Attempted Epimerization of *cis-cis*-1-Decalol.—A solution of 6.0 g. of *cis-cis*-1-decalol in 15 ml. of dry pyridine was cooled to 0° and 8 g. of *p*-toluenesulfonyl chloride was added. The mixture was stored at 5° for 18 hr., then poured into 100 ml. of ice and water. The precipitate was collected by filtration, washed first with 10% sodium bicarbonate solution, then with water and dried. The tosylate (10.3 g.) melted at 95–97° without further purification (lit.[7] m.p. 96–98° dec.). It was dissolved in 50 ml. of acetone (reagent grade), to which was added 6 g. of potassium acetate and 10 g. of tetraethylammonium acetate monohydrate, and the mixture was heated under reflux for 40 hr. The solid was removed by filtration and washed thoroughly with acetone. The filtrate was concentrated to a sirupy residue, which was diluted with 200 ml. of water and extracted with three 100-ml. portions of petroleum ether (30–60°). Removal of the solvent left a liquid residue that was dissolved in 10 ml. of methanol and heated on a steam-bath for 20 min. with 10 ml. of 40% potassium hydroxide solution. The mixture was added to 100 ml. of water and extracted with four 75-ml. portions of ether. The ether solutions were combined, dried, and concentrated. The residue was distilled through a semimicro column giving 3.04 g. of 1,9-octalin, b.p. 83° (18 mm.), $n^{25}D$ 1.4945, with an infrared spectrum identical with the spectrum of an authentic sample.[7]

trans-trans-1-Decalol.—*trans-trans*-1-Decalol was prepared according to the procedure of Dauben, Tweit and Mannerskantz.[16] The infrared spectrum of the *trans-trans*-1-decalol showed a band of medium intensity at 950 cm.$^{-1}$ which is not present in the spectrum of *cis-trans*-1-decalol (II). The acid phthalate of the *trans-trans*-1-decalol melted at 166.8–168° (lit.[6] m.p. 167°) after several recrystallizations from aqueous methanol.

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[16] W. G. Dauben, R. C. Tweit and C. Mannerskantz, This Journal, **76**, 4421 (1954).

Cambridge, Massachusetts

[Contribution from the Department of Chemistry, Massachusetts Institute of Technology]

Proximity Effects. XV. The Reaction of Phenylmagnesium Bromide with Methyl Cycloöctene-1-carboxylate

By Arthur C. Cope and Morton Brown[1]

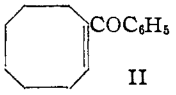
Received December 12, 1957

Addition of phenylmagnesium bromide to methyl cycloöctene-1-carboxylate has been shown to yield, besides the expected normal products, phenyl 2-phenylcycloöctyl ketone and methyl 2-phenylcycloöctane carboxylate, an abnormal product which has been shown by degradation and synthesis to be phenyl *endo-cis*-bicyclo[3.3.0]oct-2-yl ketone.

Certain reactions of medium-sized ring compounds have been shown to give rise to abnormal reaction products,[2] the formation of which has been ascribed to a "proximity effect" due to the conformation of the ring, which brings atoms that are unreactive by classical theory in such close proximity to the reactive center that they participate in the reaction.

Using the concept that development of a partial or full positive charge on one of the ring carbon atoms was responsible for the hydride ion shift that characterizes the transannular reaction that occurs in the solvolysis of epoxides with medium-sized carbocyclic rings, we have investigated another reaction in which a partially positively charged center is generated to determine whether a transannular reaction would occur. The reaction investigated was the addition of phenylmagnesium bromide to methyl cycloöctene-1-carboxylate (I). In such a case the incipient positive charge would be developed at the β-position in the conjugated system.

Methyl cycloöctene-1-carboxylate (I) was prepared from the crystalline acid[3] and treated with a 10% molar excess of phenylmagnesium bromide at −10°. The product, a yellow oil, was separated by means of Girard Reagent T into a "ketonic" fraction (approximately 1% yield) and a much larger "non-ketonic" fraction. The oily ketone was not analytically pure, but its infrared spectrum showed carbonyl absorption at 1667 cm.$^{-1}$ characteristic of a substituted acetophenone.[4] Analytical data on the crystalline 2,4-dinitrophenylhydrazone, m.p. 153.4–154.2°, indicated that it had the molecular formula $C_{21}H_{22}N_4O_4$. One possible structure considered for this ketone was phenyl 1-cycloöctenyl ketone (II). However, an independent synthesis of this ketone from 1-cycloöctenoyl chloride and diphenylcadmium gave a product which formed a 2,4-dinitrophenylhydrazone that was not identical with the corresponding derivative of the ketone isolated from the Grignard reaction.



II

The ketone formed from methyl cycloöctene-1-carboxylate subsequently was shown to be a phenyl *cis*-bicyclo[3.3.0]oct-2-yl ketone by a modified Barbier–Wieland degradation, involving in the final step oxidative cleavage to the known *cis*-bicyclo[3.3.0]octan-2-one (III), identified as the 2,4-dinitrophenylhydrazone. Determination of the configuration of the benzoyl group (*endo* or *exo*) relative to the hydrogen atoms at the point of ring fusion was accomplished by the synthesis of the epimeric ketones IV and V.

The "non-ketonic" fraction mentioned above partially crystallized on refrigeration to give a ketone, $C_{21}H_{24}O$, m.p. 135.5–136.5°. Although a crystalline 2,4-dinitrophenylhydrazone could not be obtained from this ketone by any of the usual methods, the infrared spectrum with absorption at 1667 cm.$^{-1}$ and the ultraviolet spectrum with a maximum at 243 mμ (ϵ_{max} 11,200, ethanol) gave evidence for the presence of a benzoyl group.[5] This ketone was shown to be phenyl 2-phenylcycloöctyl ketone (VI) by the same type of degrada-

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[1] National Science Foundation Fellow, 1955–1957.

[2] A. C. Cope, M. Brown and H. H. Lee, This Journal, **80**, 2855 (1958), and preceding papers in this series and references cited therein.

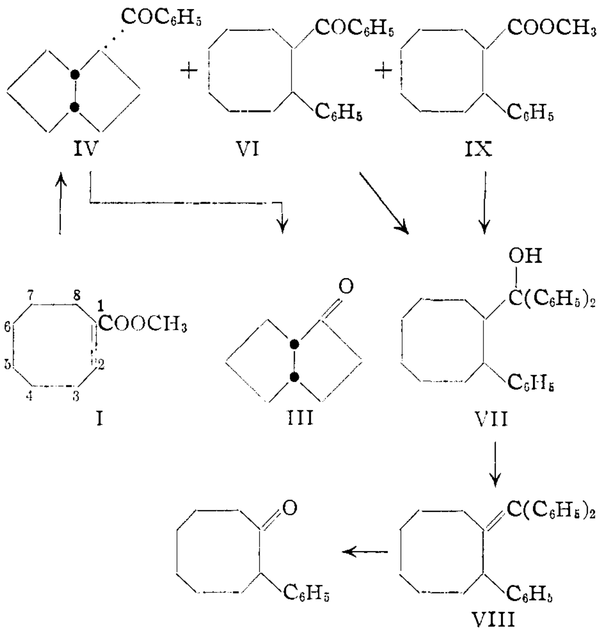
[3] A. C. Cope, M. Burg and S. W. Fenton, *ibid.*, **74**, 173 (1952).

[4] A. H. Soloway and S. L. Friess, *ibid.*, **73**, 5000 (1951); R. P. Barnes and G. E. Pinkney, *ibid.*, **75**, 479 (1953).

[5] M. Pestemer and E. Mayer-Pitsch, *Monatsh.*, **70**, 104 (1937).

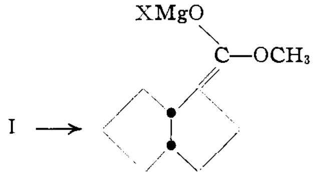
tion used for IV. Addition of excess phenyllithium produced a crystalline tertiary alcohol, diphenyl 2-phenylcyclooöctylcarbinol (VII), which was dehydrated by heating with boric acid to a high-boiling viscous oil that was not obtained analytically pure. The olefin, however, did show a maximum ultraviolet absorption at 250 mμ (ϵ_{max} 11,300, ethanol), in agreement[6] with the structure of 1-phenyl-2-benzhydrilidene-cyclooöctane (VIII). The olefin was cleaved by treatment with warm chromium trioxide in aqueous acetic acid, forming benzophenone and 2-phenylcyclooöctanone.[7] The latter ketone was isolated by fractional crystallization of its semicarbazone.

The major portion of the "non-ketonic" fraction after removal of the crystalline ketone VI was chromatographed on alumina, and an additional small amount of VI was isolated. The major oily fractions were distilled under reduced pressure and yielded 83% (based on the ester I) of a methyl ester with an analysis corresponding to the formula $C_{16}H_{22}O_2$. Addition of excess phenylmagnesium bromide to this ester gave the same tertiary alcohol (VII) that was obtained from VI, thereby showing the ester to be methyl 2-phenylcyclooöctane 1-carboxylate (IX).



It will be seen that this proof of structure requires VI and IX to have the same stereochemical configuration since they both give the same tertiary alcohol VII in good yield. The actual configuration (*cis* or *trans*) of both was not determined. The proof of structure of the ketone IV outlined in the accompanying equations leaves the configuration of the benzoyl group relative to the ring fusion in doubt; indeed, even the isolation of III as its 2,4-dinitrophenylhydrazone in the degradation does not conclusively prove the existence of a *cis* ring fusion in IV, because *trans*-bicyclo[3.3.0]octan-2-one (if formed) would be expected to isomerize to the *cis*-ketone during the isolation procedure.[8] The configuration of IV was shown by synthesis to correspond to phenyl *endo-cis*-bicyclo[3.3.0]oct-2-yl ketone.

The formation of the ester IX and ketone VI are readily explained by the mechanisms proposed[9] for the conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds. Alternatively, the conjugated system may become polarized in the presence of the Lewis acids present (phenylmagnesium bromide and magnesium bromide) with simultaneous loss of a proton at C_6 to the Grignard reagent. The carbanion formed could then add to the conjugated system as in a Michael reaction. Further reaction of the enolate salt with another molecule of Grignard reagent would form IV. Formation of the *endo* (less stable) isomer during hydrolysis of the complex is, perhaps, somewhat surprising. However, Kohler[10] has noted that often the products obtained in such reactions are not those favored thermodynamically. Recent work by Zimmerman[11] has shown that protonation of such enolates sometimes results in formation of kinetically controlled rather than thermodynamically controlled products.



The epimeric phenyl *cis*-bicyclo[3.3.0]oct-2-yl ketones were synthesized from the known *cis*-bicyclo[3.3.0]octan-2-one,[8] readily available from the eight-membered cyclic dimer of chloroprene, 1,6-dichloro-1,5-cyclooöctadiene.[12] This ketone formed a crystalline sodium bisulfite addition product which was converted to the cyanohydrin in good yield. Dehydration with thionyl chloride in pyridine afforded the unsaturated nitrile, bicyclo-[3.3.0]oct-1(2)-ene-2-carbonitrile (X) in 68% overall yield from III. The double bond was assigned to the 1(2)-position on the basis of the infrared spectrum which showed a conjugated nitrile band at 2220 cm.$^{-1}$, a double-bond stretching band at 1660 cm.$^{-1}$, but no olefinic hydrogen band at 3030 cm.$^{-1}$.[13] The double bond in X was reduced in the presence of 10% palladium-on-Norit, and the resulting saturated nitrile hydrolyzed with ethanolic alkali to give a liquid acid. The homogeneity of this acid was established by partition chromatography[14] on silicic acid using a brom cresol green indicator, and by absorption chromatog-

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(6) M. Calvin and R. E. Buckles, THIS JOURNAL, **62**, 3324 (1940).

(7) A. C. Cope and D. S. Smith, *ibid.*, **74**, 5136 (1952).

(8) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934), and A. H. Cook and R. P. Linstead, *ibid.*, 955 (1934), discuss the case of rearrangement of the (unknown) *trans*- to the *cis*-ketone.

(9) E. P. Kohler and G. Heritage, *Am. Chem. J.*, **33**, 21 (1905); M. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 196, 563.

(10) E. P. Kohler, M. Tishler and H. E. Potter, THIS JOURNAL, **57**, 2517 (1935).

(11) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955), and succeeding papers.

(12) A. C. Cope and W. R. Schmitz, THIS JOURNAL, **72**, 3056 (1950).

(13) N. Sheppard and D. M. Simpson, *Quart. Revs.*, **6**, 1 (1952).

(14) L. L. Ramsey and W. J. Patterson, *J. Assoc. Offic. Agr. Chem.*, **31**, 139 (1948).

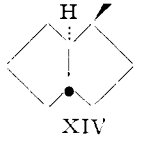
raphy on silica gel. Fractions taken at various points during the absorption chromatogram gave the same crystalline amide, m.p. 178.0–178.9° dec. This acid was therefore assigned the most stable (*exo*) configuration[15] since it was obtained by alkaline hydrolysis.

The corresponding phenyl ketone V was obtained by treatment of the acid chloride with diphenylcadmium. The crystalline 2,4-dinitrophenylhydrazone, m.p. 121.6–122.4°, prepared from V was not identical with the corresponding derivative obtained from the ketone formed from phenylmagnesium bromide and the ester I.

endo-cis-Bicyclo[3.3.0]octane-2-carboxylic acid (XIII) was synthesized by reversal of the two steps required in converting X to XI. Hydrolysis of X using potassium hydroxide in diethylene glycol[16] gave an α,β-unsaturated acid formulated as XII. Again the double bond was placed in the 1(2)-position on the basis of an ultraviolet maximum at 223 mμ (ϵ_{max} 7,350, ethanol), and double-bond stretching at 1635 cm.$^{-1}$, but no absorption at 3030 cm.$^{-1}$ in the infrared spectrum attributable to an olefinic hydrogen.

The acid XII was reduced to a saturated carboxylic acid whose infrared spectrum differed only slightly from the spectrum of XI and which behaved in a similar fashion when subjected to chromatography on silica gel. However, fractions taken at various points in the chromatogram gave the same crystalline amide, m.p. 162.4–163.3°, which differed from the amide of XI in melting point, mixed melting point and infrared spectrum. This new carboxylic acid was assigned structure XIII, *endo-cis*-bicyclo[3.3.0]octane-2-carboxylic acid, and this structure is supported by the observation that XIII could be isomerized to XI by heating with alcoholic base or concentrated hydrochloric acid.

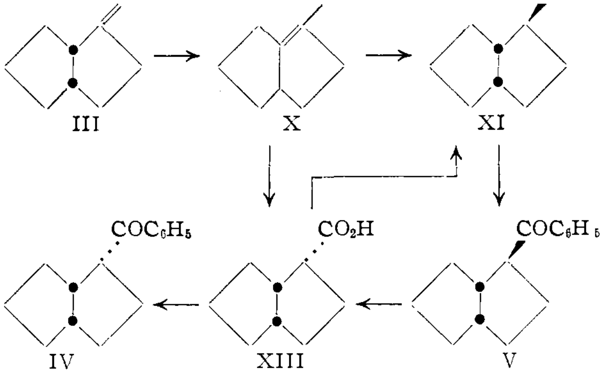
Mechanistically, formation of XIII on reduction of XII is quite reasonable. Inspection of molecular models shows that entrance of hydrogen above the plane of the ring to give the *endo-cis* product is somewhat less hindered than reduction from below to give a *trans* ring fusion (XIV). Formation of the far more stable[8] *cis* ring fusion may be a controlling factor since the *trans* ring fusion is energetically unfavorable. An analytical sample of the *endo*-acid solidified on refrigeration and was recrystallized from pentane at low temperatures to a constant melting point of 39.0–40.5°.



XIV

The *endo*-phenyl ketone IV was prepared in the same manner as the *exo* isomer and gave a 2,4-dinitrophenylhydrazone identical in all respects with the derivative formed by the ketone isolated from the reaction of I with phenylmagnesium bromide.

It might be argued that formation of IV could have resulted from the reaction of a bicyclic isomer of I present in the ester I as an impurity. However, the acid from which the ester I was prepared was a high-melting crystalline solid which absorbed one molar equivalent of hydrogen, forming cycloöctanecarboxylic acid.[3] The physical properties of the acids XI and XIII lead one to conclude that, had they been present as impurities in crude cycloöctene-1-carboxylic acid, they would have been removed by recrystallization. The ester I possessed only one carbonyl absorption peak in the infrared spectrum and also gave a single peak (evidence for homogeneity) when analyzed by vapor-phase chromatography on a column of 30% silicone oil (Dow-Corning 550) on Celite 545 at 250°.



It will be seen that this synthetic approach does not rigorously fix the ring fusion in IV as *cis*. However, perbenzoic acid oxidation of the methyl ketones corresponding to IV and V gave the known corresponding *cis*-bicyclo[3.3.0]octan-2-ols.[17]

Experimental[18]

Methyl Cycloöctene-1-carboxylate (I).—Cycloöctene-1-carboxylic acid[3] (1.12 g.) was treated with an ethereal solution of diazomethane prepared from 1.43 g. of nitrosomethylurea. The excess diazomethane was destroyed by addition of a few drops of formic acid and, after the ether solution was washed with saturated sodium bicarbonate and dried over magnesium sulfate, distillation through a semimicro column yielded the methyl ester, b.p. 74–75° (1.5 mm.), n^{25}D 1.4855, yield 1.07 g. (89%).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.40; H, 9.57. Found: C, 71.24; H, 9.39.

Reaction of Phenylmagnesium Bromide with Methyl Cycloöctene-1-carboxylate (I).—In a 200-ml. three-necked flask equipped with a ball-joint Hershberg stirrer, dropping funnel and nitrogen inlet was placed 9.14 g. of methyl cyclooctene-1-carboxylate (I) in 50 ml. of anhydrous ether. The solution was cooled to −10° in a Dry Ice–acetone-bath and 1.10 molar equivalents of an ethereal solution of phenylmagnesium bromide was added dropwise over a period of 15 min. The mixture was stirred at −10° for 2 hr. and at room temperature for 2 hr., during which time a yellow complex separated. The complex was decomposed by addition of 50 ml. of a saturated solution of ammonium chloride which had been made basic to phenolphthalein by addition of several drops of concentrated ammonium hydroxide. The layers were separated and the aqueous layer was extracted with three 100-ml. portions of ether which were combined, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate and concentrated to give 15.95 g. of a yellow oil. This oil was extracted with Girard Reagent

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(15) K. Alder and M. Stein, *Ann.*, **514**, 211 (1934).

(16) A. C. Cope and E. M. Osman, THIS JOURNAL, **66**, 881 (1944).

(17) A. C. Cope, M. Brown and H. E. Petree, *ibid.*, **80**, 2852 (1958).

(18) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses.

T in the usual manner to give a ketonic fraction consisting of 220 mg. of crude phenyl *endo-cis*-bicyclo[3.3.0]oct-2-yl ketone (IV) and a "non-ketonic" fraction that partially crystallized on standing to give 327 mg. of phenyl 2-phenylcycloöctyl ketone (VI), m.p. 122–126°. Recrystallization from petroleum ether raised the melting point to VI to 135.5–136.5°.

Anal. Calcd. for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.46; H, 8.43.

The residual oil from the "non-ketonic" fraction, totaling 14.25 g., was chromatographed on 420 g. of Activity I alumina, and yielded 11.66 g. of a yellow oil on elution with 30–60° petroleum ether and an additional 2.11 g. of phenyl 2-phenylcycloöctyl ketone (VI) on elution with 5% benzene in 30–60° petroleum ether. The yellow oil on distillation through a semimicro column yielded 11.09 g. (83%) of pure methyl 2-phenylcycloöctanecarboxylate (IX), b.p. 101–103° (0.01 mm.), $n^{25}D$ 1.5240.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.02; H, 9.00. Found: C, 78.25; H, 8.87.

Crude phenyl *endo-cis*-bicyclo[3.3.0]oct-2-yl ketone (IV) (101 mg.) was treated with 2,4-dinitrophenylhydrazine, and yielded 177 mg. of a crude 2,4-dinitrophenylhydrazone, m.p. 140–147° dec. Four recrystallizations from ethanol–ethyl acetate furnished an analytical sample with a constant melting point of 153.4–154.2°. The ultraviolet spectrum of the 2,4-dinitrophenylhydrazone has an absorption peak at 368 mμ (ϵ_{max} 24,300, chloroform).

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 13.98. Found: C, 63.98; H, 5.78; N, 14.20.

1-Cycloöctenoyl Chloride.—Five grams of cycloöctene-1-carboxylic acid was dissolved in a 2.5 molar excess of thionyl chloride (9.6 g.) and allowed to stand overnight at room temperature. The excess thionyl chloride was removed at 30–50 mm. and the residue distilled under reduced pressure through a semimicro column. The acid chloride, a colorless liquid boiling at 75–78° (1.5 mm.), $n^{25}D$ 1.5155–1.5162, amounted to 4.75 g. (85%). An analytical sample had b.p. 78° (1.5 mm.), $n^{25}D$ 1.5162.

Anal. Calcd. for $C_9H_{13}OCl$: C, 62.61; H, 7.59. Found: C, 62.88; H, 7.35.

Phenyl 1-Cycloöctenyl Ketone (II).—To an ethereal solution of phenylmagnesium bromide prepared from 1.3 g. of magnesium turnings and 8.9 g. of bromobenzene was added in small portions 5.7 g. of anhydrous cadmium chloride. Stirring was continued under reflux for 1 hr., at the end of which time the solution gave a negative Gilman test for the presence of phenylmagnesium bromide. The ether was distilled and replaced by 25 ml. of benzene. To this solution was added dropwise with stirring a solution of 3.88 g. of 1-cycloöctenoyl chloride in 20 ml. of benzene. After stirring at room temperature for 5 min. and under reflux for 1 hr., the mixture was poured into 100 g. of ice and 50 ml. of 20% sulfuric acid. After separation of the layers, the aqueous layer was further extracted with two 50-ml. portions of benzene. The combined extracts were washed with saturated sodium chloride solution, and finally dried over magnesium sulfate. Concentration and distillation through a semimicro column afforded 3.0 g. (63%) of phenyl 1-cyclooctenyl ketone, a colorless liquid boiling at 123–126° (0.2 mm.), $n^{25}D$ 1.5618–1.5630. An analytical sample had b.p. 125–126° (0.2 mm.), $n^{25}D$ 1.5630.

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.08; H, 8.46. Found: C, 83.94; H, 8.18.

The ultraviolet spectrum of the ketone showed a maximum at 247 mμ (ϵ_{max} 13,600, ethanol) while the infrared spectrum showed conjugated carbonyl absorption at 1634 cm.$^{-1}$.

The 2,4-dinitrophenylhydrazone of this ketone melted at 161.5–163.2° after three recrystallizations from ethanol. A mixture of this 2,4-dinitrophenylhydrazone and the 2,4-dinitrophenylhydrazone of phenyl *endo-cis*-bicyclo[3.3.0]-oct-2-yl ketone (IV) melted from 132.4–151.4°, showing that they were not identical. The ultraviolet spectrum of this derivative showed a maximum at 377 mμ (ϵ_{max} 24,300, chloroform).

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 13.98. Found: C, 63.83; H, 5.69; N, 14.11.

Diphenyl-(2-phenylcycloöctyl)-carbinol (VII) from Phenyl 2-Phenylcycloöctyl Ketone (VI).—To an ethereal solution of phenyllithium prepared from 0.735 g. of lithium wire and 7.85 g. of bromobenzene was added with stirring a solution of 0.340 g. of phenyl 2-phenylcycloöctyl ketone in 25 ml. of anhydrous ether. The solution was refluxed for 1 hr. and then poured over 100 g. of ice and 100 ml. of 10% hydrochloric acid. The layers were separated and the aqueous layer extracted with two additional 50-ml. portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution, water and saturated sodium chloride solution. After drying over magnesium sulfate, concentration of the solution yielded 0.363 g. (85%) of yellow crystals of diphenyl-(2-phenylcycloöctyl)-carbinol, m.p. 104.5–120°. Three recrystallizations from hexane gave an analytical sample as white needles, m.p. 124.2–125°. The infrared spectrum of this compound in carbon tetrachloride showed absorption at 3413 cm.$^{-1}$ attributable to an unassociated hydroxyl group.

Anal. Calcd. for $C_{27}H_{30}O$: C, 87.52; H, 8.16. Found: C, 87.40; H, 8.31.

Diphenyl-(2-phenylcycloöctyl)-carbinol from Methyl 2-Phenylcycloöctane Carboxylate (IX).—To an ethereal solution of phenylmagnesium bromide prepared from 0.487 g. of magnesium turnings and 3.3 g. of bromobenzene was added dropwise a solution of 0.542 g. of methyl 2-phenylcycloöctanecarboxylate in 2 ml. of dry ether. After heating under reflux for 1 hr., the reaction mixture was cooled in an ice-bath and 65 ml. of saturated ammonium chloride solution was added dropwise. After separation of the ethereal layer, the aqueous layer was extracted with two 30-ml. portions of ether. The combined extracts were washed with sodium bicarbonate solution and with saturated sodium chloride solution. After drying over magnesium sulfate, evaporation of the ether yielded 1.26 g. of a yellow oil which, on refrigeration, yielded 0.30 g. of the crystalline carbinol, m.p. 119–123.1°. The residual oil after chromatography on 10 g. of Activity I alumina yielded an additional 0.27 g. of carbinol, m.p. 116–121° (71% total yield). A sample recrystallized from pentane had m.p. 123.8–125.0° and showed no depression on admixture with the carbinol obtained from phenyl 2-phenylcycloöctyl ketone. Infrared spectra of the two samples were identical.

Barbier–Wieland Degradation of Diphenyl-(2-phenylcycloöctyl)-carbinol.—In a short-path distillation tube was placed a mixture of 0.176 g. of diphenyl-(2-phenylcycloöctyl)-carbinol and 0.850 g. of boric acid. The heating block temperature was raised to 170° over a period of 30 min. while the pressure was gradually reduced to 0.05 mm., where it was kept for another 30 min., at which time 0.123 g. (78%) of a clear viscous oil had distilled. Attempts to induce crystallization of the oil were unsuccessful; however, the ultraviolet spectrum showed a maximum at 250 mμ (ϵ_{max} 11,300, ethanol), supporting the structure 1-phenyl-2-benzhydrylidine-cycloöctane for the product.

To a solution of 0.200 g. of the hydrocarbon in 2 ml. of chloroform and 10 ml. of glacial acetic acid was added with stirring a solution of 0.500 g. of chromium trioxide in 1 ml. of water and 7 ml. of glacial acetic acid, keeping the temperature below 50° with a cold water-bath. After the addition was completed, the temperature was kept at 50° for 20 min. with a warm water-bath. After removal of the volatile components at 30–50 mm., water was added to the residue, along with enough base to neutralize any acid still present, and the mixture was extracted with three 30-ml. portions of ether. The combined extracts were dried and concentrated to give 0.215 g. of a mixture of crystals and an oil. This oil was treated with semicarbazide hydrochloride and sodium acetate in hot aqueous ethanol, and formed 0.128 g. of a mixture of semicarbazones, m.p. 139.6–151.2°. Fractional crystallization from 70% ethanol afforded 0.076 g. of 2-phenylcycloöctanone semicarbazone, m.p. 153.7–154.6°, undepressed on admixture with an authentic sample. The combined mother liquors afforded a small amount (0.010 g.) of benzophenone semicarbazone.

Barbier–Wieland Degradation of Phenyl *endo-cis*-Bicyclo[3.3.0]oct-2-yl Ketone (IV).—To an ethereal solution of phenylmagnesium bromide prepared from 0.50 g. of magnesium turnings and 3.32 g. of bromobenzene was added a solution of 0.20 g. of crude phenyl *endo-cis*-bicyclo[3.3.0]-oct-2-yl ketone in 2 ml. of ether. After heating under reflux for 30 min., the reaction mixture was poured into 25 g. of ice and 50 ml. of saturated ammonium chloride solution. After separation of the organic layer, the aqueous phase was extracted twice with 30-ml. portions of ether. The extracts, after washing with dilute sodium bicarbonate solution and drying over magnesium sulfate, yielded 0.40 g. of a yellow oil on concentration. This oil was mixed with 0.75 g. of boric acid in a short-path distillation tube and heated to 180° over a period of 30 min. while the pressure was gradually reduced to 0.05 mm. and maintained there for an additional 30 min. The oily distillate (0.36 g.) was dissolved in 4 ml. of chloroform and 10 ml. of glacial acetic acid, and to this was added dropwise with stirring a solution of 0.5 g. of chromium trioxide in 1 ml. of water and 7 ml. of glacial acetic acid, keeping the temperature below 40° with an ice-bath. After the addition was complete, the mixture was heated to 50° for 30 min. Methanol (5 ml.) was added to destroy the excess oxidizing agent and the volatile components were removed by evaporation under reduced pressure. The residue was dissolved in 50 ml. of 2% sodium hydroxide and the solution extracted with three 20-ml. portions of ether. The combined extracts were washed with water, dried over magnesium sulfate and concentrated to give 0.45 g. of a viscous mixture of crystals and oil. This oil was dissolved in 10 ml. of 95% ethanol and treated with a solution of 0.5 g. of 2,4-dinitrophenylhydrazine in ethanolic sulfuric acid to give 0.71 g. of a crude mixture of 2,4-dinitrophenylhydrazones. The mixture was chromatographed on 20 g. of a 2:1 mixture of silicic acid–Celite. Elution with 80% benzene in hexane afforded 0.086 g. of crude *cis*-bicyclo[3.3.0]octan-2-one 2,4-dinitrophenylhydrazone,[11] m.p. 93.1–97.5°, which after three recrystallizations from ethanol melted at 110.5–113.5° and did not depress the melting point of authentic material.[10] Elution with pure benzene afforded benzophenone 2,4-dinitrophenylhydrazone, identified by melting point and mixed melting point with an authentic sample.

Bicyclo[3.3.0]oct-1(2)-ene-2-carbonitrile (X).—In a 500-ml. bottle was placed 200 ml. of a saturated sodium bisulfite solution and 15.8 g. of *cis*-bicyclo[3.3.0]octan-2-one.[12] The solution was shaken vigorously for 1–2 min. until a crystalline bisulfite addition product formed. The solution was cooled to 10° and a solution of 20 g. of potassium cyanide in 50 ml. of water was added in small portions with stirring. After the addition was completed, 20 ml. of ether was added and the mixture was shaken mechanically overnight, after which time the crystalline addition product had disappeared and was replaced by an oily layer. The oily layer was separated and the aqueous solution extracted with two 40-ml. portions of ether. The combined oil and extracts were dried over magnesium sulfate and concentrated. The residual oil, on distillation through a semimicro column, afforded 3.97 g. (25%) of recovered ketone and the crude cyanohydrin, remaining as the residue, amounted to 13.1 g. (91% based on the ketone not recovered).

In a 200-ml. three necked flask equipped with a ball-joint Hershberg stirrer, dropping funnel and reflux condenser was placed a solution of 13.1 g. of crude *cis*-bicyclo[3.3.0]octan-2-one cyanohydrin in 47 ml. of ether and 23 g. of pyridine. To this was added dropwise with cooling and stirring 18 g. of thionyl chloride. The mixture was heated under reflux for 2 hr., then poured over 200 g. of ice and extracted with three 100-ml. portions of ether. The ether extracts were washed with a saturated solution of sodium bicarbonate, dried, concentrated, and distilled through a semimicro column, yielding 8.60 g. (75%) of bicyclo[3.3.0]oct-1(2)-ene-2-carbonitrile (X), b.p. 86–88° (5 mm.), $n^{25}\mathrm{D}$ 1.5000. The infrared spectrum of this nitrile showed a band of medium strength at 2220 cm.$^{-1}$ (conjugated nitrile) and a band at 1660 cm.$^{-1}$ attributable to a double bond. No bands characteristic of an olefinic hydrogen were observed.

Anal. Calcd. for $C_9H_{11}N$: C, 81.29; H, 8.26; N, 10.44. Found: C, 81.26; H, 8.26; N, 10.35.

***cis*-Bicyclo[3.3.0]octane-2-carbonitrile.**—Bicyclo[3.3.0]-oct-1(2)-ene-2-carbonitrile (4.40 g.) was hydrogenated at atmospheric pressure in 25 ml. of absolute ethanol using 0.25 g. of 10% palladium-on-Norit as a catalyst. Hydrogen uptake was complete and amounted to 100% in 2.5 hr. The catalyst was separated by filtration and the solvent distilled. The residue on distillation afforded 3.96 g. (89%) of *cis*-bicyclo[3.3.0]octane-2-carbonitrile, b.p. 69–71° (1.4 mm.), $n^{25}\mathrm{D}$ 1.4800–1.4810. An analytical sample had b.p. 71° (1.4 mm.), $n^{25}\mathrm{D}$ 1.4810. The infrared spectrum showed a weak nitrile band at 2250 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.24; H, 9.55; N, 10.46.

***exo-cis*-Bicyclo[3.3.0]octane-2-carboxylic Acid (XI).**—*cis*-Bicyclo[3.3.0]octane-2-carbonitrile (2.81 g.) was heated under reflux for 20 hr. in a solution of 8 g. of sodium hydroxide in 33 ml. of ethanol and 10 ml. of water. Part of the ethanol was removed under reduced pressure, and the residue added to 50 g. of ice and acidified to congo red with 6 *N* sulfuric acid. The oil was extracted with three 30-ml. portions of ether which were combined, dried over magnesium sulfate, concentrated, and distilled through a semimicro column. The liquid acid, b.p. 105.5–107° (0.7 mm.), $n^{25}\mathrm{D}$ 1.4840, amounted to 2.77 g. (87%).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.11; H, 9.10. Found: C, 70.33; H, 9.04.

The homogeneity of this acid was established by chromatography on silica gel and elution with 2–5% ether in benzene. Fractions taken at various points gave the same amide of sharp melting point. *exo-cis*-Bicyclo[3.3.0]octane-2-carboxylic acid (0.146 g.) was warmed for 15 min. with 1 ml. of thionyl chloride, and after removal of some of the excess thionyl chloride by evaporation, the residue was added dropwise to 5 ml. of cold concentrated ammonium hydroxide. The crystalline amide, m.p. 171.8–175.2° dec., amounted to 0.130 g. (90%). Three recrystallizations from water (Norit) brought the melting point to 178–178.9° dec.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.54; H, 9.87. Found: C, 70.41; H, 10.07.

Bicyclo[3.3.0]oct-1(2)-ene-2-carboxylic Acid (XII).—To a solution of 3.68 g. of potassium hydroxide in 0.7 ml. of water and 18 ml. of diethylene glycol was added 4.38 g. of *cis*-bicyclo[3.3.0]octane-2-carbonitrile. The mixture was heated under reflux for 48 hr., poured into 120 ml. of water, and extracted with three 50-ml. portions of benzene. The aqueous layer was acidified with 6 *N* hydrochloric acid and further extracted with three 50-ml. portions of benzene. The benzene extracts of the acid solution were washed with saturated sodium chloride solution, dried over magnesium sulfate, concentrated, and distilled through a semimicro column. The bicyclo[3.3.0]oct-1(2)-ene-2-carboxylic acid, b.p. 112.5–114° (0.65 mm.), $n^{25}\mathrm{D}$ 1.5060, amounted to 2.32 g. (46%). The ultraviolet spectrum of this acid showed a maximum at 223 mμ ($\epsilon_{\max}$ 7,350, ethanol). The infrared spectrum showed an absorption peak at 1634 cm.$^{-1}$, attributable to a carbon–carbon double bond, but no absorption attributable to an olefinic hydrogen was observed.

Anal. Calcd. for $C_9H_{12}O_2$: C, 70.11; H, 7.95. Found: C, 70.21; H, 8.07.

***endo-cis*-Bicyclo[3.3.0]octane-2-carboxylic Acid (XIII).**—Bicyclo[3.3.0]oct-1(2)-ene-2-carboxylic acid (2.0 g.) was hydrogenated at atmospheric pressure in the presence of 0.25 g. of 10% palladium-on-Norit in 25 ml. of absolute ethanol. Hydrogen uptake was complete (102%) in 2 hr., and after filtration to separate the catalyst and concentration to remove the solvent, distillation afforded 1.98 g. (98%) of the liquid *endo-cis*-bicyclo[3.3.0]octane-2-carboxylic acid, b.p. 99–100° (0.25 mm.), $n^{25}\mathrm{D}$ 1.4840–1.4855. An analytical fraction had b.p. 100° (0.25 mm.), m.p. 39.0–40.5° (from pentane), $n^{25}\mathrm{D}$ 1.4850.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.11; H, 9.10. Found: C, 70.35; H, 9.17.

Chromatography of this acid on a 230 × 28-mm. column of 28–200 mesh silica gel and elution with 2–5% ether in benzene established its homogeneity. Fractions taken at various points gave the same sharp-melting amide. The acid (0.119 g.) was warmed for 15 min. with 1 ml. of thionyl chloride. The excess thionyl chloride was distilled and the residue added dropwise to 5 ml. of cold concentrated ammonium hydroxide. The product was filtered, yielding 0.073 g. (61%) of the crude amide, m.p. 146.2–159.4°. Three recrystallizations from water (Norit) brought the melting point to 162.4–163.3°; mixed melting point with *exo-cis*-bicyclo[3.3.0]octane-2-carboxamide was 134.2–164.8°, showing that the amides were not identical.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.54; H, 9.87. Found: C, 70.63; H, 9.85.

Isomerization of *endo-cis*-Bicyclo[3.3.0]octane-2-carboxylic Acid (XIII).—*endo-cis*-Bicyclo[3.3.0]octane-2-carboxylic acid (0.20 g.) was heated under reflux overnight with a solution of 0.15 g. of potassium hydroxide in 5 ml. of 95% ethanol. Most of the ethanol was distilled under reduced pressure and the residue was acidified to congo red with 6 *N* sulfuric acid. This solution was extracted with three 10-ml. portions of ether, which were combined, dried over magnesium sulfate, and concentrated to give 0.165 g.

of an oil. This oil was treated with thionyl chloride and ammonium hydroxide as described above and gave 0.11 g. (67%) of a crude amide, m.p. 171.0–178.5°. Three recrystallizations from water brought the melting point to 177.8–178.9°, undepressed on admixture with the *exo*-amide. The infrared spectrum was also identical with the spectrum of the *exo*-amide.

Phenyl *exo-cis*-Bicyclo[3.3.0]oct-2-yl Ketone (V).—*exo-cis*-Bicyclo[3.3.0]octane-2-carboxylic acid (1.8 g.) was allowed to stand overnight with 3.5 g. of thionyl chloride. The excess thionyl chloride was removed under reduced pressure, and the residual crude acid chloride was dissolved in 10 ml. of dry benzene and used directly in the following preparation.

To an ethereal solution of phenylmagnesium bromide prepared from 0.485 g. of magnesium turnings and 3.3 g. of bromobenzene was added in small portions 2.37 g. of anhydrous cadmium chloride. When the addition was completed, the mixture was heated under reflux for 1 hr., at which time a negative Gilman test for phenylmagnesium bromide was obtained. The ether was then distilled and replaced by dry benzene; the benzene solution of the crude acid chloride described above was added dropwise with cooling in ice. After the addition was complete, the mixture was heated under reflux for 30 min. and then poured over 50 g. of ice and 10 ml. of 6 *N* sulfuric acid. The aqueous layer was separated and extracted with two 50-ml. portions of benzene, which were combined with the original benzene layer, washed with saturated sodium bicarbonate and saturated sodium chloride solution, dried over magnesium sulfate, and concentrated. Distillation of the residue through a semimicro column afforded 1.9 g. (75%) of liquid phenyl *exo-cis*-bicyclo[3.3.0]oct-2-yl ketone, b.p. 119–122° (0.55 mm.), $n^{25}\mathrm{D}$ 1.5515–1.5555. An analytical sample had b.p. 121° (0.55 mm.), $n^{25}\mathrm{D}$ 1.5530. The infrared spectrum of this ketone showed carbonyl absorption at 1675 cm.$^{-1}$, while the ultraviolet spectrum showed a maximum at 243 mμ ($\epsilon_{\max}$ 12,600, ethanol).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.06; H, 8.47. Found: C, 84.17; H, 8.35.

Phenyl *exo-cis*-bicyclo[3.3.0]oct-2-yl ketone 2,4-dinitrophenylhydrazone was prepared by treatment of 0.2 g. of the ketone with a hot ethanolic sulfuric acid solution of 2,4-dinitrophenylhydrazine. The crude product, 0.28 g. (76%), had a melting point of 108.0–114.8°. Three recrystallizations from ethanol afforded fine orange needles, m.p. 121.6–122.4°. The ultraviolet spectrum of this compound shows a maximum at 368 mμ ($\epsilon_{\max}$ 19,500, chloroform).

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.21. Found: C, 64.21; H, 5.75; N, 14.34.

Phenyl *endo-cis*-Bicyclo[3.3.0]oct-2-yl Ketone (IV).—Under the conditions used in the above reaction for preparation of the *exo* isomer, the acid chloride prepared from 0.98 g. of *endo-cis*-bicyclo[3.3.0]octane-2-carboxylic acid gave 0.98 g. (72%) of liquid phenyl *endo-cis*-bicyclo[3.3.0]oct-2-yl ketone, b.p. 114–117° (0.2 mm.), $n^{25}\mathrm{D}$ 1.5550–1.5580. An analytical sample had b.p. 116–117° (0.2 mm.), $n^{25}\mathrm{D}$ 1.5550. The ultraviolet spectrum of this ketone shows a maximum at 243 mμ ($\epsilon_{\max}$ 12,400, ethanol).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.06; H, 8.47. Found: C, 84.07; H, 8.20.

Phenyl *endo-cis*-bicyclo[3.3.0]oct-2-yl ketone 2,4-dinitrophenylhydrazone was prepared by the method described above; m.p. 150.2–152.9°. Three recrystallizations from ethanol afforded orange plates, m.p. 153.2–154.3°, undepressed by admixture with the 2,4-dinitrophenylhydrazone isolated from the product of reaction of methyl cycloöctene-1-carboxylate with phenylmagnesium bromide. Infrared spectra of the two samples (in potassium bromide pellets and chloroform solution) also were identical.

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.21. Found: C, 64.11; H, 5.72; N, 14.11.

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[CONTRIBUTION NO. 429 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

Syntheses by Free-radical Reactions. I. Oxidative Coupling Effected by Hydroxyl Radicals

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A new synthesis of difunctional compounds has been brought about by the dimerization of free radicals formed by the action of hydroxyl radicals on monofunctional compounds in aqueous systems at room temperature. The synthesis has been accomplished with lower straight- and branched-chain carboxylic acids, nitriles, amines, amides, alcohols and ketones. Isomeric products were obtained except when symmetrical reactants containing only equivalent hydrogen atoms were used.

The action of ferrous sulfate on hydrogen peroxide in acidic aqueous solution brings about the formation of hydroxyl radicals.[1]

$$\mathrm{HOOH} + \mathrm{Fe}^{++} \longrightarrow \mathrm{HO}\cdot + \mathrm{OH}^{-} + \mathrm{Fe}^{+++} \qquad \text{(A)}$$

The combination of hydrogen peroxide and a ferrous salt is frequently referred to as Fenton reagent because of his extensive studies[2] with this powerful oxidizing system. Hydroxyl radicals generated by this single electron transfer have been used in the initiation of vinyl polymerization,[3] in the oxidation of acids, alcohols, amines and other types of aliphatic organic compounds[4] and in the hydroxylation of aromatic compounds to obtain phenols.[5]

It has now been found that, under appropriate conditions of dilution and *p*H, a wide variety of aliphatic compounds undergo oxidative coupling by hydroxyl radicals at ordinary temperatures. In this process a hydroxyl radical attacks the aliphatic compound to remove a hydrogen atom bonded to carbon, and the free radicals thus formed dimerize.

$$\mathrm{RH} + \mathrm{HO}\cdot \longrightarrow \mathrm{R}\cdot + \mathrm{H_2O} \qquad \text{(B)}$$

$$2\mathrm{R}\cdot \longrightarrow \mathrm{R{-}R} \qquad \text{(C)}$$

The hydrogen atom removed does not require activation by a carbonyl group, carbon–carbon unsaturation, etc., and the hydrogen atoms of *t*-butyl alcohol, for example, react readily. This synthesis is a non-chain radical reaction, and a mole of hydroxyl radical must be generated for each mole of organic reactant consumed. The coupling is accomplished by simply adding equimolar quantities of hydrogen peroxide and ferrous sulfate to an aqueous solution of the organic reactant.

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