

[CONTRIBUTION FROM THE ORGANISCH-CHEMISCHEN LABORATORIUM DER EIDG. TECHNISCHEN HOCHSCHULE, ZÜRICH, AND FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Relative Configurations of the Two 1-Keto-6-hydroxyspiro[4.4]nonanes and the Three 1,6-Dihydroxyspiro[4.4]nonanes¹

BY E. HARDEGGER, E. MAEDER, HENRI MANVEL SEMARNE AND DONALD J. CRAM

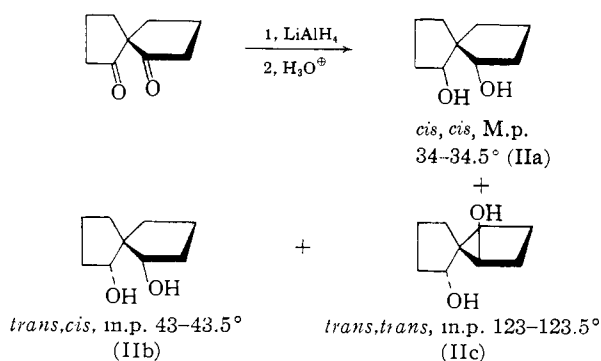
RECEIVED OCTOBER 28, 1958

All of the stereochemical relationships between the two diastereomeric 1-keto-6-hydroxyspiro[4.4]nonanes (I) and the three diastereomeric 1,6-dihydroxyspiro[4.4]nonanes (II) have been elucidated.

The objectives of this research were fourfold: (1) to prepare derivatives of the two diastereomers of ketol I; (2) to prepare the three diastereomers of diol II; (3) to convert each ketol to a mixture of two diols, and thus establish the configuration of that diol produced from both ketols; (4) to establish the relative configurations of the other two diols by an independent method and thus establish the relative configurations of the ketols. The fulfillment of these objectives is described below.



Preparation of the Three Racemic 1,6-Dihydroxyspiro[4.4]nonanes (II) and Identification of the Relative Configuration of One of Them.—The bis-*p*-nitrobenzoates of the three diols II were prepared in a pure state in a previous investigation,² but the individual diols were not isolated. In the present work, a substantial amount of diketone III³ was prepared, and the compound was characterized through a number of new derivatives. A diastereomeric mixture of the three diols IIa, IIb and IIc was obtained by reduction of III with lithium aluminum hydride. A sample of the diol mixture was oxidized back to diketone III with chromic acid in 20% yield. The three diols were separated through their *p*-nitrobenzoate derivatives as in the previous investigation² by a combination of fractional crystal-



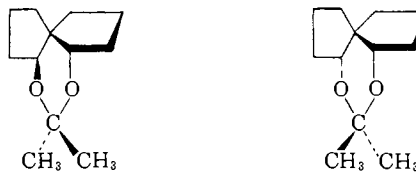
(1) The Swiss authors wish to thank F. Hoffmann-La Roche and Co., A. G. Basle, Switzerland, for financial support of this work. The part of this research carried out at the University of California at Los Angeles was conducted under contract AF 33(616)-146 with the United States Air Force, the sponsoring agency being the Aeronautical Research Laboratory of the Wright Air Development Center Air Research and Development Command.

(2) D. J. Cram and H. Steinberg, *THIS JOURNAL*, **76**, 2753 (1954).

(3) (a) A. Horeau, *Compt. rend.*, **228**, 2039 (1949); (b) D. J. Cram and B. L. van Duuren, *THIS JOURNAL*, **77**, 3576 (1955).

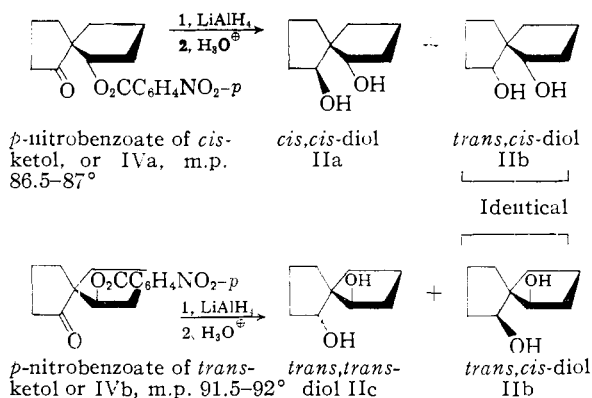
lization and chromatographic procedures. Each of the three esters was converted to diol by ester interchange with methanol, and the three diols IIa, IIb and IIc, were isolated in a pure crystalline state. The three diacetates of these diastereomeric racemates were prepared, and the bis-acid phthalate of IIa was also synthesized.

Each of the three diols was subjected to the action of dry acetone and hydrogen chloride gas under the same conditions. Diol IIa gave an acetonide in 63% yield and a 2% recovery of starting material. Diol IIb gave an acetonide in 33% yield and a 40% recovery of starting material. Diol IIc gave back 80% of starting material, and no acetonide was formed. These results demonstrate that diol IIc possesses the *trans, trans* configuration, since the distance between the two hydroxyl groups in this isomer is much too large to accommodate a six-membered acetonide ring. On the other hand, acetonides of the *cis, cis* and *trans, cis* isomers are sterically feasible. Thus IIa must have the *cis, cis* and IIb the *trans, cis* configuration, or vice versa. Molecular models suggest that the *cis, cis* isomer might form an acetonide faster than the *trans, cis* isomer, and this observation implies that IIa possesses the *cis, cis* and IIb the *trans, cis* configuration. This assignment is verified by experiments described in the next section.



acetonide *cis, cis*-diol IIa acetonide of *trans, cis*-diol IIb

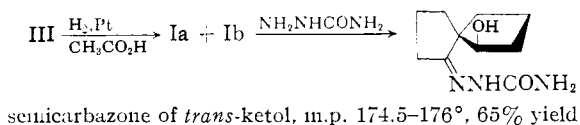
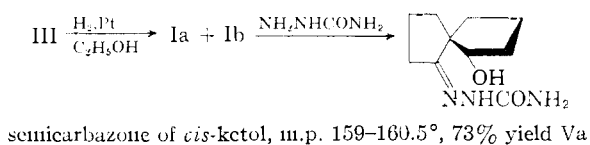
Preparation of Derivatives of the Two 1-Keto-6-hydroxyspiro[4.4]nonanes, and Identification of their Configurations and Those of *cis, cis*- and *trans, cis*-1,6-dihydroxyspiro[4.4]nonane.—A mixture of diastereomeric racemates of 1-keto-6-hydroxyspiro[4.4]nonane was prepared by ring closure of γ -(1-carbethoxy-1-cyclopentyl-2-hydroxy)-butyric acid ethyl ester.² This ketol mixture was converted to the *p*-nitrobenzoate derivatives, which were separated by chromatography into each of the two diastereomeric racemates, IVa and IVb. When reduced with lithium aluminum hydride, IVa gave a mixture of diol IIa and IIb whose composition was demonstrated by separation of the bis-*p*-nitrobenzoate derivatives of these two racemates. When similarly reduced, IVb gave a mixture of diols IIb and IIc, whose composition was also found through use of the bis-*p*-nitrobenzoate derivatives.



These transformations allow the configurations of the *p*-nitrobenzoates IVa and IVb and of the three diols to be assigned. Diol IIb must possess a *trans, cis* configuration because *only this isomer can be produced from both ketol esters*. Diol IIc has already been demonstrated (see previous section) to be the *trans,trans* isomer, so the third diol must have the *cis,cis* configuration. Since only ester of *cis*-ketol can give *cis,cis*-diol, and since IVa gives *cis,cis*-diol, IVa must have the *cis* configuration. Similarly, only ester of *trans*-ketol can produce *trans,trans*-diol, and therefore IVb must be the *trans* isomer.

In the above transformations racemates were used. If the optically pure ketols that are formulated had been used, the *trans,cis*-diol from IVa would have been identical with that material from IVb.

The two diastereomeric ketols Ia and Ib were also prepared by catalytic reduction of diketone III. The rate of reduction of the first carbonyl group was greater than that of the second, and if stopped after one mole of hydrogen was absorbed, the reaction yielded largely ketol. When conducted in ethanol, a ketol mixture rich in the *cis* racemate was produced. When the reduction was carried out in glacial acetic acid, a ketol mixture rich in *trans* racemate was obtained.



The semicarbazones of these ketols were prepared, and *trans*-ketol Ib was liberated from its derivative by semicarbazide exchange with pyruvic acid. The configuration of this ketol (and therefore its semicarbazone) was demonstrated by its conversion to the *p*-nitrobenzoate, whose properties corresponded to those of authentic *p*-nitrobenzoate of *trans*-ketol IVa.

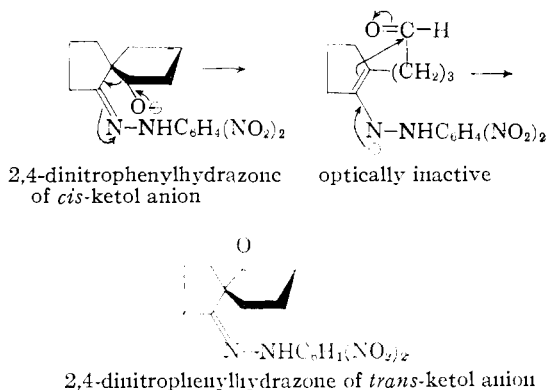
Other derivatives such as the 2,4-dinitrophenylhydrazone and the acid phthalate were prepared from *trans*-ketol. The double derivative, the acid

phthalate-2,4-dinitrophenylhydrazone of *trans*-ketol was prepared from both the 2,4-dinitrophenylhydrazone and from the acid phthalate. The 2,4-dinitrophenylhydrazone of *cis*-ketol was also prepared, both from ketol prepared by reduction of diketone III in ethanol, as well as from ketol prepared from γ -(1-carbethoxy-1-cyclopentyl-2-hydroxy)-butyric acid. The *p*-nitrobenzoate-2,4-dinitrophenylhydrazone of both *cis* and *trans*-ketol were prepared from the respective *p*-nitrobenzoates of the two ketols. Thus a large number of derivatives of the two ketols are now known whose diastereomeric configurations are established through the above interlocking relationships.

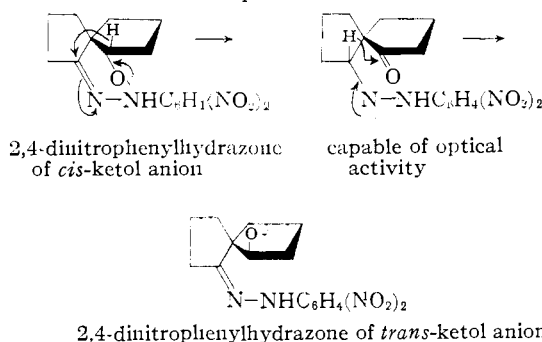
When the *p*-nitrobenzoate-2,4-dinitrophenylhydrazones of *cis*- and *trans*-ketol were subjected to base-catalyzed ester interchange, the 2,4-dinitrophenylhydrazone of *trans*-ketol was obtained from both starting materials. The epimerization that must have occurred in conversion from the *cis* to *trans* isomer might have involved either a reverse and forward aldol reaction, or a reversible oxidation-reduction sequence involving hydride shifts

from HCO^- to $\text{C}=\text{N}-$ and back. These two possibilities could be differentiated by working with optically active starting materials. If aldol sequences were involved, active *cis* derivative should give racemic *trans* derivative. If oxidation-reduction sequences were responsible, active *cis* derivative should give active *trans* derivative. These possibilities are being examined.

Aldol sequence



Oxidation-reduction sequence



Ketol was also prepared by a third series of reactions, in which diketone III was converted to

monoöxime VI, which was reduced with sodium borohydride⁴ to 1-hydroxy-6-oximospiro[4.4]-nonane. Regeneration of the carbonyl function yielded ketol I which proved to be rich in the *cis* racemate.

Direction of Asymmetric Induction in the Preparation of Ketols I and Diols II.—The catalytic reduction of dione III in 95% ethanol gave at least a 6/1 ratio of *cis*-ketol to *trans*-ketol, whereas in glacial acetic acid the same catalyst provided a ratio of at least 2/1 in the opposite direction. This result contrasts with the behavior of 2-methylcyclohexanone which upon reduction provides the least hindered *trans*-2-methylcyclohexanol in neutral medium and the more hindered *cis* form in acid medium.⁵ Possibly the second carbonyl group in III plays an electronic and not simply a steric role in determining the course of reduction.

Reduction of the *p*-nitrobenzoate of *cis*-ketol with lithium aluminum hydride gave a mixture of *cis,cis*- and *trans,cis*-diols in which the former isomer dominated by a factor of approximately ten. Thus in this reaction the hydride ion predominantly entered the molecule from the least hindered side "steric approach control."⁶ Similar reduction of the *p*-nitrobenzoate of *trans*-ketol gave a mixture of *trans,cis*- and *trans,trans*-diols in which the latter isomer dominated by a factor of about two. Thus in this case, hydride ion approached the molecule from the more hindered side. The multiplicity of functional groups in the starting material makes interpretation of this result impossible.

Resolution of *p*-Aminobenzoate of *cis*-Ketol.—The bis-*p*-nitrobenzoates of the three diastereomeric diols II were catalytically reduced to the corresponding bis-*p*-aminobenzoates. Similarly, the *p*-nitrobenzoates of the *cis*- and *trans*-ketols Ia and Ib were reduced to their corresponding *p*-aminobenzoates. Although *d*-camphorsulfonate salts of both diastereomeric ketol derivatives were prepared, resolution was carried out on only the *cis* isomer. The salt of this isomer was recrystallized to constant rotation, but was optically impure. The salt was converted to the free amine which was recrystallized to optical purity, as indicated by its sharp melting point and lack of change of rotation with further recrystallization.

Differences in Infrared Absorption Spectra between Diastereomerically Related Compounds.—A number of interesting differences in infrared absorption spectra are exhibited by certain sets of diastereomers described in this paper.^{7,8} The 2,4-dinitrophenylhydrazone of *trans*-ketol (m.p. 127–128°) gives in dilute carbon tetrachloride solution

two bands,⁹ one at 3625 cm.⁻¹ due to the free O–H group, and a second at 3317 cm.⁻¹ attributable to the free N–H group. The 2,4-dinitrophenylhydrazone of *cis*-ketol (m.p. 152–153°) gives besides these same two bands, a broad band at 3480 cm.⁻¹, which is due to intramolecular hydrogen-bonding of the linkages, O–H ··· N= . The presence of this band¹⁰ in the *cis* isomer and absence in the *trans* is entirely consistent with expectations based on examination of molecular models, and confirms the configurational assignments made to these diastereomers earlier in the paper.

The infrared spectra of the three diastereomeric diols were also examined in the 3 μ region, and the results fully confirm the configurational assignments made on the basis of chemical interconversions (see previous sections). The results and their interpretation are as follows.

Kuhn¹¹ has examined cyclic diols in carbon tetrachloride solutions in concentrations as strong as 0.005 molar, and has made the following observations. Only those diols in which the calculated distance for the interval H ··· O bond is as small as 3.3 Å. show two bands in the infrared in the 3- μ region. The relative intensities of these bands depend on the concentration. At greater concentration, the band due to intermolecular hydrogen-bonding appears at considerably lower frequencies than the band due to intramolecular hydrogen bonding.

The geometry of the *trans,trans*-diol IIc allows no intramolecular hydrogen bonding. In saturated solution (the diol is only slightly soluble in carbon tetrachloride), the diol exhibits only a single sharp band at 3625 cm.⁻¹, which is due to a free hydroxyl group. The spectrum of a Nujol mull of this isomer possesses a single broad band at 3300 cm.⁻¹, which demonstrates that the same hydroxyl group is capable of entering into intermolecular hydrogen bonds.

The *cis,trans*-diol IIb possesses a structure ideal for intramolecular hydrogen bonding, and which at the same time permits external hydrogen bonding. At suitable concentration (0.040 molar cell, 3-mm. thickness) this diol exhibits three bands. The first is at 3630 cm.⁻¹, and is due to the free hydroxyl group; the second occurs at 3562 cm.⁻¹, and involves the internal hydrogen bond; the third is found at 3419 cm.⁻¹, and involves external hydrogen bonding. At lower concentrations (0.012 molar) the band due to external bonding almost disappears, while the other two bands remain relatively the same.

In the *cis,cis*-diol IIa, little can be predicted from the measurements of others¹¹ concerning the existence of internal hydrogen bonding. The oxygen–oxygen distance is so small that no hydrogen bridge appears feasible without distortion of the

(4) H. I. Schlesinger, H. C. Brown, H. R. Hoekstra and L. R. Rapp, *THIS JOURNAL*, **75**, 199 (1953).

(5) Possible explanations for this stereospecificity in reduction of cyclohexanones have been discussed by J. H. Brewster, *ibid.*, **76**, 6362 (1954). References are summarized in this article.

(6) W. G. Dauben, G. J. Fonken and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

(7) Others have also observed that diastereomers sometimes have different spectral properties, e.g.: (a) ref. (2); (b) N. H. Cromwell, *et al.*, *ibid.*, **73**, 1044 (1951); (c) F. Hawthorne and D. J. Cram, *ibid.*, **74**, 5859 (1952).

(8) A more detailed discussion of these and other results are found elsewhere: Th. Bürer, E. Maeder and Hs. H. Gunthard, *Helv. Chim. Acta*, **40**, 1823 (1957).

(9) The spectral surveys were carried out with a Perkin–Elmer infrared spectrophotometer, model 21, with sodium chloride optics. Detailed spectra were taken on a Perkin–Elmer infrared spectrophotometer, model 12C, with lithium fluoride prism. Spectra of the solutions were subtracted from that of the solvent. The carbon tetrachloride was first shaken with activated alumina, and then distilled from phosphorus pentoxide.

(10) E. D. Bergmann, E. Gil-Av and S. Pinchas, *THIS JOURNAL*, **75**, 68 (1953).

(11) L. P. Kuhn, *ibid.*, **74**, 2492 (1952).

bond angles. However, our measurements show unambiguously the presence of an internal hydrogen bond. It is remarkable that the degree of hydrogen bonding depends somewhat on concentration. In dilute solution four O-H bands appear, which are not all sharply exhibited at a single concentration. The band at 3624 cm^{-1} is attributable to free hydroxyl groups, the one at 3572 cm^{-1} to a weak internal hydrogen bond, and those at 3524 and 3381 cm^{-1} , to two types of external hydrogen bonds. These assignments are consistent with the behavior of these bands as the solutions became more dilute. At 0.041 molar concentration, (1.05-mm. cell thickness), the broad bands at 3524 and 3381 cm^{-1} are very evident, but decrease in intensity and disappear at 0.002 molar concentration (30-mm. cell thickness). The bands at 3624 and 3572 cm^{-1} grow in intensity as the solution becomes more dilute and the polymeric bands disappear.

Experimental

Derivatives of 1,6-Diketospino[4.4]nonane(III).—From 180 g. of 1,4,4,7-heptanetetracarboxylic acid^{2,3} was obtained 47 g. of colorless diketone (b.p. 118–122° at 12 mm.). Two crystallizations of this material from methanol coupled with a distillation gave 36.5 g. (37% yield) of crystalline material, m.p. 37–37.5° (reported m.p. 37.2–37.8°,² m.p. 41–42°^{3a}).

Anal. Calcd. for $\text{C}_8\text{H}_{12}\text{O}_2$: C, 71.02; H, 7.95. Found: C, 71.02; H, 7.92.

The monosemicarbazone of this material was prepared: A filtered solution of 2.5 g. of semicarbazide hydrochloride and 4 g. of sodium acetate in 15 ml. of methanol was prepared, and 1.47 ml. (3.29 millimoles) of this solution was allowed to stand for 10 hours mixed with 0.50 g. (3.29 millimoles) of diketone III. The solvent was removed under vacuum, and the remaining fine crystals were washed with potassium bicarbonate solution and dried to give 0.52 g. of semicarbazone of III, m.p. 209–211°, yield 76%. A sample of this material was recrystallized from ethyl acetate and from ethanol, and dried for 48 hours under high vacuum at 90° to give material, m.p. 211°.

Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{O}_2\text{N}_3$: C, 57.40; H, 7.23. Found: C, 57.60; H, 7.13.

The disemicarbazone of diketone III was prepared from 0.700 g. (4.5 millimoles) of III and 4.2 ml. (9.2 millimoles) of the semicarbazide solution prepared above. The product was obtained as 1.140 g. of white powder (93% yield), m.p. 258–260°. Recrystallization of this material from hot water gave disemicarbazone melting at 262°. The analytical sample was dried in high vacuum at 80° for 100 hours.

Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_2\text{N}_6$: C, 49.61; H, 6.81. Found: C, 49.85; H, 6.67.

The mono-*p*-nitrophenylhydrazone of diketone III was prepared: A mixture of 0.400 g. (2.63 millimoles) of III 0.402 g. (2.63 millimoles) of *p*-nitrophenylhydrazine, 10 ml. of absolute ethanol and 0.25 ml. of acetic acid was heated to reflux for 10 minutes. The hot solution was diluted with a small amount of water and allowed to cool. Three recrystallizations from methanol-water of the solid that separated gave 0.517 g. (68%) of constant melting product, m.p. 211–212° (yellow powder). An analytical sample was prepared by recrystallizing this material from methanol and water twice, and drying the product for 60 hours in high vacuum at 80°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{O}_2\text{N}_3$: C, 62.70; H, 5.96. Found: C, 62.57; H, 6.06.

The bis-(*d,l*)- α -phenylethylsemioxamhydrazide derivative of diketone III was prepared: A mixture of 1.00 g. (6.58 millimoles) of III, 1.326 g. (6.58 millimoles) of racemic α -phenylethyl semioxamhydrazide, a trace of iodide and 50 ml. of benzene was heated at reflux for 30 minutes. The solution was reduced to a small volume, and much petroleum ether was added in the cold. The flocculent brown precipitate that separated (2.24 g.) was chromatographed on

65 g. of activity III¹² alumina without separation into fractions. The white powder obtained (1.51 g., m.p. 140–160°) was submitted to a second chromatograph on 45 g. of alumina (activity II¹²), and partial purification resulted. The benzene-ethyl acetate eluate was recrystallized four times from benzene-petroleum ether to give material, m.p. 134–140°, which was dried in high vacuum for 20 hours at 80°.

Anal. Calcd. for $\text{C}_{20}\text{H}_{34}\text{O}_4\text{N}_6$: C, 65.64; H, 6.46; N, 15.84. Found: C, 65.62; H, 6.60; N, 15.96.

The chloroform-methanol eluate was recrystallized three times from benzene-petroleum ether to give material, m.p. 201–207°, which was dried in high vacuum for 20 hours at 80°.

Anal. Calcd. for $\text{C}_{20}\text{H}_{34}\text{O}_4\text{N}_6$: C, 65.64; H, 6.46; N, 15.84. Found: C, 65.42; H, 6.48; N, 15.96.

Preparation of Mixture of Diastereomeric 1,6-Dihydroxy-spiro[4.4]nonanes (II) by Reduction of 1,6-Diketospino[4.4]nonane(III).—From 30 g. (0.197 mole) of diketone I and 15 g. of lithium aluminum hydride was obtained 27.6 g. (90%) of colorless viscous oil (II), b.p. 150–151° (11 mm.), n_D^{20} 1.5042.

Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{O}_2$: C, 69.19; H, 10.32. Found: C, 69.18; H, 10.22.

A sample of this diol was converted back to diketone III as follows. A solution of 0.590 g. of diol II in a 1% solution of chromium trioxide in acetic acid was allowed to stand at room temperature for two days. Methanol (2 ml.) was added, and the mixture was cooled and allowed to stand an additional hour. The mixture was then diluted with 250 ml. of water and extracted with 100 ml. of petroleum ether. The organic layer was washed with a little water, dried and evaporated to a small volume. When cooled the resulting solution deposited large white crystals of ketone III, 0.112 g. (20%), m.p. 36.5–37°, undepressed by admixture with an authentic sample.

***cis,cis*-1,6-Dihydroxyspiro[4.4]nonane (IIa) from Mixture of Diols Prepared by Reduction of Diketone III.**—The three bis-*p*-nitrobenzoates were prepared from the mixture of diastereomeric diols (see above) by the procedure reported previously.² The *cis,cis* isomer (4.0 g., m.p. 210.5–211°) was dissolved in 20 ml. of chloroform and mixed with a solution of 0.115 g. of sodium hydride in 115 ml. of methanol. The mixture was allowed to stand at room temperature for 150 hours. Since the ester was only slightly soluble in methanol, the mixture was occasionally mixed and warmed, until finally all of the ester remained in solution. The solution was finally neutralized by addition of 2.5 g. of ammonium chloride, the solvent evaporated under vacuum, and the residue was twice triturated with 200-ml. portions of water. The resulting mixture was filtered to give methyl *p*-nitrobenzoate (solid) and a solution of the diol. The solution was made alkaline with potassium bicarbonate, and extracted continuously with ether for 60 hours. The ether solution was dried and evaporated, and the residual oil was distilled at 160–165° under aspirator pressure. The distillate (1.55 g. of yellow oil), which still contained methyl *p*-nitrobenzoate, was dissolved in benzene and was chromatographed on 50 g. of alumina (activity II to III¹²). The yellow oil that was eluted with benzene-ether (1.233 g.) was distilled at 160–165° under aspirator pressure to give 1.162 g. of colorless oil (85%), which when cooled to –10° formed a hard, crystalline mass, m.p. 31–32°. Recrystallization of this material from cold methylcyclohexane gave white needles of IIa, m.p. 34–34.5°. For analysis a sample was distilled in high vacuum at 110–115°.

Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{O}_2$: C, 69.19; H, 10.32. Found: C, 69.20; H, 10.30.

***cis,trans*-1,6-Dihydroxyspiro[4.4]nonane (IIb).**—The *cis,trans*-diol was prepared from its ester by the same method as was applied to the *cis,cis* isomer. The bis-ester (4.0 g., 8.8 millimoles) gave 0.958 g. (70%) of diol obtained as a colorless oil which distilled at 155–160° at atmospheric pressure. This material crystallized when cooled to –10°, m.p. 42–43.5°. The substance was chromatographed on 25 g. of alumina and crystallized from methylcyclohexane to give fine white needles of IIb, m.p. 43–43.5°. A small

(12) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

sample of this *cis,trans*-diol was distilled at 110–115° in high vacuum for analysis.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.42; H, 10.23.

trans,trans-1,6-Dihydroxyspiro[4.4]nonane (IIc).—By the same procedure, 2.00 g. (4.41 millimoles) of *trans,trans*-bis-ester was converted to *trans,trans*-diol. This compound was isolated by chromatography on 70 g. of alumina (activity II¹²), the diol being eluted after methyl *p*-nitrobenzoate with methanol. The material that was obtained (0.45 g. or 66%), m.p. 122–123°, was recrystallized from carbon tetrachloride to give fine white needles of IIc, m.p. 123–123.5°. For analysis a sample was sublimed in high vacuum.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 69.06; H, 10.16.

Bis-phthalic Acid Ester of *cis,cis*-1,6-Dihydroxyspiro[4.4]nonane.—A mixture of 0.156 g. (1 millimole) of *cis,cis*-diol Ia and 0.296 g. (2 millimoles) of phthalic anhydride in 1 ml. of dry pyridine was heated at 100° for 15 hours. The solution was cooled, mixed with 50 ml. of methylene chloride, and the resulting solution was extracted twice with dilute hydrochloric acid and then with water. The solution was dried, evaporated, and the acid ester that separated was recrystallized from acetone-petroleum ether, m.p. 201–204°. For analysis, the sample was dried at 60° in high vacuum for 15 hours.

Anal. Calcd. for $C_{25}H_{24}O_8$: C, 66.36; H, 5.35. Found: C, 66.31; H, 5.48.

cis,cis-1,6-Diacetoxyspiro[4.4]nonane.—A mixture of 0.211 g. (1.35 millimoles) of *cis,cis*-diol Ia, 1 ml. of acetic anhydride and 5 mg. of acetyl chloride was heated at 100° for 15 hours. After the excess anhydride had been evaporated under reduced pressure at 50 to 60°, the crystalline residue was chromatographed on 15 g. of alumina of activity II–III.¹² Elution of the column with benzene-petroleum ether (4:1) gave ester which was distilled in high vacuum at 90–95° to give 0.267 g. (82%) of product, m.p. 77.5–78°. For analysis, a sample was crystallized from petroleum ether, and sublimed in high vacuum, m.p. 78°. This melting point compared with diacetate prepared previously of unknown stereochemical structure,^{3b} m.p. 80°.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.03; H, 8.37.

cis,trans-1,6-Diacetoxy[4.4]nonane.—With the same procedure as was applied to preparation of the *cis,cis*-ester, 0.250 g. (1.60 millimoles) of *cis,trans*-diol IIB was converted to 0.330 g. (86%) of diacetate, obtained as a colorless oil, b.p. 90–95° in high vacuum. For analysis, a sample was distilled at aspirator pressure at 150–155°, and again under high vacuum, n_D^{20} 1.4679.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.00; H, 8.48.

trans,trans-1,6-Diacetoxy[4.4]nonane.—With the same procedure that was applied to the preparation of the other two diastereomers, 0.450 g. (2.88 millimoles) of *trans,trans*-diol IIC was converted to 0.575 g. (83%) of diacetate, obtained as a colorless oil after distillation at 150–155° (aspirator pressure). When cooled to –10°, this oil crystallized, m.p. 15–16°. For analysis, a sample was redistilled in high vacuum at 90–95°, n_D^{20} 1.4681.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.84; H, 8.24.

Acetonide of *cis,cis*-1,6-Dihydroxyspiro[4.4]nonane.—A solution of 0.307 g. of *cis,cis*-diol Ia in 10 ml. of a 1% mixture of hydrogen chloride gas in dry acetone was mixed with 3 g. of dry sodium sulfate, and the resulting mixture was allowed to stand at room temperature protected from air for 40 hours. The reaction mixture was cooled and saturated with dry ammonia gas and filtered free of ammonium chloride. The solvent was evaporated under vacuum and the yellow residual oil was dissolved in 10 ml. of benzene-petroleum ether (1:1) and chromatographed on 10 g. of alkaline alumina, activity I.¹² The benzene-petroleum ether eluate yielded upon distillation at 100–105° at aspirator pressure, 0.244 g. (63%) of a colorless, mobile oil. For analysis the acetonide was distilled twice at aspirator pressure, n_D^{20} 1.4699. An infrared absorption spectrum of this material in methylene chloride gave no O–H band, but showed an ether band at 1080 and 1125 cm^{-1} .

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.18; H, 10.39.

When the above alumina column was eluted with methanol and the product distilled, 7 mg. (2%) of starting diol was obtained.

Acetonide of *cis,trans*-1,6-Dihydroxyspiro[4.4]nonane.—With the method used for preparation of the acetonide of the *cis,cis*-diol, the acetonide of the *cis,trans*-diol was prepared. From 0.201 g. (1.29 millimoles) of diol IIB was obtained 0.077 g. (33%) of acetonide as a colorless, mobile oil which distilled at 105–110° at aspirator pressure, n_D^{20} 1.4780. An infrared absorption spectrum of this material in methylene chloride gave no O–H bands, but contained ether bands at 1085 and 1120 cm^{-1} .

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.48; H, 10.34.

The methanol eluate from the chromatograph column yielded 0.080 g. (40%) of recovered starting material.

Attempted Preparation of Acetonide of *trans,trans*-1,6-Dihydroxyspiro[4.4]nonane.—When the above procedure was applied to 0.290 g. of *trans,trans*-diol IIC no acetonide was eluted from the chromatograph column, and 0.230 (80%) of the starting material was recovered.

Mixture of *cis* and *trans*-1-Keto-6-hydroxyspiro[4.4]nonane (I).—In two separate runs, 240 g. (0.88 mole) of γ -(1-carbethoxy-1-cyclopentyl-2-hydroxy)-butyric acid ethyl ester² was cyclized with 92.4 g. (3.86 mole) of sodium hydride. The reaction products from each run were combined and distilled in high vacuum to give 84 g. (31%) of colorless oil, b.p. 90–114° at 0.8 mm., n_D^{20} 1.491. This material was distilled at aspirator pressure, and was divided into two fractions, which became colored during the distillation. The first fraction (58 g.) distilled at 124–130°, n_D^{20} 1.491. An analytical sample was twice distilled in high vacuum at 75–80°.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.71; H, 9.27.

The second fraction amounted to 22.5 g., b.p. 130–138°, n_D^{20} 1.490. An analytical sample was prepared by distilling a sample twice in high vacuum at 85–90°.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.75; H, 9.21.

Mixture of Acid Succinates of *cis*- and *trans*-1-Keto-6-hydroxy[4.4]spirononane.—A mixture of 1.540 g. (10 millimoles) of 1-keto-6-hydroxy[4.4]nonane (diastereomeric mixture) and 1.0 g. (10 millimoles) of succinic anhydride was heated in an evacuated flask at 140° for 3.5 hours. The dark-colored reaction mixture was dissolved in 100 ml. of ether, and the solution was extracted with four successive portions of water saturated with potassium bicarbonate. The combined extracts were acidified, extracted with 100 ml. of ether, and the ether was dried and evaporated. The dark residual oil was distilled at 175–180° in high vacuum to give 1.852 g. (73%) of colorless, heavy oil, n_D^{20} 1.4905. For analysis, a sample was twice distilled in high vacuum.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.27; H, 6.99.

***p*-Nitrobenzoate of *cis*- and *trans*-1-Keto-6-hydroxy[4.4]nonane.**—A solution of 10 g. (64.9 millimoles) of *cis*- and *trans*-ketol I (b.p. 124–130° at 11 mm.) and 16 g. (86.2 millimoles) of *p*-nitrobenzoyl chloride in 75 ml. of dry pyridine was heated to 100° for one hour in a flask protected from moisture. The reaction mixture was cooled, dissolved in 500 ml. of benzene, and the solution was extracted several times with dilute hydrochloric acid. The benzene solution was washed with potassium bicarbonate solution, with water, and was evaporated under vacuum. The dark brown residual oil, which did not crystallize, was dissolved in 500 ml. of benzene-petroleum ether and chromatographed on 600 g. of alumina of activity II.¹² Benzene-petroleum ether and benzene eluted 14.33 g. of crystalline product of m.p. 82–84°. This material when recrystallized from benzene-petroleum ether and methanol gave 12.2 g. (62%) of *cis-p*-nitrobenzoate as well-formed yellow-tinted prisms, m.p. 86.5–87°. For analysis, a sample was recrystallized from methanol and dried at 50° under high vacuum. In the ultraviolet, the spectrum of this compound had λ_{max} 260 $m\mu$, ϵ 13,400.

Anal. Calcd. for $C_{16}H_{17}O_6N$: C, 63.36; H, 5.65. Found: C, 63.56; H, 5.62.

Benzene-ether and ether eluted from the chromatograph column 2.490 g. of crystalline product, m.p. 80–82°. Recrystallization of this material from benzene-petroleum ether and from methanol gave 0.850 g. (4.2%) of *trans*-*p*-nitrobenzoate as light yellow needles, m.p. 91.5–92°. For analysis, a sample was recrystallized from methanol and dried in high vacuum at 50° for 140 hours. In the ultraviolet, the spectrum of this compound had λ_{max} 260 m μ , ϵ 13,600. A mixed melting point of the *cis* and *trans* esters gave 61–65°. The infrared absorption spectra of the two esters in chloroform were identical.

Anal. Calcd. for C₁₆H₁₇O₃N: C, 63.36; H, 5.65. Found: C, 63.42; H, 5.67.

Semicarbazone of *trans*-1-Keto-6-hydroxy[4.4]nonane.—A mixture of 10 g. (64.9 millimoles) of *cis,trans*-ketol mixture (b.p. 133–139° at 11 mm.) and 29 ml. (65 millimoles) of semicarbazine-acetate solution (see preparation of semicarbazones of diketone in previous section) was allowed to stand for two days at room temperature. When concentrated, the solution deposited 9.1 g. of crystalline needles, which gave a constant melting point after three recrystallizations from water, m.p. 175–176°. The yield of this isomer was 3.79 g. or 28%. For analysis, a sample was recrystallized from water and dried in high vacuum for 140 hours at 70°.

Anal. Calcd. for C₁₆H₁₇O₂N₃: C, 56.85; H, 8.11. Found: C, 56.73; H, 7.98.

3,5-Dinitrobenzoate Esters of *cis*- and *trans*-1-Keto-6-hydroxy[4.4]nonane.—A solution of 0.842 g. (5.46 millimoles) of *cis,trans*-ketol mixture (b.p. 120–140° at 11 mm.) and 1.60 g. (6.95 millimoles) of 3,5-dinitrobenzoyl chloride in 7.5 ml. of dry pyridine was heated at 100° for 1.5 hours in a flask protected from moisture. The reaction mixture was dissolved in 100 ml. of methylene chloride, the solution was washed with dilute hydrochloric acid, with potassium bicarbonate solution and with water. The solution was dried and evaporated. The residual material (wt. 1.62 g.) was found not to separate on activity II alumina,¹² and was therefore, chromatographed on 30 g. of activity I alumina.¹² Benzene and benzene-petroleum ether (9:1) eluted 0.180 g. of crystalline product, which upon one recrystallization from methanol yielded pure *cis*-3,5-dinitrobenzoate as white blades, m.p. 115–116°. For analysis, a sample was recrystallized three times from ethanol and dried in high vacuum at 70° for 50 hours. The ultraviolet absorption spectrum of this isomer in ethanol gave λ_{max} 212 m μ , ϵ 26,200.

Anal. Calcd. for C₁₆H₁₆O₇N₂: C, 55.17; H, 4.63. Found: C, 54.96; H, 4.54.

Elution of the chromatograph column with benzene-ether gave 0.096 g. of oil. This material crystallized from methanol, and two recrystallizations gave pure *trans*-3,5-dinitrobenzoate as white needles, m.p. 135.5–136.5°. For analysis, the compound was recrystallized from methanol and dried in high vacuum at 70° for 50 hours. The ultraviolet absorption spectrum of this compound in ethanol gave λ_{max} 212 m μ , ϵ 26,100. A mixture of *cis*- and *trans*-dinitrobenzoates gave m.p. 100–125°. The infrared absorption spectrum of each isomer in chloroform was identical to that of the other.

Anal. Calcd. for C₁₆H₁₆O₇N₂: C, 55.17; H, 4.63. Found: C, 55.27; H, 4.67.

2,4-Dinitrophenylhydrazone of *cis*-1-Keto-6-hydroxy-spiro[4.4]nonane.—A mixture of 1.540 g. (10 millimoles) of ketol (b.p. 120–140° at 11 mm.) and 1.980 g. (10 millimoles) of 2,4-dinitrophenylhydrazine in 49 ml. of hot methanol containing 60 drops of concentrated sulfuric acid was prepared. When cooled, a crystalline precipitate separated, which was dissolved in benzene and chromatographed on 100 g. of activity II alumina.¹² The material (0.50 g.) in the first benzene fraction was recrystallized once from carbon tetrachloride to give granular crystals, m.p. 151–153°. This material was recrystallized once again from carbon tetrachloride and once from methanol to give an analytical sample, m.p. 152–153°, which was dried for 80 hours in high vacuum at 50°. The ultraviolet absorption spectrum of the compound in ethanol gave λ_{max} 231.5 m μ , ϵ 16,200 and λ_{max} 366 m μ , ϵ 23,500.

Anal. Calcd. for C₁₅H₁₈O₆N₄: C, 53.88; H, 5.43. Found: C, 54.04; H, 5.63.

***p*-Nitrobenzoate-2,4-dinitrophenylhydrazone of *cis*-1-keto-6-hydroxy[4.4]nonane** was prepared from 1.515 g. (5 millimoles) of *p*-nitrobenzoate of *cis*-ketol Ia and a solution of 1.200 g. (6.05 millimoles) of 2,4-dinitrophenylhydrazine in 40 ml. of methanol containing 30 drops of concentrated sulfuric acid. The voluminous precipitate that formed was recrystallized from carbon tetrachloride to give 1.440 g. (60%) of well-formed yellow needles, m.p. 214–215°. For analysis a sample was recrystallized from carbon tetrachloride and from chloroform-methanol, and was dried in high vacuum for 40 hours at 80°. The ultraviolet absorption spectrum of this compound in ethanol gave λ_{max} 259 m μ , ϵ 16,400 and λ_{max} 365 m μ , ϵ 14,200.

Anal. Calcd. for C₂₂H₂₁O₈N₅: C, 54.66; H, 4.38. Found: C, 54.53; H, 4.35.

***p*-Nitrobenzoate-2,4-dinitrophenylhydrazone of *trans*-1-Keto-6-hydroxyspiro[4.4]nonane.**—From 1.515 g. (5.00 millimoles) of *p*-nitrobenzoate of *trans*-ketol was prepared the 2,4-dinitrophenylhydrazone, which when crystallized from methylene chloride-methanol amounted to 1.390 g. (58%), m.p. 169–170° (yellow prisms). For analysis a sample was recrystallized from chloroform-methanol and dried in high vacuum at 80° for 40 hours. The ultraviolet absorption spectrum of this compound in ethanol gave λ_{max} 259.5 m μ , ϵ 20,100, and λ_{max} 365 m μ , ϵ 18,500. The infrared absorption spectra of the *cis* and *trans* double derivatives in chloroform were identical.

Anal. Calcd. for C₂₂H₂₁O₈N₅: C, 54.66; H, 4.38. Found: C, 54.63; H, 4.38.

2,4-Dinitrophenylhydrazone of *trans*-Ketol from *p*-Nitrobenzoate-2,4-dinitrophenylhydrazone of *cis*-Ketol.—A solution of 0.900 g. (1.86 millimoles) of *p*-nitrobenzoate-2,4-dinitrophenylhydrazone of *cis*-ketol in 100 ml. of absolute dioxane was mixed with a solution of 0.080 g. of sodium hydride in 80 ml. of alcohol. The mixture was allowed to stand at room temperature for 190 hours. Owing to the low solubility of the starting material, the mixture was warmed slightly to bring everything into solution. The solution was neutralized with 2 g. of ammonium chloride, and the solvent evaporated under reduced pressure. The residue was shaken with 50 ml. of water and 100 ml. of benzene, and the benzene solution was concentrated under reduced pressure to 25 ml. This was chromatographed on 40 g. of alumina of activity II.¹² Benzene eluted 0.290 g. of material, which when recrystallized from carbon tetrachloride gave 0.246 g. of orange spangles, m.p. 159–160°. This compound was not identified. Ether and ethyl acetate eluted 0.188 g. of crystalline product from the column which when recrystallized from carbon tetrachloride gave 0.145 g. (23%) of orange needles of 2,4-dinitrophenylhydrazone of *trans*-ketol, m.p. 127–128°. For analysis the compound was recrystallized from carbon tetrachloride and dried in high vacuum for 60 hours at 80°. The ultraviolet absorption of this compound in ethanol showed λ_{max} 231.5 m μ , ϵ 15,000 and λ_{max} 366 m μ , ϵ 20,900.

Anal. Calcd. for C₁₅H₁₈O₆N₄: C, 53.88; H, 5.43. Found: C, 53.71; H, 5.17.

2,4-Dinitrophenylhydrazone of *trans*-Ketol from *p*-Nitrobenzoate-2,4-dinitrophenylhydrazone of *trans*-Ketol.—The double derivative of the *trans*-ketol (0.900 g. or 1.86 millimoles) was submitted to the same treatment as the double derivative of the *cis*-ketol (see above). The benzene-ether eluate of the chromatograph column contained 0.133 g. of material which when recrystallized from carbon tetrachloride gave red granular crystals, m.p. 150–151°. The ether-ethyl acetate eluate gave 0.275 g., which when crystallized from carbon tetrachloride gave both orange needles and red granular crystals, which were separated mechanically. The red granules were recrystallized from carbon tetrachloride to give material (0.107 g., m.p. 150–151°) which was not identified. The orange needles were recrystallized from carbon tetrachloride to give 0.197 g. (32%) of 2,4-dinitrophenylhydrazone of *trans*-ketol, m.p. 127–128°. For analysis a sample was dried at 80° for 60 hours in high vacuum. The ultraviolet absorption spectrum of the compound gave λ_{max} 231.5 m μ , ϵ 15,200 and λ_{max} 366 m μ , ϵ 21,100.

Anal. Calcd. for C₁₅H₁₈O₆N₄: C, 53.88; H, 5.43. Found: C, 53.88; H, 5.21.

Reduction of *p*-Nitrobenzoate of *cis*-1-Keto-6-hydroxy-spiro[4.4]nonane to a Mixture of *cis,cis*- and *trans,cis*-1,6-

Dihydroxyspiro[4.4]nonane.—To 3.0 g. of lithium aluminum hydride and 60 ml. of dry ether mixed by vibration was added dropwise a solution of 4.00 g. (13.2 millimoles) of *p*-nitrobenzoate of *cis*-ketol. After addition was complete the mixing was continued for 2.5 hours at room temperature, and then 15 ml. of ethyl acetate and 10 ml. of 10% hydrochloric acid were added dropwise and in succession. The reaction mixture was then filtered through Celite, and the ether phase was washed with a saturated aqueous solution of potassium bicarbonate. The combined aqueous phases were extracted continuously with ether for 48 hours. The combined ether phases were dried, evaporated, and the residue distilled in high vacuum at 120–140° to give 1.315 g. of yellow oil, and a resinous residue. The distillate was dissolved in 15 ml. of methanol, filtered through a 20-ml. column of acidic, ion-exchange polymer, and the column was washed with 60 ml. of methanol. The methanol was evacuated, and the residual oil was dissolved in 1:1 benzene-ether and chromatographed on a column of 40 g. of alumina of activity II.¹² The diol was eluted with methanol, and distilled under aspirator pressure at 155–160° as a colorless oil, 0.756 g. (37%). For analysis a sample was distilled in high vacuum at 110–115°.

Anal. Calcd. for C₉H₁₆O₂: C, 69.19; H, 10.32. Found: C, 68.81; H, 10.29.

From 0.626 g. (4.01 millimoles) of this material was prepared the bis-*p*-nitrobenzoate derivative by the procedure recorded earlier in the Experimental. The reaction product was 1.945 g. of yellow solid which was recrystallized first from ethyl acetate and then from carbon tetrachloride to give 1.030 g. of white needles, m.p. 210.5–211°. The mother liquor was evaporated, dissolved in 40 ml. of benzene and chromatographed on 50 g. of alumina of activity I.¹² The chromatogram was developed with 7:3 benzene-methylene chloride, and twelve 50-ml. fractions were collected which contained crystalline material. Fractions 1–5 gave 0.321 g. of product, m.p. 210.5–211°. Thus a total of 1.296 g. (71%) of needles of *cis,cis*-ester was obtained whose melting point was undepressed by admixture with authentic material. The infrared absorption spectrum of this compound was identical with that of an authentic sample. The ultraviolet spectrum in ethanol had λ_{\max} 260.5 μ , ϵ 25,200.

Fraction 6 from the chromatogram was a mixture. Fractions 7–12 were recrystallized from ethyl acetate and carbon tetrachloride to give 0.105 g. (6%) of *cis,trans*-diester, m.p. 192–192.5°, undepressed by admixture with an authentic sample of the *cis,trans*-diester. The infrared spectrum of this compound was identical to that of an authentic sample. The ultraviolet spectrum in ethanol had λ_{\max} 259.2 μ , ϵ 22,600, and λ_{\max} 261.5 μ , ϵ 20,900.

Reduction of *p*-Nitrobenzoate of *trans*-1-Keto-6-hydroxyspiro[4.4]nonane to a Mixture of *cis,trans*- and *trans,trans*-1,6-Dihydroxyspiro[4.4]nonane.—The same procedure was applied to this conversion as was employed for the other diastereomer (see above). From 4 g. of *trans*-ester was obtained 0.965 g. (47%) of oily solid which distilled at 155–160° under aspirator pressure. For analysis a sample was redistilled in high vacuum.

Anal. Calcd. for C₉H₁₆O₂: C, 69.19; H, 10.32. Found: C, 69.09; H, 10.32.

A sample of 0.850 g. (5.45 millimoles) of this diol mixture was converted to the bis-*p*-nitrobenzoate derivative by the procedure recorded earlier in the Experimental. The crude ester amounted to 2.620 g. of a yellow solid material. Fractional crystallization of this material from acetone and carbon tetrachloride gave 1.104 g. of needles, m.p. 221.5–222°, and 0.340 g. of more soluble compound, m.p. 192–192.5°. The mother liquors were concentrated, dissolved in 25 ml. of benzene and chromatographed on 50 g. of alumina, activity I.¹² The column was developed with 6:4 benzene-methylene chloride, and ten 50-ml. fractions were eluted, of which the first five gave 0.216 g. of material, m.p. 192–192.5°. This isomer combined with that obtained above gave 0.556 g. (23%) of *cis,trans*-bis-*p*-nitrobenzoate, whose melting point was undepressed by admixture with an authentic sample.

Fraction 6 of the column was a mixture. From fractions 7–10 was obtained 0.110 g. of needles, m.p. 221.5–222°, to give, when combined with similar material obtained above, a total of 1.214 g. (49%) of *trans,trans*-bis-*p*-nitrobenzoate, whose melting point was undepressed by admixture with an

authentic sample. The infrared spectrum of this compound was identical to that of an authentic sample. The ultraviolet absorption spectrum in ethanol gave λ_{\max} 260.5 μ , ϵ 24,800.

***p*-Aminobenzoate of *cis*-1-Keto-6-hydroxyspiro[4.4]nonane.**—A solution of 31.13 g. (0.103 mole) of *p*-nitrobenzoate of *cis*-ketol in 200 ml. of ethyl acetate and 50 ml. of ethanol was mixed with 3 g. of palladium-charcoal and shaken in an atmosphere of hydrogen. After the calculated amount of hydrogen was absorbed (one hour) the mixture was filtered, and the filtrate was evaporated to dryness. The white, crystalline residue was recrystallized once from 95% ethanol to give 25.8 g. (92%) of *p*-aminobenzoate of *cis*-ketol, m.p. 130–130.5°. With a Raney nickel catalyst a 75% yield of the same product was obtained. For analysis a sample was recrystallized from methanol and dried for 150 hours in high vacuum at 60°.

Anal. Calcd. for C₉H₁₅O₃N: C, 70.31; H, 7.01. Found: C, 70.18; H, 7.18.

The picrate of this compound was prepared by dissolving 0.500 g. of it in 5 ml. of hot ethanol saturated with picric acid and adding 6 drops of water. The yellow, fine needles that separated in the cold gave m.p. 121–123°, and were recrystallized from 60% methanol to give material, m.p. 122–123°. For analysis a sample was dried in high vacuum at room temperature for 240 hours.

Anal. Calcd. for C₂₂H₂₂O₁₀N₄: C, 52.59; H, 4.41. Found: C, 52.70; H, 4.53.

***d*-Camphorsulfonate of *p*-Aminobenzoate of *cis*-1-Keto-6-hydroxyspiro[4.4]nonane.**—A solution of 46.15 g. (0.169 mole) of *p*-aminobenzoate of *cis*-ketol and 39.2 g. (0.169 mole) of optically pure *d*-camphorsulfonic acid was dissolved in hot methanol, and the solution was diluted with ether until cloudy. In 10 hours 73 g. (86%) of well-formed prisms were deposited, which after several recrystallizations from methanol-ether gave 20.8 g. (24%) of salt with a constant specific rotation, $[\alpha]_D +23^\circ$ (*c* 1.5 in CHCl₃), m.p. 144–148°. The compound was not optically pure. For analysis the salt was dried in high vacuum at 60° for 120 hours.

Anal. Calcd. for C₂₆H₃₂O₇NS: C, 61.77; H, 6.98. Found: C, 61.72; H, 6.98.

(+)-***p*-Aminobenzoate of *cis*-1-Keto-6-hydroxyspiro[4.4]nonane.**—A solution of 20 g. (39.6 millimoles) of the above *d*-camphorsulfonate ($[\alpha]_D +23^\circ$) in 200 ml. of methanol was filtered through a column of 500 g. of alumina, activity II.¹² The eluate amounted to 9.34 g. (86%) of crystalline product. A sample after being dried in high vacuum at 70° for 40 hours gave $[\alpha]_D +22.5^\circ$ (*c* 1, CHCl₃). This material gave, after 3 recrystallizations from methanol, 3.48 g. of racemic ketol ester. From the mother liquor was crystallized 5.26 g. of ester, $[\alpha]_D +66^\circ$ (*c* 1, CHCl₃). The last fraction that could be crystallized from the mother liquor was 0.875 g. of ester, $[\alpha]_D +120^\circ$ (*c* 1, CHCl₃). The recrystallizations of this material from methanol resulted in no change in optical activity. A sample for analysis was dried in high vacuum for 50 hours, m.p. 157–157.5°, $[\alpha]_D +119.7^\circ$ (*c* 1, CHCl₃).

Anal. Calcd. for C₁₆H₁₉O₃N: C, 70.31; H, 7.01. Found: C, 70.23; H, 6.90.

***p*-Aminobenzoate of *trans*-1-Keto-6-hydroxyspiro[4.4]nonane.**—A solution of 1.100 g. of *p*-nitrobenzoate of *trans*-ketol in 25 ml. of ethyl acetate and 5 ml. of ethanol was reduced in the presence of 0.22 g. of palladium-carbon in 20 minutes. The non-crystalline product was distilled in high vacuum at 190–195° to give 0.992 g. (100%) of a clear glass. For analysis a sample was distilled in high vacuum.

Anal. Calcd. for C₉H₁₅O₃N: C, 70.31; H, 7.01. Found: C, 70.23; H, 6.97.

The *d*-camphorsulfonate of this ester was prepared by dissolving 0.98 g. (3.59 millimoles) of the ester and 0.835 g. (3.59 millimoles) of *d*-camphorsulfonic acid in a small amount of hot acetone, and adding ether until the solution was cloudy. A fine crystalline material slowly separated, wt. 1.730 g. (95%). For analysis the material was recrystallized three times from acetone-ether, and dried in high vacuum at 60° for 50 hours, m.p. 143–146°.

Anal. Calcd. for C₂₆H₃₂O₇NS: C, 61.77; H, 6.98. Found: C, 61.73; H, 7.01.

Bis-*p*-aminobenzoate of *cis,cis*-1,6-Dihydroxyspiro[4.4]nonane.—Hydrogenation of 1.525 g. (3.36 millimoles) of *cis,cis*-diol bis-ester in 90 ml. of ethyl acetate and 10 ml. of ethanol and 0.300 g. of palladium-charcoal gave a crystalline reaction product, which gave on recrystallization from methanol 1.160 g. (88%) of fine white needles, m.p. 207.5–208.5°. For analysis a sample was recrystallized from methanol and dried in high vacuum at 100° for 15 hours, m.p. 209.5–210.5°. Less vigorous drying treatment gives an impure analytical sample.

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 70.03; H, 6.64. Found: C, 69.88; H, 6.58.

Bis-*p*-aminobenzoate of *cis,trans*-1,6-Dihydroxyspiro[4.4]nonane.—Hydrogenation of 1.50 g. (3.3 millimoles) of *cis,trans*-bis-ester with 0.300 g. of palladium-charcoal gave 1.310 g. of resinous product which could not be crystallized. For analysis a sample was distilled twice in high vacuum at 220–225° to give a clear glass.

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 70.03; H, 6.64. Found: C, 70.09; H, 6.77.

Bis-*p*-aminobenzoate of *trans,trans*-1,6-Dihydroxyspiro[4.4]nonane.—Hydrogenation of 1.100 g. (2.42 millimoles) of *trans,trans*-bis-ester with 0.250 g. of palladium-charcoal gave an oily reaction product which crystallized when treated with methanol. Recrystallization of the substance from methanol gave 0.782 g. (82%) of methanol, m.p. 177–178°. For analysis a sample was recrystallized from ethanol, and dried in high vacuum at 80° for 50 hours, m.p. 180–181°.

Anal. Calcd. for $C_{22}H_{26}O_4N_2$: C, 70.03; H, 6.64. Found: C, 69.86; H, 6.65.

***cis*-1-Keto-6-hydroxyspiro[4.4]nonane from 1,6-Diketospiro[4.4]nonane.**—After prereducing 0.292 g. of freshly prepared platinum oxide in 26 ml. of 95% ethanol with hydrogen at atmospheric pressure, 0.994 g. of dione was added, and the reduction was allowed to proceed until the rate of hydrogen uptake had decreased from about 5 ml. per minute at the start to less than 0.1 ml. per minute at the point where 163 ml. of hydrogen (1 mole) had been absorbed. The resulting mixture was filtered, and the solvent was evaporated from the filtrate under reduced pressure. The residual oil was dissolved in methylene chloride. The solution was dried, evaporated, and the remaining ketol was distilled through a short path still, wt. 0.968 g. (94%). From 0.205 g. of this ketol was obtained 0.38 g. (86%) of the 2,4-dinitrophenylhydrazone of *cis*-ketol, m.p. 152–153°, undepressed by admixture with the same derivative obtained from ketol prepared from 2-carbethoxycyclopentanone.

Anal. Calcd. for $C_{17}H_{18}O_5N_4$: C, 53.88; H, 5.43. Found: C, 54.15; H, 5.41.

Semicarbazone of *cis*-1-Keto-6-hydroxyspiro[4.4]nonane.—To a filtered solution of 1.0 g. of semicarbazide hydrochloride and 1.6 g. of anhydrous sodium acetate in 5 ml. of methanol was added 1.00 g. of the above ketol. After the mixture had stood for 2 days at 5°, the product was collected in two crops which were combined and recrystallized from water to give 0.96 g. (73%) of white flakes, m.p. 159–160.5°.

Anal. Calcd. for $C_{10}H_{11}O_2N_3$: C, 56.85; H, 8.11. Found: C, 56.68; H, 8.24.

Acid Phthalate of *cis*-1-Keto-6-hydroxyspiro[4.4]nonane.—A mixture of 0.219 g. of phthalic anhydride, 0.232 g. of the above ketol and 0.125 g. of pyridine (dry) was heated at 100° for 7 hours. The resulting mixture was shaken with ether and 3 *N* hydrochloric acid solution, the ether layer was washed with water, dried and evaporated. The remaining paste was triturated with methanol, filtered, and the cake was recrystallized from methanol to give 0.168 g. of product (37%) as needles, m.p. 165–167°.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.31; H, 5.85.

***trans*-1-Keto-6-hydroxyspiro[4.4]nonane from 1,6-Diketospiro[4.4]nonane.**—After reducing 0.300 g. of platinum oxide in 30 ml. of glacial acetic acid at atmospheric pressure, 1.00 g. of diketone was added and the reduction allowed to proceed until one mole of hydrogen was taken up. The hydrogen uptake proceeded initially at a rate of 6 ml. per minute, and fell to 0.5 ml. per minute near the point where

one mole of hydrogen had been absorbed. The product was filtered, and the filtrate was evaporated at reduced pressure at slightly above room temperature to an oil. This oil was distilled to give 0.916 g. (90%) of crude ketol rich in the *trans* racemate. This material was purified through its semicarbazone (see previous procedure). From 1.00 g. of ketol was obtained 0.85 g. (65%) of this derivative, m.p. 174.5–176° (fractional crystallization from water).

Anal. Calcd. for $C_{10}H_{11}O_2N_3$: C, 56.85; H, 8.11. Found: C, 56.55; H, 8.12.

A small crop (0.131 g. or 10%) of the semicarbazone of the *cis*-ketol was also isolated, m.p. 158–161°, undepressed by admixture with an authentic sample.

The pure *trans*-ketol was liberated from its semicarbazone as follows. A mixture of 2.30 g. of the derivative, 15 ml. of pyruvic acid and 15 ml. of water was heated at 100° for one hour, cooled and shaken with a mixture of methylene chloride and water. The organic layer was washed with water, with a saturated potassium bicarbonate solution and again with water. The solution was dried, evaporated, and the residual oil was chromatographed on 40 g. of activity III alumina.¹² The *cis*-ketol was eluted with 25% methanol-ether to give 1.51 g. (90%) of *trans*-ketol, distilled at 140° at 10 mm. pressure, n_D^{25} 1.4910.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.31; H, 9.28.

The 2,4-dinitrophenylhydrazone of this *trans*-ketol was prepared from 0.050 g. of material, and 0.090 g. of derivative was obtained, m.p. 123–124° (from methanol).

Anal. Calcd. for $C_{15}H_{18}O_5N_4$: C, 53.88; H, 5.43. Found: C, 54.14; H, 5.55.

The *p*-nitrobenzoate was also prepared, m.p. 91–92°, undepressed by admixture with an authentic sample.

Acid Phthalate of *trans*-1-Keto-6-hydroxyspiro[4.4]nonane.—By the procedure applied to the other diastereomer, 0.289 g. of *trans*-ketol was converted to 0.343 g. (60%) of acid phthalate of *trans*-ketol, m.p. 186–188° (recrystallized from methanol).

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.61; H, 5.97.

Acid Phthalate-2,4-dinitrophenylhydrazone of *trans*-1-Keto-6-hydroxyspiro[4.4]nonane.—This double derivative was prepared both from the hydrazone and from the acid phthalate. The procedures used are similar to those recorded previously in the Experimental. From 0.580 g. of 2,4-dinitrophenylhydrazone of *trans*-ketol, 0.603 g. (72%) of the double derivative was obtained, m.p. 197–199° dec. (orange-yellow plates from methanol). From 0.302 g. of acid phthalate of *trans*-ketol was obtained 0.330 g. (67%) of the double derivative, m.p. 197.5–198.5, dec. (orange-yellow plates from methanol). A mixture of these two samples gave the same melting point as either sample taken separately.

Anal. Calcd. for $C_{22}H_{22}O_8N_4$: C, 57.26; H, 4.60. Found: C, 57.15; H, 4.69.

1-Keto-6-oximospiro[4.4]nonane.—A mixture of 0.916 g. of diketone, 2.5 ml. of 95% ethanol and a 0.6-ml. portion of a concentrated solution of hydroxylamine hydrochloride in water was cooled to –12°, and to this mixture with stirring was added 0.64 g. of a 20% sodium hydroxide solution. The mixture was maintained at 0° or below with stirring for 90 minutes, was then diluted with 8 ml. of water and neutralized with 6 *N* hydrochloric acid. The mixture was extracted with ether, the ether layer was washed with water, dried and evaporated. The residue was fractionally recrystallized (seven crops) from ether-pentane, the dioxime³ coming out in the first three drops, the monoöxime in the last four. Recrystallization of this latter material gave 0.410 g. (40%) of monoöxime, m.p. 77–78.5°.

Anal. Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.84. Found: C, 64.60; H, 7.66.

1-Keto-6-hydroxyspiro[4.4]nonane from 1-Keto-6-oximospiro[4.4]nonane.—To a stirred mixture of lithium borohydride³ (1.5 g.) in 20 ml. of anhydrous ether was added 2.30 g. of the above monoöxime and the resulting mixture was stirred for 2 hours at 30°. The mixture was then treated with 5 ml. of ethyl acetate and at once acidified with 50 ml. of 10% sulfuric acid. The aqueous layer was ex-

tracted with methylene chloride, and the combined organic layers were dried, evaporated and the residual oil was distilled through a short path still to give 1.61 g. (74%) of colorless ketol, b.p. 120° at 11 mm., n_D^{25} 1.4883. This crude ketol gave a 67% yield of the 2,4-dinitrophenyl-

hydrazone of *cis*-ketol, m.p. 151–153° (undepressed by admixture with an authentic sample).

ZURICH, SWITZERLAND
LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in Stereochemistry. XXIX. Neighboring Hydrogen Participation in Ionization to Give Ethylene Protonium Ions as Intermediates in the Wagner–Meerwein Rearrangement¹

BY DONALD J. CRAM AND JACK TADANIER

RECEIVED OCTOBER 28, 1958

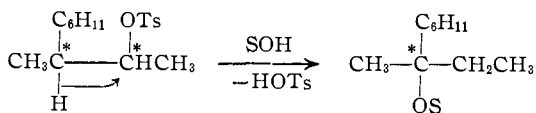
The optically pure diastereomeric *p*-toluenesulfonate esters of 3-cyclohexyl-2-butanol have been prepared, and the rates and solvolysis products have been examined. The yields of solvolysis products varied between 12 and 29% depending on the nucleophilicity of the solvent. The other product was olefin. In 20% water–80% dioxane, 2-cyclohexyl-2-butanol was the major and 3-cyclohexyl-2-butanol the minor solvolysis product. Starting material of the *threo* configuration gave tertiary alcohol (product of hydrogen migration) which was 59% optically pure, and secondary alcohol (simple solvolysis product) 90% inverted. Starting material of the *erythro* configuration gave tertiary alcohol 44% optically pure, and secondary alcohol 72% inverted. The relative configurations of starting material and rearranged tertiary alcohol were demonstrated in independent experiments, and thus the predominant steric course of hydrogen migration with respect to the migration origin could be determined. Solvent was found to react at the tertiary carbon atom from the side originally occupied by hydrogen. The rates of solvolysis of the diastereomeric 3-cyclohexyl-2-butyl *p*-toluenesulfonates differed by factors of 2.38 to 2.97 depending on solvent and temperature, with the *erythro* isomer the faster. These rates are greater than those of 2-butyl tosylate by factors of from 6 to 31 depending on solvent and diastereomer. The diastereomeric 3-cyclohexyl-2-butyl-3-*d* *p*-toluenesulfonates were prepared, and their rates of acetolysis were compared with those of the undeuterated compounds. For the *erythro* isomer, $k_H/k_D = 1.85$, and for the *threo* isomer, $k_H/k_D = 1.72$. The only satisfactory interpretation of the data is as follows. (1) Neighboring hydrogen participates in ionization of the starting esters to form a bridged protonium ion. (2) This bridged ion partitions between secondary and tertiary carbonium ions, which in turn give secondary and tertiary alcohol, respectively, and olefin. (3) Solvent hydrogen-bonds with the bridged ion (conjugate acid of a weak base) and is therefore, well oriented to attack carbon from the side of the bridge, which offers little steric resistance to such a process.

Extensive studies have been made of the Wagner–Meerwein rearrangement with phenyl or methylene as the migrating group, but relatively little has been done with hydrogen migration, particularly with respect to stereochemistry. Cope² and Prelog³ have studied transannular hydrogen migration in the medium sized rings in solvolysis reactions, whereas hydrogen migration in bicyclic systems has been examined by Roberts,⁴ and in six-membered rings by Winstein.⁵ Rearrangements involving hydrogen migration have been observed in open-chain systems in deamination reactions,^{6,7} in *p*-toluenesulfonate ester solvolysis,⁸ and in reactions of alkyl halides with silver acetate.⁹

This paper is concerned with the mechanism of hydrogen migration which occurs during the solvolysis of the *p*-toluenesulfonates of the diastereomeric 3-cyclohexyl-2-butanols. In the start-

ing material both the migration origin and terminus are asymmetric, whereas the migration origin is asymmetric in the product. These relationships allow the steric course of reaction at the migration origin to be examined, and the behavior of the diastereomers to be compared. Both the kinetics and reaction products of solvolyses of this system have been examined, the former with both hydrogen and deuterium as the migrating group.

Preparation and Relative Configurations of the 3-Cyclohexyl-2-butanols, and of 2-Cyclohexyl-2-butanol.—Both optically pure and racemic *threo*- and *erythro*-3-phenyl-2-butanol were prepared¹⁰ and reduced catalytically to the corresponding *threo*- and *erythro*-3-cyclohexyl-2-butanols¹¹ (I), which were characterized as their crystalline *p*-toluenesulfonates. In all cases, the *erythro* reduced about twice as fast as the *threo* isomer. This rate difference correlates with the configurations of the diastereomers. Conformations A and B present the least hindered face of the benzene ring to the catalyst surface, and since CH₃ is larger than OH,



(1) This work was sponsored by the Office of Ordnance Research, U. S. Army.

(2) A. C. Cope, S. W. Fenton and C. F. Spencer, *THIS JOURNAL*, **74**, 5884 (1952), and subsequent papers.

(3) V. Prelog and K. Schenker, *Helv. Chim. Acta*, **35**, 2044 (1952), and subsequent papers.

(4) J. D. Roberts, C. C. Lee and W. H. Saunders, *THIS JOURNAL*, **76**, 4501 (1954).

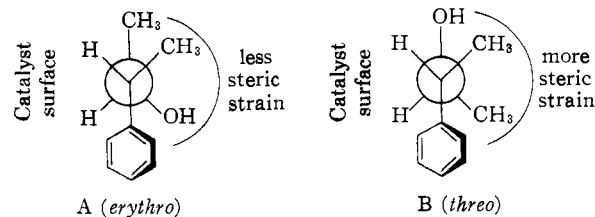
(5) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

(6) J. D. Roberts and J. A. Yancey, *ibid.*, **74**, 5943 (1952).

(7) D. J. Cram, J. E. McCarty, *ibid.*, **79**, 2866 (1957).

(8) D. J. Cram, *ibid.*, **74**, 2137 (1952).

(9) E. Linneemann, *Ann.*, **162**, 12 (1872).



(10) (a) D. J. Cram, *THIS JOURNAL*, **71**, 3863 (1949); (b) **74**, 2129 (1952).

(11) D. J. Cram and F. D. Greene, *ibid.*, **75**, 6005 (1953).