 1117 (1947).

[5] K. Kindler, B. Hedemann and E. Schärfe, *Ann.*, **560**, 215 (1948).