Summary

1. An improved method of synthesis of ketimines is reported.
2. Six ketimines have been prepared and characterized by their physical constants and derivatives.
3. Five ketones have been produced by hydrolysis of ketimines.
4. Six primary amines have been prepared by low pressure catalytic reduction of ketimines.

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Stereochemistry of the Peracid Oxidation of Ketones[1]

BY RICHARD B. TURNER

The conversion of cyclic ketones into lactones by the action of persulfuric acid was first observed by Baeyer and Villiger[2] in 1899. The general applicability of the reaction has since been demonstrated by many investigators, and numerous examples of the formation of esters from acyclic ketones, both aliphatic and aromatic, are recorded in the literature. Peracetic and perbenzoic acids have been employed successfully in place of persulfuric acid. The stereochemistry of the reaction, however, has not hitherto been explored, and a study of the steric course of the oxidation was undertaken in this Laboratory in conjunction with Gallagher's[3] investigation of the behavior of epimeric 17-acetyl steroid derivatives.

cis- and *trans*-1-acetyl-2-methylcyclohexane (II and III) were chosen as suitable model substances. Although only the *trans* isomer (III) had been prepared previously,[4] a satisfactory synthesis of the *cis* derivative was achieved by catalytic hydrogenation of 1-acetyl-2-methyl-Δ^1-cyclohexene (I). The crude hydrogenation product was purified as the semicarbazone (m. p. 182–182.5°), from which the ketone was regenerated by steam distillation in the presence of phthalic acid.[5] Evidence for the absence of inversion in the latter transformation was provided by reconversion of the purified ketone into a semicarbazone identical in melting point and mixed melting point with the starting material. The *cis* ketone (II) proved rather stable toward acid, but isomerization could be effected without difficulty by the use of sodium ethoxide. The rearrangement product was likewise purified as the semicarbazone (m. p. 177–178.5°, marked depression with the *cis* semicarbazone), which, after hydrolysis, furnished a pure sample of *trans*-1-acetyl-2-methylcyclohexane (III). Structures assigned to the isomeric ketones are based on the methods of synthesis[6,7] and on correlation of the physical constants[8] recorded in Table I.

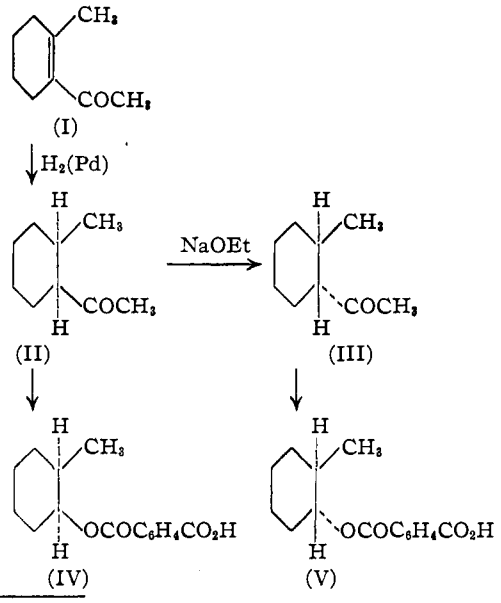


TABLE I

Compound	B. p. °C.	Mm.	d^{25}	$n^{25}D$	$M^{25}D$
II (*cis*)	67–68	10	0.9169	1.4532	41.36[a]
III (*trans*)	64–65	10	.8951	1.4464	41.80
VI (*cis*)	53–53.5	14	.9043	1.4418	36.91[b]
VII (*trans*)	53.5–54	14	.8923	1.4383	37.06

[a] Calcd. 41.59. [b] Calcd. 36.97.

Both substances (II and III) were subjected to oxidation with perbenzoic acid in chloroform solution according to the procedure employed by Gallagher.[3] The products, *cis*- and *trans*-2-methylcyclohexanyl acetate, were saponified directly and converted into the corresponding acid phthalates, which were separated from the non-alcoholic fraction by extraction with dilute alkali. From *cis*-1-acetyl-2-methylcyclohexane (II) a product (IV), m. p. 102–103°, was obtained that did not depress the melting point of an authentic sample of *cis*-2-methylcyclohexanyl acid phthal-

(1) This work was supported by funds provided by the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

(2) Baeyer and Villiger, *Ber.*, **32**, 3625 (1899); **33**, 858 (1900).

(3) Gallagher and Kritchevsky, THIS JOURNAL, **72**, 882 (1950).

(4) Darzens, *Compt. rend.*, **144**, 1124 (1907).

(5) Naves and P. Bachmann, *Helv. Chim. Acta*, **26**, 2151 (1943).

(6) *Cf.* Linstead, Doering, Davis, Levine and Whetstone, THIS JOURNAL, **64**, 1985 (1942).

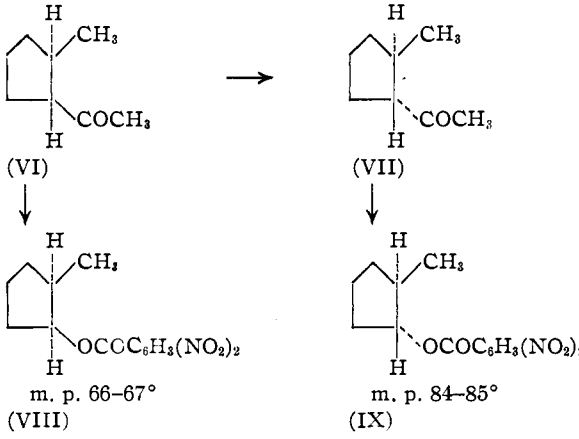
(7) *Cf.* Hückel and Goth, *Ber.*, **58**, 447 (1925).

(8) Hückel, "Theoretische Grundlagen der organischen Chemie," 5th ed., Vol. II, p. 154, Akademische Verlagsgesellschaft, Leipzig, 1948.

ate.[9] The derivative V obtained from *trans*-1-acetyl-2-methylcyclohexane (III) melted at 123–124° and showed no melting point depression when mixed with *trans*-2-methylcyclohexanyl acid phthalate.[9] The *cis* and *trans* products were isolated in sterically pure condition in yields of 63 and 55%, respectively, based on ketone utilized. No other components could be obtained from the alcoholic fractions. The results provide conclusive evidence for the retention of configuration at C-1 in the perbenzoic acid oxidation.

Similar experiments were conducted with the *cis*- and *trans*-1-acetyl-2-methylcyclopentanes[10] with analogous results. The former product was obtained by catalytic hydrogenation of 1-acetyl-2-methyl-Δ^1-cyclopentene, and the latter by base-catalyzed isomerization of the *cis* derivative. The densities and refractivities of the two products (Table I) support structures deduced for these substances from the methods employed in their preparation.

Oxidation of the *cis* and *trans* ketones (VI and VII) with perbenzoic acid was carried out as before. The alcohols resulting from saponification of the crude oxidation mixtures were isolated as the 3,5-dinitrobenzoates (VIII and IX), which melted at 66–67° and at 84–85°, respectively. The relation of the products to the starting materials is shown in the accompanying chart.



Synthesis of the stereoisomeric 2-methylcyclopentanols was claimed in 1926 by Godchot and Bedos,[11] who obtained a "*cis*" product from the reaction of cyclopentene oxide with methylmagnesium iodide, and a "*trans*" derivative by reduction of 2-methylcyclopentanone with sodium and moist ether. These investigators prepared the phenylurethans and allophanates of their products, but the melting points of the "*cis*" and "*trans*" derivatives in each series were so close that differentiation by this means was impracticable. More recently Hückel and Kindler[12] reported that catalytic hydrogenation of 2-methylcyclopentanone affords a mixture of stereoisomeric alcohols, from which 3,5-dinitrobenzoates melting at 124° and at 64° can be isolated in approximately equal amounts. Hydrolysis of these derivatives after reduction of the nitro groups furnished free alcohols, the densities and refractive indices of which were in fair agreement with the values reported by Godchot and Bedos. Reduction of 2-methylcyclopentanone with sodium and alcohol likewise yielded a mixture, from which the dinitrobenzoate melting at 64° was subsequently isolated as the major component, though in a yield of only about 30%.

On the basis of this evidence a *trans* structure was assigned to the dinitrobenzoate, m. p. 64°, and a *cis* structure to the higher melting material. Hückel and Kindler[12] further noted that the *p*-toluenesulfonate derived from "*cis*"-2-methylcyclopentanol was decomposed in refluxing methanol at a faster rate than was the corresponding derivative of the "*trans*" form. The *p*-toluenesulfonates were not obtained in crystalline condition, and no attempt was made to identify the methanolysis products.

In an effort to resolve the inconsistencies between our work and that of Hückel and Kindler, we have reinvestigated the catalytic hydrogenation (Pt) of 2-methylcyclopentanone. Treatment of the crude hydrogenation product with 3,5-dinitrobenzoyl chloride and pyridine furnished a mixture, from which 3,5-dinitrobenzoates melting at 67° and at 85° could be isolated. These products did not depress the melting points of the corresponding derivatives (VIII and IX) obtained by the reactions of *cis*- and *trans*-1-acetyl-2-methylcyclopentane, respectively, with perbenzoic acid. In no case were we able to isolate a product melting at 124°.

The claim of Godchot and Bedos[11] that the reaction of cyclopentene oxide with methylmagnesium iodide affords *cis*-2-methylcyclopentanol is also apparently in error, for the analogous reaction of cyclohexene oxide with methylmagnesium iodide, which was originally reported by these authors[13] to yield *cis*-2-methylcyclohexanol, was subsequently shown to involve rearrangement with ring contraction.[14] Moreover, Bartlett and Berry[15] have demonstrated that treatment of cyclohexene oxide with dimethylmagnesium in the absence of magnesium halide leads to the formation of the expected *trans*-2-methylcyclohexanol.

Our efforts to obtain a dinitrobenzoate corresponding either to VIII or to IX by reaction of cyclopentene oxide with methylmagnesium iodide under mild conditions and treatment of the product with dinitrobenzoyl chloride were unsuccess-

(9) Hückel and Hagenguth, *Ber.*, **64**, 2892 (1931).

(10) Colman and Perkin, *J. Chem. Soc.*, **53**, 200 (1888).

(11) Godchot and Bedos, *Compt. rend.*, **182**, 393 (1926).

(12) Hückel and Kindler, *Ber.*, **80**, 202 (1947).

(13) Godchot and Bedos, *Bull. soc. chim.*, **37**, 1451 (1925).

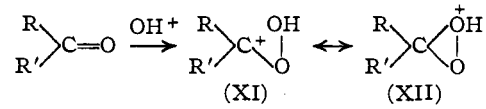
(14) Godchot and Cauquil, *Compt. rend.*, **186**, 375, 955 (1928); Vavon and Mitchovitch, *ibid.*, **186**, 702 (1928); Bedos, *ibid.*, **189**, 255 (1929).

(15) Bartlett and Berry, THIS JOURNAL, **56**, 2683 (1934).

ful. The only crystalline compound that could be isolated was identified by analysis as the 3,5-dinitrobenzoate of cyclopentene iodohydrin, formed by the action of magnesium iodide on cyclopentene oxide.[16] The reaction of cyclopentene oxide with methyllithium, however, proceeded smoothly, and a product was obtained (51% yield), the dinitrobenzoate of which melted at 82–83.5° and did not depress the melting point of IX. Identity of the three samples of IX prepared (a) by perbenzoic acid oxidation of *trans*-1-acetyl-2-methylcyclopentane, (b) by catalytic hydrogenation of methylcyclopentanone and (c) by reaction of cyclopentene oxide with methyllithium was further established by comparison of the infrared absorption of these samples. All the results described above are consistent only with the assignment of a *trans* structure to IX.

The two samples of VIII prepared by perbenzoic acid oxidation of *cis*-1-acetyl-2-methylcyclopentane and by hydrogenation of methylcyclopentanone likewise showed identical infrared absorption characteristics, and a *cis* structure is assigned to this substance. Although the explanation of the anomalous results of Hückel and Kindler is not apparent, the possibility that the "epimeric" methylcyclopentanols of Godchot and Bedos[11] are in reality samples of the *trans* compound of varying degrees of purity cannot be excluded. The peracid oxidation of *cis*- and *trans*-1-acetyl-2-methylcyclopentane therefore proceeds without inversion of configuration as does the analogous oxidation of *cis*- and *trans*-1-acetyl-2-methylcyclohexane.

Retention of configuration in the reaction of ketones with perbenzoic acid is readily explicable in terms of the mechanism proposed by Robertson and Waters[17] for oxidations with hydroperoxides, in particular persulfuric acid, since rearrangement (S_Ni) of the intermediate X involves a transition state of the pyramidal type.[18] The mechanism suggested by these authors for the formation of X is not unique, an alternate pathway being



(XI) (XII)

in which XI and XII represent two of the contributing resonance forms (*cf.* X) of the peroxide conjugate acid.

The interpretation of Robertson and Waters not only explains the experimentally observed stereospecificity, but also accounts for the fact that the migrating group is the one with greater capacity for electron release, notable examples being the transformations of α-tetralone into γ-*o*-hydroxyphenylbutyric acid lactone[19] and of benzalacetone into phenylacetaldehyde enol acetate.[20]

It is of some interest that the enol intermediate proposed by Treibs[21] and rejected by Robertson and Waters can be eliminated on purely theoretical grounds, for it would be expected to yield an α-ketol on reaction with peracids; Kritchevsky and Gallagher[22] have in fact shown that the enol acetate of pregnanolone acetate furnishes 17α-hydroxypregnanolone in excellent yield on treatment with perbenzoic acid.

The rearrangement involved in the peracid oxidation of ketones is formally analogous to the Wagner–Meerwein, Beckmann[2,17] and Arndt–Eistert rearrangements. Retention of configuration in the latter reaction has recently been demonstrated by Gutsche.[23]

Acknowledgments.—The author is greatly indebted to Mrs. Dorothy M. Voitle for technical assistance and to Mr. S. M. Nagy and Mrs. Louise Spencer of M. I. T. for analyses reported in this paper.

Experimental[24]

cis-1-**Acetyl-2-methylcyclohexane** (II).—1-Acetyl-2-methyl-Δ¹-cyclohexene[25] (20.0 g.) was hydrogenated without solvent in the presence of 1.5 g. of palladium black. The reaction became very slow after 1.1 molar equivalents of hydrogen had been absorbed. The catalyst was then removed by filtration, and the filtrate was diluted with 80 ml. of methanol. Semicarbazide hydrochloride (21.2 g.) and sodium acetate (15.5 g.) in 60 ml. of water were added, and the solution was allowed to stand at room temperature for twenty-four hours, at the end of which time considerable quantities of crystalline material had separated. The mixture was further diluted with water, and the prod-

(16) *Cf.* Meiser, *Ber.*, **32**, 2049 (1899).

(17) Robertson and Waters, *J. Chem. Soc.*, 1574 (1948).

(18) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937).

(19) Schroeter, German Patent 562,827 (1928); *Chem. Zentr.*, **104**, I, 127 (1933).

(20) Böeseken and co-workers, *Rec. trav. chim.*, **50**, 827 (1931); **52**, 874 (1933); **55**, 786 (1936).

(21) Treibs, *Ber.*, **72**, 1194 (1939).

(22) Kritchevsky and Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

(23) Gutsche, THIS JOURNAL, **70**, 4150 (1948).

(24) All melting points are corrected.

(25) Kipping and Perkin, *J. Chem. Soc.*, **57**, 16 (1890); Ruzicka, Koolhaas and Wind, *Helv. Chim. Acta*, **14**, 1151 (1931); Dimroth and Lüderitz, *Ber.*, **81**, 242 (1948). The presence of a large proportion of β,γ-isomer (1-acetyl-2-methyl-Δ²-cyclohexene) in this material at equilibrium was established by Dimroth and independently by us (unpublished data).

uct was filtered and recrystallized several times from dilute methanol. The yield of pure material, m. p. 182–182.5°, was 18.0 g.

Anal. Calcd. for $C_{10}H_{19}ON_3$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.80; H, 9.75; N, 21.17.

The semicarbazone prepared above (17.5 g.) was mixed with 26.0 g. of phthalic anhydride and 50 ml. of water and steam distilled until no further oil appeared in the distillate (about one hour). The product was then extracted with ether, washed with saturated sodium chloride solution and filtered through anhydrous sodium sulfate. The ether was finally removed on the steam-bath, and the residual oil distilled under reduced pressure. The yield of material boiling at 67–68° (10 mm.) was 11.5 g.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.19; H, 11.46.

trans-1-**Acetyl-2-methylcyclohexane** (III).—Inversion of *cis*-1-acetyl-2-methylcyclohexane was accomplished by treatment of 9.00 g. of this product with a solution of 2.00 g. of sodium in 50 ml. of absolute ethanol. After twenty-four hours a solution of 10.0 g. of semicarbazide hydrochloride in 25 ml. of water was added. The reaction mixture was allowed to stand at room temperature for three hours, water was then added, and the crystalline product was filtered and washed with water. The crude semicarbazone was recrystallized several times from dilute methanol and gave an analytical sample melting at 177–178.5°.

Anal. Calcd. for $C_{10}H_{19}ON_3$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.80; H, 9.51; N, 20.74.

Hydrolysis of the semicarbazone was carried out as described in the above procedure; the free *trans* ketone obtained in this way boiled at 64–65° (10 mm.).

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.47; H, 11.39.

cis-1-**Acetyl-2-methylcyclopentane** (VI).—1-Acetyl-2-methyl-Δ^1-cyclopentene[26] was hydrogenated over palladium black as described for the corresponding cyclohexene derivative. The semicarbazone obtained from the crude hydrogenation product after several recrystallizations from dilute methanol melted at 170–171°.

Anal. Calcd. for $C_9H_{17}ON_3$: C, 58.99; H, 9.35; N, 22.93. Found: C, 58.87; H, 9.33; N, 23.06.

Hydrolysis of the semicarbazone (17.0 g.) by steam distillation in the presence of phthalic anhydride afforded 10.8 g. of the free *cis* ketone, b. p. 53–53.5° (14 mm.).

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.17; H, 10.95.

trans-1-**Acetyl-2-methylcyclopentane** (VII).—A solution of 8.20 g. of *cis*-1-acetyl-2-methylcyclopentane in 50 ml. of absolute alcohol containing 2.00 g. of sodium was allowed to stand overnight at room temperature. The semicarbazone prepared by the addition of 10.0 g. of semicarbazide hydrochloride to the above solution weighed 8.00 g. and melted at 160–162°. Several recrystallizations from dilute methanol afforded the analytical sample, m. p. 163–164°. A mixed melting point with the *cis* semicarbazone (m. p. 170–171°) was depressed to 146–154°.

Anal. Calcd. for $C_9H_{17}ON_3$: C, 58.99; H, 9.35; N, 22.93. Found: C, 59.27; H, 9.24; N, 23.05.

Decomposition of the semicarbazone as described above furnished the *trans* ketone, b. p. 53.5–54° (14 mm.).

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.18; H, 11.13.

Oxidations with Perbenzoic Acid. (1) *cis*-1-**Acetyl-2-methylcyclohexane**.—The *cis* ketone (2.00 g., 14.3 mmoles) was added slowly to a cooled solution of 17.1 mmoles (1.2 eq.) of perbenzoic acid in 14.0 ml. of chloroform. After standing at room temperature for seven days, the reaction mixture was diluted with ether, washed with dilute sodium hydroxide solution, saturated sodium chloride and filtered through anhydrous sodium sulfate.

After removal of the solvents, the residue was separated into neutral and ketonic fractions by means of Girard's reagent T. The ketonic fraction obtained by acidification of the Girard complex with hydrochloric acid consisted of 140 mg. of oil that gave a mixed semicarbazone, m. p. 163–169°.[27]

The neutral product, consisting chiefly of *cis*-2-methylcyclohexanyl acetate, was saponified after being heated for one and one-half hours with 1.00 g. of sodium hydroxide in 10 ml. of water; enough methanol was added to prevent the formation of two layers. The reaction mixture was then diluted with water and thoroughly extracted with ether. The ether solution was washed with a little saturated sodium chloride, filtered through anhydrous sodium sulfate and concentrated on the steam-bath.

The residue (1.2 g.) was then treated with 1.6 g. of phthalic anhydride in 5 ml. of dry pyridine. After refluxing for three hours, the solution was diluted with water and extracted with ether. Repeated washing of the ethereal extract with cold 1% sodium hydroxide removed the acidic product (non-acidic material, 100 mg.), which was liberated by the addition of hydrochloric acid and taken into ether. Removal of the ether gave a residue of 2.05 g. (63% based on ketone consumed) of crystalline material, m. p. 101–102.5°. After recrystallization from ether–petroleum ether, a sample was obtained that melted at 102–103° and that did not depress the melting point of an authentic sample of *cis*-2-methylcyclohexanyl acid phthalate.[9]

(2) *trans*-1-**Acetyl-2-methylcyclohexane**.—Oxidation of 1.46 g. (10.4 mmoles) of *trans* ketone was carried out with 12.0 ml. of 1.06 molar perbenzoic acid in chloroform as described in the above procedure. The ketonic material from the Girard separation weighed 405 mg. and yielded a semicarbazone, m. p. 173–175°, identical with the semicarbazone of *trans*-1-acetyl-2-methylcyclohexane. The neutral fraction, after hydrolysis, furnished 700 mg. of oil, from which 1.00 g. (55% based on ketone utilized) of an acid phthalate, m. p. 121.5–123°, was obtained. Recrystallization from ether–petroleum ether afforded a pure product, m. p. 123–124°, that showed no melting point depression when mixed with an authentic sample of *trans*-2-methylcyclohexanyl acid phthalate.[9]

(3) *cis*-1-**Acetyl-2-methylcyclopentane**.—*cis*-1-Acetyl-2-methylcyclopentane (2.00 g., 15.9 mmoles) was allowed to react with 14.6 ml. of 1.31 molar perbenozic acid in chloroform for seven days at room temperature. The unreacted ketone amounted to 195 mg. Saponification of the non-ketonic fraction afforded 950 mg. of oil, which was treated directly with 2.50 g. of 3,5-dinitrobenzoyl chloride and 10 ml. of dry pyridine. After standing overnight at room temperature, the reaction mixture was diluted with ether, washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide solution, saturated sodium chloride, filtered through anhydrous sodium sulfate and concentrated to dryness. The yield of material melting at 59–62° was 2.80 g. (66% based on ketone consumed).

After several recrystallizations from ether–petroleum ether and from methanol, the analytical sample was obtained as lath-shaped crystals, m. p. 66–67°.

Anal. Calcd. for $C_{13}H_{14}O_6N_2$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.34; H, 4.88; N, 9.36.

(4) *trans*-1-**Acetyl-2-methylcyclopentane**.—The *trans* ketone (2.00 g.) was treated with 14.6 ml. of 1.31 molar perbenzoic acid in chloroform as described previously. The unreacted ketone recovered by treatment with Girard reagent weighed 95 mg. The 3,5-dinitrobenzoate prepared from the saponified non-ketonic fraction consisted of 2.87 g. (64% based on ketone consumed) of crystalline material melting at 80–83°. The analytical sample, m. p. 84–85°, was obtained in the form of small plates after several recrystallizations from dilute methanol.

(26) Marshall and Perkin, *J. Chem. Soc.*, **57**, 242 (1890); Blaise and Koehler, *Compt. rend.*, **148**, 852 (1909).

(27) Partial isomerization was apparently effected during the Girard separation.

Anal. Calcd. for $C_{13}H_{14}O_6N_2$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.24; H, 4.94; N, 9.65.

Catalytic Hydrogenation of 2-Methylcyclopentanone.—2-Methylcyclopentanone (5.3 g.) was hydrogenated in the presence of 1.0 g. of platinum oxide catalyst. After the absorption of hydrogen had ceased, the catalyst was filtered and the concentrated filtrate was treated with 14.6 g. of 3,5-dinitrobenzoyl chloride in 35 ml. of dry pyridine (twenty-four hours, room temperature). The reaction mixture was then diluted with water and extracted with ether and a small amount of methylene chloride. The extracts were combined and washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide solution and saturated sodium chloride, filtered through anhydrous sodium sulfate and concentrated to dryness. The residue was fractionally crystallized from methanol and gave small amounts of two pure products, A, m. p. 66–67°, and B, m. p. 82–84°. Mixed melting point determinations with VIII and IX, respectively, showed no depression.

Reaction of Cyclopentene Oxide with Methylmagnesium Iodide.—Cyclopentene oxide[16] (3.90 g.) was added slowly to an ethereal solution of 2 molar equivalents of methylmagnesium iodide. After standing overnight at room temperature in an atmosphere of dry nitrogen, the reaction mixture was acidified with dilute hydrochloric acid. The aqueous phase was repeatedly extracted with ether, and the combined extracts were washed with saturated sodium chloride solution containing a little sodium bisulfite to remove traces of iodine. The 3,5-dinitrobenzoate was prepared by the usual procedure and after purification by recrystallization from ethanol, in which it was rather insoluble, a pure sample of cyclopentene iodohydrin 3,5-dinitrobenzoate melting at 117–118° was obtained.

Anal. Calcd. for $C_{12}H_{11}O_6N_2I$: C, 35.48; H, 2.73; N, 6.90; I, 31.25. Found: C, 35.24; H, 2.80; N, 6.82; I, 30.97.

Reaction of Cyclopentene Oxide with Methyllithium.—Cyclopentene oxide (2.00 g.) was added to a solution of 1.2 molar equivalents of methyllithium in ether. The reaction mixture was refluxed under an atmosphere of nitrogen for one hour, and the ether was evaporated in a stream of nitrogen. After the residue had been heated on the steam-bath for two hours, a small amount of water was added, and the product taken into ether. The residue obtained after removal of the solvent afforded 3.60 g. (51%) of a dinitrobenzoate melting at 78–81°. Two recrystallizations from methanol gave a sample, m. p. 82–83.5°, that did not depress the melting point of IX or of B, described above.

Summary

The reactions of *cis*- and *trans*-1-acetyl-2-methylcyclohexane with perbenzoic acid yield, respectively, *cis*- and *trans*-2-methylcyclohexanyl acetate, identified by saponification and conversion into the corresponding acid phthalates. Analogous oxidations of *cis*- and *trans*-1-acetyl-2-methylcyclopentane similarly yield *cis*- and *trans*-2-methylcyclopentanyl acetate, respectively. The latter products were saponified and converted into 3,5-dinitrobenzoates, the structures of which were established by independent syntheses. These products are not identical with the 3,5-dinitrobenzoates of "*cis*-" and "*trans*"-2-methylcyclopentanol reported by Hückel and Kindler.

CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 20, 1949

[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Perbenzoic Acid Oxidation of 20-Ketosteroids and the Stereochemistry of C-17[1]

BY T. F. GALLAGHER AND THEODORE H. KRITCHEVSKY

The oxidation of 20-ketosteroids to acetoxy derivatives of C_{19} steroids by means of persulfuric acid has been described by Marker[2]; Burckhardt and Reichstein[3] and Sarett[4] have examined the same reaction with perbenzoic acid as the oxidizing agent. These authors studied the reaction only with 20-keto derivatives having the normal or 17β orientation of the side chain and noted that only a single diastereoisomer was isolated from the reaction. In order to provide more complete information about the stereochemical course of the reaction and to gain an insight into the reaction mechanism, we have investigated the oxidation of 3α-acetoxy-17α-pregnan-20-one where the side chain is attached in the opposite configuration to that studied in the previous investigations. At the same time Dr. Richard B. Turner at Harvard University undertook an investigation of this reaction upon simpler diastereoisomers.[5] The results of both investigations leave little doubt of the course and mechanism of the reaction. It is shown that the oxidation proceeds without inversion of configuration at C-17 and as a result the procedure can be useful for the determination of configuration as well as a valuable preparative tool. The reactions are summarized in Fig. 1.

(1) This investigation was supported by grants from the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, the Lillia Babbit Hyde Foundation, and the National Cancer Institute, United States Public Health Service.

(2) Marker, THIS JOURNAL, **62**, 2543 (1940).

(3) Burckhardt and Reichstein, *Helv. Chim. Acta*, **25**, 1434 (1942).

(4) Sarett, THIS JOURNAL, **69**, 2899 (1947).

Experimental

3α,17β-Etiocholanediol from 3α-Acetoxypregnan-20-one.—A solution containing 230 mg. of 3α-acetoxypregnan-20-one and 88.5 mg. of perbenzoic acid in 1.1 ml. of chloroform was stored at room temperature for seven days. The neutral fraction was isolated in the usual manner and fractionated with the Girard reagent T. 95 mg. of ketonic material and 127 mg. of non-ketonic product were obtained. The non-ketonic fraction was sublimed in high vacuum and yielded 100 mg. of sublimate. 10 mg. of crystalline product, m. p. 215–220°, was removed and the remainder was saponified with 0.25 *N* sodium hydroxide in 50% alcohol at 60° for one-half hour. The crystalline product upon neutralization was recrystallized from ethanol and yielded 69 mg. of 3α,17β-etiocholanediol, m. p. 229–232°; $[\alpha]_D$ +23° (ethanol). One recrystallization gave the pure product which melts 236–236.5°;

(5) Turner, *ibid.*, **72**, 878 (1950).