(1:1). It was freely soluble in 1 *M* sodium hydroxide and precipitated on neutralization with phosphoric acid.

The N-2,4-dinitrophenyl derivative of 2-(4′-aminobutyl)-pyrrole (IV) was prepared by boiling for 1 hour a solution of 53 mg. (0.38 mmole) of the amine in 10 ml. of benzene containing 1 ml. of triethylamine and 75 mg. (0.40 mmole) of 2,4-dinitrofluorobenzene. The solvents were evaporated and the residue was chromatographed on alumina (4 g., activity III), giving 75 mg. (0.25 mmole, 64% yield) of product, eluted with benzene, which was crystallized from acetone–hexane; m.p. 79–79.5°; ultraviolet absorption: λ_{max} 347 mμ (ϵ 17,200), 259 (7,900), 214 (19,200).

Anal. Calcd. for $C_{14}H_{16}O_4N_4$: C, 55.3; H, 5.3; N, 18.4. Found: C, 54.9; H, 5.5; N, 18.5.

2,2′-(1′-Ethoxycarbonylpyrrolidinyl)-pyrrole (V).—2,2′-(Pyrrolidinyl)-pyrrole (5 g., 36.7 mmoles) was dissolved in 100 ml. of 50% aqueous methanol, the solution was cooled to 5°, and 4 ml. (37 mmoles) of ethyl chloroformate was added rapidly with stirring, followed by the dropwise addition of 3.90 g. (37 mmoles) of sodium carbonate in 25 ml. of water over a 1-hour period. After the addition was complete, the reaction mixture was stirred at room temperature for an additional 3 hours. The mixture was then extracted with three 50 ml. portions of ether, each extract being washed with 10 ml. of *p*H 4 phosphate buffer. From the acid washes, 1.55 g. (31%) of starting material was recovered. The ether layer was dried over sodium carbonate and after solvent was removed, distillation of the residue at 103° (0.2 mm.) gave 4.0 g. (52.3% yield) of product.

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.4; H, 7.7; N, 13.5. Found: C, 63.1; H, 7.8; N, 13.3.

2,2′-(1′-Pyrrolinyl)-pyrrole (III) from 2-Pyrrolidinone and Pyrrole.—To 20 g. (0.3 mmole) of pyrrole, maintained at 0.5° in a nitrogen atmosphere, was added with stirring 9.0 g. (60 mmoles) of phosphorus oxychloride over a 30-minute period, followed by the addition of 6.0 g. (70 mmoles) of 2-pyrrolidinone over a 1-hour period. After the addition was complete, the reaction mixture was stirred an additional 30 minutes at room temperature. Then 25 ml. of chloroform was added, the solution was poured into an ice-cold solution of 40 g. (0.3 mole) of sodium acetate in 100 ml. of water, and 10*M* potassium hydroxide was added slowly while maintaining the temperature at 0° (by adding ice) until the *p*H reached 10. A white precipitate formed and dissolved into the chloroform. The chloroform layer was separated and washed twice with water and the aqueous layer was extracted three times with 50-ml. portions of chloroform, each chloroform portion being washed twice with water. The combined chloroform solutions were then extracted three times with 50-ml. portions of *p*H 4 phosphate solution, and the combined aqueous phase was basified to *p*H 10 and extracted with chloroform. Drying and evaporating of the chloroform left 7.2 g. (92.4% yield) of a white solid which was sublimed at 80° (0.2 mm.) and crystallized from ethanol, yielding 6.2 g. (80% yield) of pure 2,2′-(1′-pyrrolinyl)-pyrrole (III), m.p. 162–163°.

2,2′-Bipyrrole by Catalytic Dehydrogenation of 2,2′-(1′-Pyrrolinyl)-pyrrole (III).—A mixture of 2,2′-(1′-pyrrolinyl)-pyrrole (2.17 g., 16 mmoles), 10% palladium-on-charcoal (7.5 g., 16 mmoles of palladium), and di-*n*-hexyl ether (250 ml.) was heated at 200° with vigorous stirring for 2 hours, continuously sweeping with nitrogen. The hot mixture then was filtered, the filtrate was cooled to room temperature, 500 ml. of hexane was added, and the solution was stored at −80° for 12 hours. The precipitated bipyrrole was collected, washed with hexane, and sublimed (80° (0.2 mm.)) to give 0.8 g., 38% yield, of pure bipyrrole, m.p. 189–190°.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN, MADISON, WISC., AND OF STANFORD UNIVERSITY, STANFORD, CALIF.]

Stereochemical Control of the Angular Methylation of Fused Ring Ketones[1]

BY WILLIAM S. JOHNSON,[2] DUFF S. ALLEN, JR., RAYMOND R. HINDERSINN, GEORGE N. SAUSEN AND RAPHAEL PAPPO

RECEIVED NOVEMBER 10, 1961

Methylation of 2-benzylidene-1-decalone (II), with potassium *t*-butoxide and methyl iodide, gives a mixture of epimeric angularly methylated products: *cis*-(III) and *trans*-(IV) in a ratio of 3/1. Similar stereoselective behavior has been noted in a number of other cases, and the method is accordingly stereochemically unfavorable for the synthesis of *trans*-fused rings, *e.g.*, the C/D ring systems of the steroids. The present study reports attempts to find variables controlling this *cis/trans* ratio in favor of the *trans* isomer. The empirical approach, *i.e.*, altering conditions, etc., failed to uncover any such variable. Two hypotheses then were examined: that the geometry of the transition state approximates (1) that of the products and (2) that of the reactants. Experiments to test hypothesis 1 gave increases in some cases but no significant decrease in the *cis/trans* ratio. Thus this ratio was 3.5/1 for the methylation of the furfurylidene derivative of XIV; 9/1 for XXVII; at least 3/2 for the C_4-epimer of XXVII; and about 8/1 for the tetrahydropyranyl ether furfurylidene derivative of XXXVIII. Experiments designed to test hypothesis 2 led to successful results. On the premise that introduction of an olefinic bond at 6, 7 in the decalone system (Fig. 1) would remove one axial hydrogen at 7 interfering with the *trans* approach of the methyl group, the methylation of XLII was examined and found to give the *trans* product in at least 56% yield. Similarly, methylation of XLVII (R = H) afforded XLVII (R = CH_3) in 69% yield. The latter was in turn converted to a steroid XLIX, the total synthesis of which was thus stereoselective at every step. The principle has also been applied to a stereoselective total synthesis of estrone since methylation of LI (R = H) gave a preponderance of LI (R = CH_3). It was noted that with olefinic bonds in the 3,4- or 5,6-position of 1-decalone (Fig. 1), the effect of eliminating an axial hydrogen on the *trans*-approach side was overshadowed by angular distortion favoring *cis* approach. Thus methylation of LIV and of LVII gave *cis* products exclusively.

Certain previous total syntheses of steroids, namely estrone,[3] epiandrosterone,[4] 3β,11β-dihydroxyandrostane-17-one[5] and testosterone,[6,1a] have embodied a common sequence for the elaboration of ring D involving as key intermediates the corresponding 18-nor-D-homo compounds (*e.g.*, formula XLV). This angular methylation–ring contraction sequence is typified, in its simplest form, by the conversion of 1-decalone (I) into *trans*-8-methyl-1-hydrindanone (VI).[7] Thus the former substance was converted, by condensation with

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(1) (a) This represents paper XIII of the series entitled "Steroid Total Synthesis—Hydrochrysene Approach." For part XII, see W. S. Johnson, W. A. Vredenburgh and J. E. Pike, *J. Am. Chem. Soc.*, **82**, 3409 (1960). (b) For a preliminary report of part of this work, see W. S. Johnson and D. S. Allen, Jr., *ibid.*, **79**, 1261 (1957).

(2) To whom inquiries should be directed, Department of Chemistry, Stanford University, Stanford, Calif.

(3) W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, *J. Am. Chem. Soc.*, **74**, 2832 (1952).

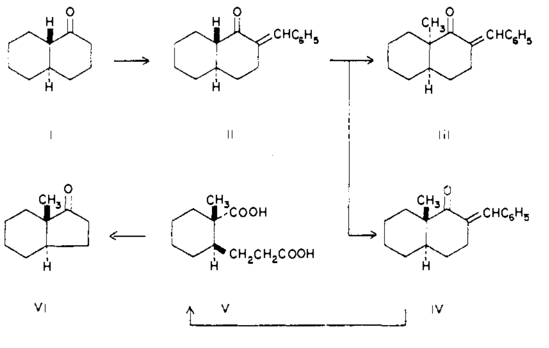
(4) W. S. Johnson, B. Bannister and R. Pappo, *ibid.*, **78**, 6331 (1956).

(5) W. S. Johnson, R. Pappo and W. F. Johns, *ibid.*, **78**, 6339 (1956).

(6) W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *ibid.*, **78**, 6354 (1956).

(7) W. S. Johnson, *ibid.*, **65**, 1317 (1943); **66**, 215 (1944).

benzaldehyde, to the benzylidene derivative II, which on treatment with potassium *t*-butoxide and methyl iodide afforded a mixture of the *cis*-(III) and *trans*-(IV) angularly methylated products. The *trans* isomer IV on oxidation to the dibasic acid V, followed by cyclization, was transformed into the *trans*-fused five-ring ketone VI, the C/D counterpart of a 17-keto steroid.



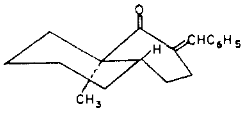
This angular methylation–ring contraction sequence has one serious drawback, namely that in a number of cases examined[8] the methylation step produces a preponderance of the undesired *cis* isomer. Thus in the methylation of II, the products III and IV were produced in a ratio of 3/1. The unfavorable consequence of this behavior is emphasized by the fact that in the synthesis of testosterone[6,1a] the methylation step was the only stage that was not stereoselective. The present paper contains a report of a study directed toward the determination of the factors influencing the stereochemical course of this reaction in the hope of discovering a method of controlling the isomer ratio so as to favor the formation of the *trans* epimer. Before realizing this hope we were obliged to give considerable attention to the problem of the geometry of the transition state in the SN2 reaction of a ketocarbanion. The results that are set forth below have thus afforded some conclusions of theoretical as well as practical interest.

In the early stages of our work the empirical approach was briefly explored. When the isopropoxymethylene instead of the benzylidene group was used to block the 2-position of 1-decalone, the methylation reaction appeared to favor the formation of the *trans* isomer.[9] Alkoxymethylene ketones, however, are sensitive to strong bases, and the yields in the methylation step were not good. In the hope of finding a related but more stable blocking group, we turned to the *p*-methoxy- and *p*-dimethylaminobenzylidene derivatives.[8] However, the *cis/trans* ratios were reduced only slightly to 2/1 in each case as compared with 3/1 in the parent series. When it was discovered[8] that with the *p*-nitrobenzylidene blocking group the *cis/trans* ratio was also 2/1, it was decided that this effect was not electronic. Other blocking groups examined were the furfurylidene (*cis/trans* ratio, 3/1), *p*-chlorobenzylidene (5/1) and the 2-α-naphthylmethylene (2/1). In six cases of steroid systems the *cis/trans* ratios varied from 2–11/1 when either the benzylidene or furfurylidene blocking group was employed.[8]

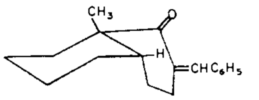
R. J. Highet[10] has made a preliminary search for other variables that might affect the *cis/trans* ratio. Altering the steric requirement of the methylating agent by use of methyl bromide and chloride instead of the iodide had no significant effect. When methyl *p*-toluenesulfonate was used, the product consisted mainly of O-methylated material. Attempts to conduct the methylation at higher or lower temperatures also gave unpromising results.

In view of our failure to discover any simple variations that would significantly influence the stereochemical course of the methylation reaction, attention was turned toward attempts to make modifications which would affect the relative stabilities of the transition states for the *cis*- and *trans*-methylation processes.

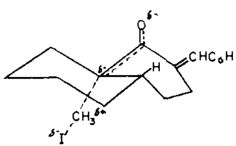
In considering the geometry of the two transition states we did not consider it possible, *a priori*, to estimate how much, if any, tetrahedral character would reside at the α-carbon atom of the keto carbanion portion of the array. Insofar as this carbon has tetrahedral character, the transition state resembles in geometry the products of the reaction, *i.e.*, formula VII for the *trans* and formula VIII (or its flipped version, see below) for the *cis* isomer. We chose first to consider the hypothesis that the transition states in the methylation reaction resemble the products rather than reactants, thus approaching the geometry represented by expression IX for the *trans* and X for the *cis* process. This hypothesis requires that the ratio of products formed would approach that determined by their relative thermodynamic stability. Consistent with this corollary is the demonstration that the *cis/trans* ratio of 9-methyldecalone-1 at equilibrium is in favor of the *cis* isomer (3/2) at 250°.[11]



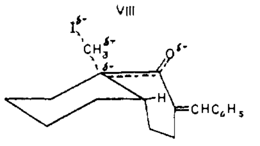
VII



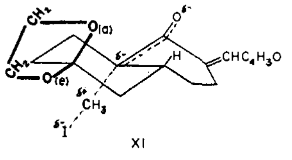
VIII



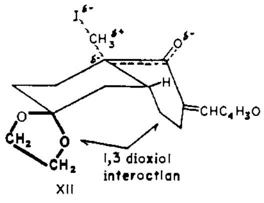
IX



X



XI



XII

Now in considering the two expressions IX and X, it becomes clear that introduction of an ethylene-

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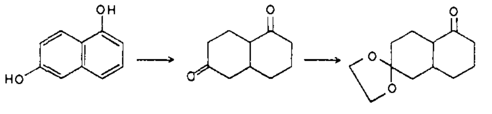
[8] W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood and E. T. Jones, *J. Am. Chem. Soc.*, **80**, 661 (1958).

[9] W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947).

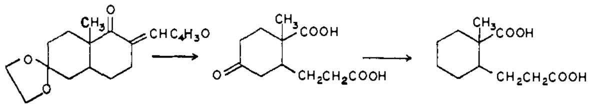
[10] R. J. Highet, Ph.D. Dissertation, University of Wisconsin, 1953.

[11] A. Ross, P. A. S. Smith and A. S. Dreiding, *J. Org. Chem.*, **20**, 905 (1955).

dioxy group at the 6-position (see XI and XII) would destabilize the latter with respect to the former due to the 1,3-diaxial interaction between one of the oxygen atoms and the C_4-methylene group. Hence if expressions IX and X were to represent true approximations of the geometry of the transition states of the *trans*- and *cis*-methylation processes, the effect of the introduction of the 6-ethylenedioxy group would be to decrease the *cis/trans* ratio.



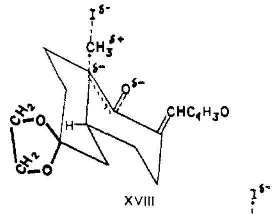
XIII XIV



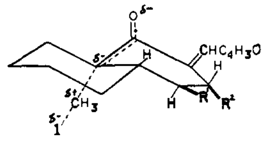
XV XVI XVII

To test this hypothesis 6-ethylenedioxy-1-decalone (XIV) was prepared by selective reaction of ethylene glycol with 1,6-decalindione (XIII) which in turn was produced from 1,6-dihydroxynaphthalene by hydrogenation to the diol, followed by oxidation with chromic acid. Condensation of the monoketal with furfuraldehyde afforded the furfurylidene derivative, m.p. 122.5–123.5°. Methylation with potassium *t*-butoxide and methyl iodide gave a mixture of isomers XV: A, m.p. 89.3–90°, λ_{max} 325.5 mμ, and B, m.p. 89.5–90.5°, λ_{max} 322 mμ, isolated in about 67 and 19% yields, respectively. The fact that isomer A not only was eluted first on chromatography but absorbed at higher wave length in the ultraviolet spectrum than isomer B suggested[8] that the former was the *cis* isomer. Proof of this assignment was provided by the following degradation. Ozonization of the methylated furfurylidene derivative, followed by acid hydrolysis gave the keto acid XVI which, without purification, was reduced to the diacid XVII. The A isomer thus afforded the known *cis*-diacid and the B isomer gave the known *trans*-diacid V.

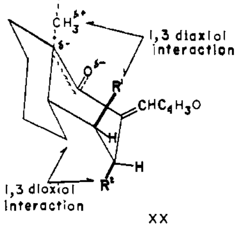
In view of the *cis/trans* ratio of 3.5/1 observed in the methylation of the furfurylidene derivative of XIV, it may be concluded that the expression XII does not represent a close approximation of the geometry of the transition state for the *cis* process. If the conformationally flipped version of XII, namely XVIII, is considered, it may be seen that there is no new 1,3-diaxial interaction due to the ketal group. Therefore, if expressions XI and XVIII were to approximate the transition states for the *trans* and *cis* processes, the effect of the ketal residue would be cancelling, and the ratio of methylation products should be (just as was observed) approximately the same as found in the parent compound. The expression XVIII is also attractive, *a priori*, because in this form the methyl group is becoming axially bonded to the keto ring, a process which seems to be stereoelectronically somewhat favored relative to the equatorial approach in the alkylation[12] as well as bromination[13] reaction.



XVIII

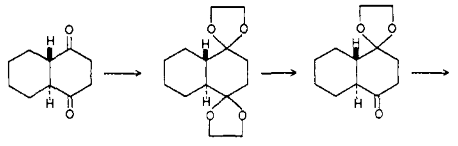


XIX

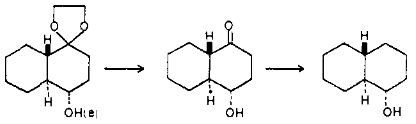


XX

If the transition states for the *trans* and *cis* processes are indeed approximated by the expressions XIX and XX, equatorial substituents R^1 and R^2 at the 3-and/or 4-positions in the *trans* form XIX would (if the chair-like conformation is preserved) become pseudo axial in the *cis* form XX leading to destabilization of the latter but not the former isomer relative to the parent compounds ($R^1 = R^2 = H$), resulting in a decrease in the *cis/trans* ratio of products. This hypothesis was tested as described below.



XXI XXII XXIII



XXIV XXV XXVI

We first chose to synthesize the hydroxydecalone XXV with an equatorial hydroxyl group at C_4, which, as the derivative XXVII, would provide the key substance for testing the validity of the expressions XIX and XX with $R^2 = H$, R^1 = tetrahydropyranyloxy. The previously known[14] crystalline 1,4-decalindione (XXI) was prepared by a new procedure consisting of catalytic hydrogenation of naphthoquinone over ruthenium oxide followed by chromic acid oxidation of the diol and alkali-catalyzed isomerization of the *cis*- to the *trans*-dione. Incidental to the study at hand, Flowers[15] has determined the dipole moments of *cis*- and *trans*-1,4-decalindione. The moments were 1.07 and 1.19 D., respectively, and were comparable to that (1.21 D.) of 1,4-cyclohexanedione.[16] According to the arguments of Le Fevre and Le

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(12) W. S. Johnson, *Chemistry & Industry*, 167 (1956).

(13) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953), *et seq.*

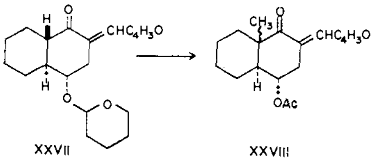
(14) K. Alder and G. Stein, *Ann.*, **501**, 247 (1933).

(15) D. Flowers, Ph.D. Dissertation, University of Wisconsin, 1960.

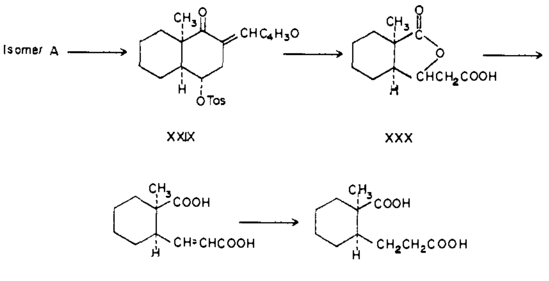
(16) C. G. Le Fevre and R. J. W. Le Fevre, *J. Chem. Soc.*, 1696 (1935).

Fevre, therefore, the dione ring of the bicyclic substances may be in the boat form about 10% of the time.

An attempt to effect selective reduction of the dione with sodium borohydride in pyridine[17] gave unpromising results. A more satisfactory approach to the hydroxy ketone involved conversion to the bis-ethylene ketal XXII, m.p. 76–77°, followed by acid-catalyzed ketal exchange equilibration with one mole-equivalent of the dione to give the monoketal, m.p. 61–62.5°.[18] Reduction with lithium and alcohol in ammonia or with lithium aluminum hydride afforded the equatorial hydroxy ketal XXIV, m.p. 100–101°, which on acid hydrolysis was converted into the hydroxy ketone XXV, m.p. 93.5–94°. Evidence for the configuration of the hydroxyl group was provided by Wolff–Kishner reduction[19] of the hydroxy ketone XXV which gave a decalol, m.p. 60–61.5°, which was identical with the known[20] isomer obtained by reduction of 1-decalone with lithium aluminum hydride. The stereochemical integrity of epimerizable hydroxyl groups seems to be preserved during such treatment.[21] Confirmation of the configuration of the 94° hydroxy ketone follows from a study of the epimeric alcohol (see below).



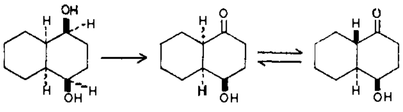
XXVII XXVIII



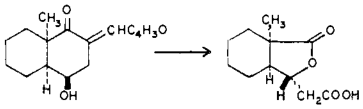
XXIX XXX

XXXI

The hydroxy ketone XXV was converted into the furfurylidene derivative, m.p. 124–125°, which in turn was transformed into the tetrahydropyranyl ether XXVII and submitted to the methylation treatment. Acid hydrolysis to cleave the tetrahydropyranyl ether, followed by acetylation gave a mixture of two methylated acetates XXVIII: A, m.p. 86–87.5°, $\lambda_{\max}$ 326.5 mμ, and B, m.p. 135–137.5°, $\lambda_{\max}$ 324.5 mμ, in a ratio of about 9/1. The configuration of isomer A was proved as follows. Saponification followed by reaction with *p*-toluenesulfonyl chloride in pyridine gave the *p*-toluenesulfonate XXIX, m.p. 133.5–134.5°, which, on ozonolysis, was converted into a γ-lactonic acid XXX, m.p. 165.5–166.5°. Treatment of the lactone with boiling aqueous sodium carbonate converted it into the unsaturated dibasic acid XXXI, m.p. 150.5–152.5°. The good yield (83%) and mild conditions employed[22] suggest that the β-elimination process was unaccompanied by α,β-β,γ-tautomerism and that the stereochemical integrity of the angular carbon carrying the hydrogen atom was preserved. Moreover, had there been equilibration at this stage the product would have been that with the carboxyl groups *trans* oriented whereas, in fact, it was proved to be the *cis* compound[23] by catalytic hydrogenation over palladium-on-carbon to give the known *cis*-β-(2-carboxy-2-methylcyclohexyl)-propionic acid. Hence the effect of the 4-equatorial substituent on the course of the methylation reaction in this series was to increase rather than to decrease the *cis*/*trans* ratio.



XXXII XXXIII XXXIV



XXXV XXXVI

At this point it seemed desirable to prepare the epimeric (at C_4) hydroxydecalone XXXIV and to ascertain its behavior on methylation in order to determine the effect of a 4-axial substituent on the *cis*/*trans* ratio. Naphthoquinone was hydrogenated over ruthenium oxide to give a product which was considered to be mainly the *cis*-1,4-decalindiol (XXXII). Selective oxidation with one equivalent of chromic acid gave a mixture from which a hydroxy ketone, m.p. 113.5–114.5°, was isolated. That this substance was the expected *cis* compound XXXIII followed from the fact that on treatment with base it underwent isomerization to a new ketone, the *trans* compound XXXIV, m.p. 64.5–66°. The product of this isomerization, however, was a mixture, and the 66° isomer was isolated only in poor (22%) yield. Although equilibration studies were not carried out, this experimental result suggests that the *cis* and *trans* forms XXXIII and XXXIV are of comparable stability, a condition which is consistent with the configurational assignments. In one (the more stable) of the two flipped conformations of XXXIII, the hydroxyl group is equatorial, while in the all-chair form of XXXIV this group must be axial. The effect of this hydroxyl group, there-

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(17) O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953).

(18) This method was first used independently by J. Szmuszkovicz and by G. N. Sausen for the preparation of the monoethylene ketal of 1,5-decalindione; see G. N. Sausen, Ph.D. Dissertation, University of Wisconsin, 1953. We wish to thank Dr. Szmuszkovicz for advising us of his unpublished results.

(19) By the procedure of Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(20) W. Hückel, *Ann.*, **441**, 27 (1925).

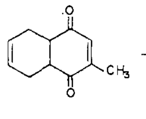
(21) *Cf.* the reduction of ethyl $3\alpha,12\alpha$-dihydroxy-7-ketocholanate; Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(22) *Cf.* R. P. Linstead, L. N. Owen and R. F. Webb, *J. Chem. Soc.*, 1211, 1218 (1953).

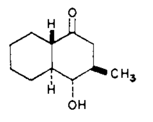
(23) The configuration about the olefinic bond is undoubtedly *trans* (ref. 22).

fore, is to destabilize the *trans* but not the *cis* form relative to the corresponding unsubstituted compounds, namely the 1-decalones where the *trans* is more stable than the *cis* isomer by about 1.5 kcal./mole.[24] The difference in enthalpy between XXXIV and XXXIII would therefore be expected to be less than 1 kcal./mole, and it would be reasonable to find that significant amounts of each were present at equilibrium.

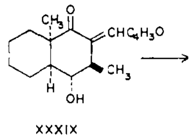
The *cis–trans* mixture of hydroxydecalones XXXIII and XXXIV was converted to the furfurylidene derivative, m.p. 164–165.5°, which was treated with dihydropyran to give the tetrahydropyranyl ether. Methylation with potassium *t*-butoxide and methyl iodide afforded, after acid hydrolysis, a mixture of hydroxy ketones which could not be readily separated. In order to obtain an estimation of the amount of *cis* isomer XXXV in this mixture, the methylated tetrahydropyranyl ether was ozonized directly and the ozonide cleaved with alkaline hydrogen peroxide. The product was then submitted to acid hydrolysis to cleave the tetrahydropyranyl ether, and a crystalline lactone carboxylic acid was isolated in 59% yield. This product proved to be identical with the *cis*-lactone carboxylic acid XXX obtained in the degradation of the A isomer of the epimeric series described above; hence the *cis/trans* ratio in the present case was at least 3/2. The mode of formation of the lactonic carboxylic acid in the experiments described above provides evidence for its complete configuration. In the series derived from XXV, the lactone evidently was formed from a dicarboxylic acid precursor *via* an intramolecular displacement of the *p*-toluenesulfonate group by the carboxyl group in juxtaposition for ring formation. Since this process (SN2) requires stereochemical inversion of the carbon holding the *p*-toluenesulfonate group, the product may be represented by formula XXXVI. The experiments described directly above in the 4-epi series confirm this configuration, since conditions for lactonization were deliberately chosen which would not effect inversion at the carbon in question.



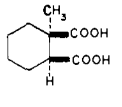
XXXVII



XXXVIII



XXXIX



XL

The effect of a substituent at $R^2(CH_3)$ as well as R^1 (tetrahydropyranyloxy) in the models XIX and XX was examined. The adduct XXXVII of butadiene and toluquinone was converted, by reduction with zinc in acetic acid followed by hydrogenation over palladium catalyst, into *cis*-2-methyldecalin-1,4-dione, m.p. 44–45°. Alkaline isomerization gave a new compound, m.p. 137–138.5°, which may be assumed to be the *trans*-dione with the methyl group equatorial. On treatment with ethylene glycol, the 138° dione was readily transformed into a monoketal, m.p. 85–86°. As shown below, the carbonyl group which failed to react was, as expected,[25] the one flanked by two equatorial alkyl groups. The monoketal was reduced with lithium and alcohol in ammonia and the resulting hydroxyl ketal, m.p. 126.5–127.5°, hydrolyzed to a hydroxy ketone, m.p. 134.8–135.5°. Its mode of formation assured a *trans* ring fusion with equatorial methyl and hydroxyl groups, *i.e.*, the configuration represented by formula XXXVIII. This substance was readily converted to a furfurylidene derivative, m.p. 112.2–113.1°, which confirmed the structure by demonstrating the presence of a methylene adjacent to the keto group. The furfurylidene derivative was then converted into the tetrahydropyranyl ether, which was submitted to the methylation treatment (see above). After acid hydrolysis, the mixture of methylated hydroxy ketones was separated by chromatography into two glassy fractions: A, yielding a crystalline acetate, m.p. 136.8–138°, and B (acetate non-crystalline) in a ratio of about 8/1. The fact that the ultraviolet absorption of the A isomer, λ_{max} 318.5 mμ, was at higher wave length than that, λ_{max} 301.7 mμ, of the B fraction suggested[8] that the former was the *cis* substance (acetate of XXXIX). Proof of configuration followed from oxidative degradation of the A-acetate to yield a diacid (XL) which was shown to be identical with the known *cis* isomer.[26]

The foregoing series of experiments, which were aimed at testing the hypothesis that the geometry of the transition states for the *trans* and *cis* processes approaches the expression XIX and XX, respectively, showed clearly that, at least when R^1 was tetrahydropyranyloxy and R^2 was either H or CH_3, the expression XX is not correct. It is, of course, possible that in these cases the *cis* process takes place *via* a transition state corresponding to the flipped version (like X) in which those substituents at positions 3 and 4 remain in the equatorial conformation. Rather than to introduce a further group, *e.g.*, the ketal residue at C_5, which would destabilize this form also, we chose to consider another working hypothesis.

We were next prompted to examine the postulate that the geometry of the transition state for the methylation process resembles that of the reactant, namely the ketocarbanion (see Fig. 1). In this sense the mechanism of the methylation process would be related more to that of the protonation of a carbanion,[27] and the hypothesis is consistent with the probability that these methylation reactions are highly exothermic processes.[28]

Examination of this model (Fig. 1) reveals that

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[24] *Cf.* W. Klyne, *Experientia*, **XII/3**, 119 (1956).

[25] D. H. R. Barton, *Tilden Lecture*, 1952; *J. Chem. Soc.*, 1027 (1953).

[26] A by-product, m.p. 106–107.5°, was isolated in the ozonization experiment. The compositional analysis and infrared spectrum, λ_{max} 5.68 μ, were consistent with the homologous lactone carboxylic acid structure (XXXVI with a CH_3 α to the carboxyl group).

[27] *Cf.* for example H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955); and E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).

[28] *Cf.* G. S. Hammond, *ibid.*, **77**, 334 (1955).

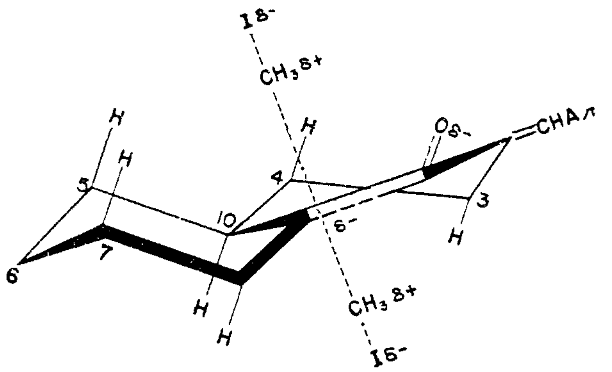
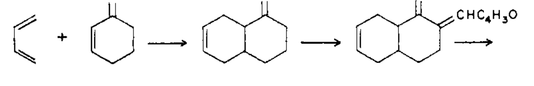


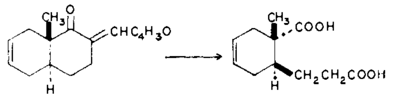
Fig. 1.

the effect of substitution at any available position will be either negligible or to increase, but never to decrease, the *cis/trans* ratio. In addition to the data presented above, which are consistent with this analysis, it may be mentioned that the *cis/trans* ratio obtained on methylation of 17-furfurylidene-18-nor-D-homo-8-isoestrone methyl ether is about 11/1.[8] This case would involve a transition state as shown in Fig. 1 but with a methylene group substituted for the axial hydrogen at C_5, thus introducing a destabilizing 1,3-diaxial interaction with the incoming methyl group in the *trans* process, which is accordingly made less favorable.

According to the expression in Fig. 1, the approaching methyl group in the *trans* process bears a 1,3-diaxial relationship with respect to the axial hydrogen atom at C_4, C_5 and C_7, while there are no such interactions involved in the *cis* process (approach from below in Fig. 1). According to the hypothesis under consideration, it would be expected that the elimination of one or more of these axial hydrogen atoms would decrease the activation energy of the *trans* relative to the *cis* process. Thus an olefinic linkage between carbons 6 and 7 not only would serve to eliminate one of these 1,3-interactions (involving the axial hydrogen atom at C_7), but would also relieve somewhat another of these interactions involving the axial hydrogen atom at C_5 which, by virtue of the olefinic linkage, is in the less severe pseudo axial conformation. A study of the methylation of the furfurylideneoctalone (XLII) was therefore undertaken.

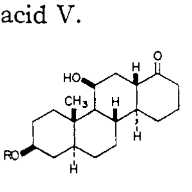


XLI XLII

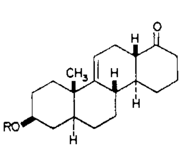


XLIII XLIV

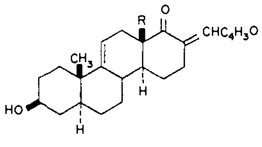
Δ^6-1-Octalone (XLI) was transformed, on condensation with furfuraldehyde, into the furfurylidene derivative XLII, m.p. 136–137.2°. Methylation with potassium *t*-butoxide and methyl iodide afforded a mixture from which the preponderant isomer, m.p. 75.7–76.5° (when pure), was easily separated in 56% yield by direct crystallization. That this was indeed the *trans* isomer XLIII was shown as follows. Oxidation with alkaline hydrogen peroxide[6] gave the unsaturated dicarboxylic acid XLIV which on hydrogenation over palladium was converted into the known *trans*-diacid V.



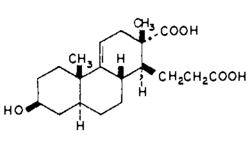
XLV



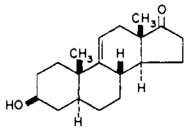
XLVI



XLVII



XLVIII



XLIX

Having realized for the first time a significant decrease in the *cis/trans* ratio so that the *trans* product was predominant, we turned our attention to the application of the principle to steroid synthesis. The totally synthetic dihydroxyketone XLV (R = H)[5] was converted, by treatment with succinic anhydride in pyridine, into the half succinate XLV (R = $COCH_2CH_2COOH$), m.p. 211.1–213.2°. The methyl ester XLV (R = $COCH_2CH_2COOCH_3$), m.p. 168.3–169.5°, on dehydration with phosphorus oxychloride in pyridine yielded the 9,11-dehydro compound XLVI (R = $COCH_2CH_2COOCH_3$), m.p. 126.5–127.5°, which on saponification was converted into the hydroxy ketone XLVI (R = H), m.p. 144.2–145.4°. The furfurylidene derivative XLVII (R = H), m.p. 190–191.5°, was prepared, converted to the tetrahydropyranyl ether and methylated as described above. Acid hydrolysis gave a mixture from which one product, m.p. 199.5–202° (after purification), was isolated in 69% yield. This material was shown to be the desired *trans* isomer XLVII (R = CH_3) by its conversion to a steroid as follows. Alkaline hydrogen peroxide oxidation effected conversion of XLVII (R = CH_3) into the diacid XLVIII, m.p. 242–244°. Cyclization of the dimethyl ester of XLVIII by the Dieckmann method followed by hydrolysis and decarboxylation gave *dl* - 3*β* - hydroxy - 9,11 - dehydroandrostane - 17-one (XLIX), m.p. 160.2–162.3°. The infrared spectrum of this compound in solution was identical with that of the naturally derived *d*-compound prepared from cortisone.[29] *The total synthesis of dl-XLIX was thus stereoselective at every stage.*

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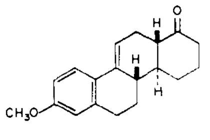
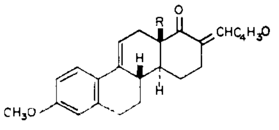
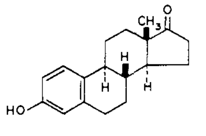
(29) A. D. Kemp, A. Kappas, I. I. Salamon, F. Herling and T. F. Gallagher, *J. Biol. Chem.*, **210**, 123 (1954).



L

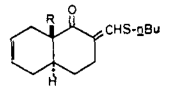


LI



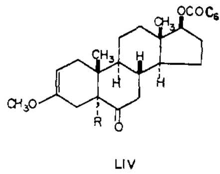
LII

The new principle has also been applied to the total synthesis of estrone (LII) and the details are reported elsewhere.[30] The 9,11-dehydro compound L was condensed with furfuraldehyde and the resulting furfurylidene derivative LI (R = H) methylated to produce a mixture which was predominantly (3/2 by n.m.r. spectroscopy) the *trans* isomer LI (R = CH_3), isolated in 56% yield. Alkaline hydrogen peroxide oxidation, followed by reduction of the resulting 9,11-dehydro diacid with sodium in liquid ammonia afforded *dl*-homomarrianolic acid which has been converted into estrone.



LIII

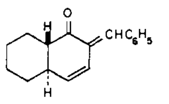
In a preliminary report, Ireland and Marshall[31] disclosed the use of the alkylthiomethylene blocking group for performing angular methylation. This elegant method has the advantage that the alkylthiomethylene like the alkoxymethylene derivative (see above) seems to have an intrinsic property which somewhat lowers the *cis/trans* ratio. Moreover, the former affords the enolate more readily than the latter derivative and gives good yields of methylation products. In the 1-decalone series the *cis/trans* ratio was lowered from 3/1 to 3/2. Using the principle set forth in the present work, Ireland and Marshall methylated the substance LIII (R = H) to give pure *trans* product LIII (R = CH_3) in 80% yield. Unfortunately this new method did not seem to give correspondingly promising results in the estrone series.[32]



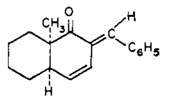
LIV

Recently Fried, Nutile and Arth[33] disclosed that the enol ether LIV (R = H) of 17β-benzoyloxyandrostane-3,6-dione, on methylation with sodium hydride and methyl iodide gave only one product of monomethylation, namely the *trans* product LIV (R = CH_3). We regard this as another example of the principle set forth in this paper, the direction of the methylation being determined by steric as well as possibly by stereoelectronic effects. It is of interest to note here that methylation of a 6-keto-3-ethylenedioxy steroid gave only the 5β-methyl compound, *i.e.*, the product of *cis*-methylation.[34] This corresponds to the case (Fig. 1) where the axial hydrogen at C_7, which interferes with the *trans* approach, is substituted by the larger oxygen atom.

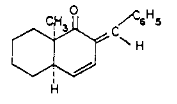
It was considered of interest to determine the effect on the *cis/trans* ratio of introducing an olefinic carbon between C_3 and C_4 of the 1-decalone system. In considering the *trans* process in Fig. 1, this structural change produces two opposing effects. It removes one of the destabilizing axial hydrogens (at C_4). On the other hand, it results in an angular deformation of the 10,5-bond, which brings the C_5-carbon into a pseudo equatorial conformation, forcing the attached axial hydrogen atom into a more severe interaction with the approaching methyl group.[35] Not knowing the relative magnitude of these effects, we felt incapable of predicting the results with any degree of certainty.



LV

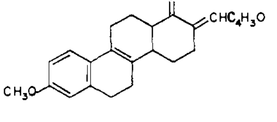


LVI

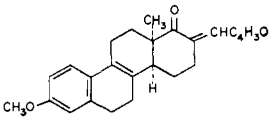


LVII

The introduction of a 3,4-olefinic bond into 2-benzylidene-1-decalone (I) was readily effected by bromination (at C_3) with N-bromosuccinimide followed by dehydrohalogenation with pyridine. The 3,4-dehydro compound LV thus obtained melted at 114–115°. Methylation as described above gave a single product, m.p. 77.5–78.5° (after purification), in 89% yield. This substance was different from either of the 3,4-dehydro compounds, m.p. 86.5–87.5° and 105.5–106.5°, respectively, prepared by a similar procedure from *cis*- and *trans*-9-methyl-2-benzylidene-1-decalone. The 78° isomer was shown to belong to the *cis* series by ozonolysis to produce the known *cis*-1-methylcyclohexane-1,2-dicarboxylic acid (XL). This same acid was, as expected, produced by degradation of the 87° substance; hence the 78° and 87° compounds must be geometrical isomers LVI and LVII although it is not known which of these configurations corresponds to which compound. In any case it is clear that the methylation step is highly stereoselective in favor of the *cis* product.



LVIII



LIX

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[30] J. E. Cole, Jr., W. S. Johnson, P. A. Robins and J. Walker, *Proc. Chem. Soc.*, 114 (1958); *J. Chem. Soc.*, 244 (1962).

[31] R. E. Ireland and J. A. Marshall, *J. Am. Chem. Soc.*, **81**, 6336 (1959).

[32] Collaborative study: R. E. Ireland, J. A. Marshall and J. E. Cole, Jr. See J. E. Cole, Jr., Ph.D. Dissertation, University of Wisconsin, 1960.

[33] J. H. Fried, A. N. Nutile and G. E. Arth, *J. Am. Chem. Soc.*, **82**, 5704 (1960).

[34] J. H. Fried, G. E. Arth and L. H. Sarett, *ibid.*, **82**, 1684 (1960).

[35] This effect was first noted by E. J. Corey and R. A. Sneen, *ibid.*, **77**, 2505 (1955), who calculated the atomic distances in *trans*-Δ^1-octalin.

In view of the foregoing results it was not surprising to find that the furfurylidene ketone LVIII—with an olefinic bond between positions 8 and 9, which corresponds to the 5,6-position in Fig. 1—gave, on methylation, a single product in 91% yield and that this was the *cis* isomer LIX.[30] Just as in the case of the 3,4-dehydro compound (see above), the stereochemical course of the reaction in the 5,6-dehydro system (Fig. 1) appears to be determined by a severe crowding exerted on the methyl group (*trans* position) by the axial hydrogen on that methylene (C_4 in Fig. 1 or C_{15} in the case of LVIII) which assumes a pseudo equatorial conformation because of the olefinic bond.

Acknowledgment.—We wish to express thanks to the following agencies for lending support to this study: The National Science Foundation, Standard Oil Company of Indiana, Sterling-Winthrop Research Institute, U. S. Public Health Service, and the Wisconsin Alumni Research Foundation.

Experimental[36]

1,6-Decalindione.[37]—Commercial 1,6-dihydroxynaphthalene (Allied Chemical and Dye Corp.), m.p. 135–136° (with previous softening), was purified by treatment with Norit and recrystallization from benzene–absolute ethanol. A solution of 20.0 g. of this product, m.p. 138–139° (with previous softening), in 100 ml. of absolute ethanol was heated under reflux for 0.5 hr. with one-quarter teaspoonful of W-1 Raney nickel catalyst. The mixture was filtered, 0.4 g. of ruthenium oxide (Baker and Co., Inc.) catalyst was added to the filtrate, and the hydrogenation carried out at 75° and an initial pressure of 2500 p.s.i. After 3 hr., reaction appeared to be complete, and approximately 5 mole-equivalents of hydrogen had been absorbed. The product was filtered, the filtrate evaporated and the crystalline residue triturated with 50 ml. of ether. The solid, which was separated by filtration and washed with cold ether–benzene, amounted to 15.2 g., m.p. 55–120°. This specimen of 1,6-decalindione gave practically the same yield of diketone as the diol, m.p. 90–130°, described below.

When the hydrogenation was carried out on a 175-g. scale, the temperature rose somewhat due to the exothermicity of the reaction, and the yield of decalindiol was lower: 96.5 g., m.p. 90-130°.

The oxidation of 1,6-decalindiol was effected by essentially the same procedure already described for the 1,5-isomer.[38] Thus 96.0 g. of crude decalindiol, m.p. 90–130°, suspended in 3.9 l. of benzene was treated at 5–9° with a mixture of 136 g. of sodium dichromate, 102 ml. of glacial acetic acid, 184 ml. of concentrated sulfuric acid and 600 ml. of water. After the prescribed workup,[38] the organic layer containing the crude product was concentrated by distillation to a volume of about 300 ml., then 200 ml. of absolute methanol and 1.5 g. of sodium methoxide were added, and this mixture was refluxed under nitrogen for 1.5 hr. Benzene and water were added, most of the methanol was removed by azeotropic distillation, then more water was added and the aqueous layer was saturated with salt and extracted with benzene. The combined benzene extracts were washed with saturated brine and dried over anhydrous sodium sulfate. The crystalline residue obtained on evaporation was recrystallized twice from cyclohexane to yield 57.4 g. (61%) of 1,6-decalindione, m.p. 85–90° (with previous softening), which was of satisfactory purity for conversion to the monoketal. Repeated recrystallization from cyclohexane gave colorless felted needles, m.p. 89.3–90.1.°

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.0; H, 8.7.

The di-semicarbazone was so insoluble that a satisfactory recrystallization solvent was not found. It was therefore prepared under "aseptic" conditions,[39] and the product was separated by filtration and washed thoroughly with warm methanol and warm water to give a microcrystalline powder, m.p. 256° dec., when the sample was placed on the micro hot-stage at 250°.

Anal. Calcd. for $C_{12}H_{20}O_2N_6$: C. 51.41; H. 7.19. Found: C, 51.2; H, 7.2.

6-Ethylenedioxy-1-decalone.—A solution of 1.005 g. of 1,6-decalindione (see above), 0.785 g. of ethylene glycol and 0.041 g. of *p*-toluenesulfonic acid monohydrate in 80 ml. of dry benzene was slowly distilled for 35 min. A total of 68 ml. of distillate was collected. The residue was washed with 5% sodium carbonate solution, followed by saturated brine, then dried over anhydrous sodium sulfate. Crystallization of the residue, obtained on evaporation of the solvent, from 5 ml. of cyclohexane gave 0.450 g. of crude starting diketone, m.p. 66–87° (87.3–89.6° after recrystallization). The filtrate was concentrated and the yellow oily residue chromatographed on 10 g. of F-20 Alcoa alumina. The fraction eluted with 20% benzene in 60–68° petroleum ether amounted to 0.101 g. of 1,6-bis-ethylenedioxydecalin, m.p. 65–66°. Repeated recrystallization from 33–38° petroleum ether gave colorless plates, m.p. 67.5–67.8°.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.8; H, 8.8.

Further elution with 50% benzene in 60–68° petroleum ether gave 0.161 g. of crude, partially crystalline monoketal which was converted directly to the furfurylidene derivative without further purification.

2-Furfurylidene-6-ethylenedioxy-1-decalone.—To a solution of 0.115 g. of the aforementioned crude 6-ethylenedioxy-1-decalone in 1.0 ml. of 95% ethanol were added 0.4 ml. of 15% aqueous sodium hydroxide solution, 0.055 g. of freshly distilled furfuraldehyde and 0.15 ml. of water. Seeds from a preliminary experiment were added and the mixture allowed to stand at room temperature for 3 hr. The precipitate which had formed was separated by filtration and washed with cold 60% ethanol followed by water. The yield was 0.103 g. (18% over-all conversion, neglecting recovered starting material), m.p. 119–122° (with previous softening). Repeated recrystallization from 60–68° petroleum ether gave pale yellow plates, m.p. 122.5–123.5° (with previous softening), $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 324 mμ (ε 22,200).

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.7; H, 7.1.

When the crude monoketal was converted directly to the furfurylidene derivative without chromatographic purification, some dark, insoluble resinous material was obtained along with the desired product. Repeated recrystallization gave a 13% over-all yield of material, m.p. 121.3–123.5° (with previous softening), suitable for the methylation step. An additional 7% yield of less pure product, m.p. 111–121°, was obtained.

Methylation of 2-Furfurylidene-6-ethylenedioxy-1-decalone.—A 3.50-g. sample of the furfurylidene derivative, m.p. 121.3–123.5°, was treated, in the cold (under nitrogen), as previously described,[4] with a solution of 2.35 g. of potassium in 59 ml. of *t*-butyl alcohol and 17 g. of methyl iodide. The reaction mixture was finally allowed to warm slowly to room temperature and stirred overnight. (Heating under reflux resulted in a dark product which was difficult to crystallize.) The solvent was evaporated at room temperature and reduced pressure, and the residual oil dissolved in benzene. Water was added, and the aqueous layer extracted thoroughly with benzene. The combined organic layers were washed with saturated brine and dried over anhydrous sodium sulfate. The yellow oily residue obtained on evaporation of the solvent at reduced pressure was fractionally crystallized from methanol with the aid of seeds of the pure *cis* and *trans* isomers obtained from a pilot experiment. After recrystallization the following crops were obtained: (1), 2.11 g. of *cis*, m.p. 84–88°; (2), 0.132 g. of *cis*, m.p. 85.5–87.5°; (3), 0.501 g. of *trans*, m.p. 89.3–90.1°; (4), 0.111 g. of *cis*, m.p. 83.5–87°. The filtrates from the fractional crystallizations were combined and the solvent evaporated to give 0.823 g. of brown oil. A 0.326-g. portion of this oil was chromatographed on 33 g. of F-20 Alcoa alumina. Elution with benzene gave 0.157 g. of an oil which, on fractional crystallization from methanol, gave 0.044 g. of *cis*, m.p. 83–87.5°, and 0.039 g. of *trans* isomer, m.p. 85–88° (with previous softening). Further elution of the column

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[36] All melting points are corrected for stem exposure.

[37] *Cf.* I. N. Nazarov and L. D. Bergel'son, *J. Gen. Chem.* (*USSR*), **22**, 515 (1952).

[38] W. S. Johnson, C. D. Gutsche and D. K. Banerjee, *J. Am. Chem. Soc.*, **73**, 315 (1951).

[39] E. P. Kohler and P. Allen, Jr., *ibid.*, **45**, 1987 (1923).

with 50% benzene in ether gave 0.072 g. of oil from which 0.036 g. of *trans* isomer, m.p. 87.2–88.4°, was obtained by crystallization.

Thus a total of 67% *cis* and 19% *trans* isomer was isolated.

Repeated recrystallizations of **2-furfurylidene-6-ethylenedioxy-9-methyl-*cis*-1-decalone** from 60–68° petroleum ether gave pale yellow prisms, m.p. 89.3–90° (with previous softening), $\lambda_{max}^{95\%\ EtOH}$ 325.5 mμ (ε 22,200).

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.8; H, 7.5.

Repeated recrystallization of 2-furfurylidene-6-ethylenedioxy-9-methyl-*trans*-1-decalone from 60–68° petroleum ether and from methanol gave colorless plates, m.p. 89.5–90.6°, $\lambda_{max}^{95\%\ EtOH}$ 322 mμ (ε 21,850).

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.4; H, 7.4.

Proof of Configuration. (a) **Of the *cis* Isomer.**—Ozone was passed through a cooled (−70°) solution of 0.953 g. of 2-furfurylidene-6-ethylene-dioxy-9-methyl-*cis*-1-decalone, m.p. 87.5–89.4°, in 50 ml. of ethyl acetate until ozone was detected in the exit gases. The mixture was concentrated to dryness at reduced pressure and room temperature, and 100 ml. of 5% sodium hydroxide solution and 5 ml. of 30% hydrogen peroxide were added to the oily residue. The solution was boiled under reflux for 45 min. during which period an additional 9 ml. of 30% hydrogen peroxide was added in portions. Refluxing was then continued for an additional 15 min. to destroy any excess peroxide, and the colorless solution was extracted with ether to remove neutral material (0.01 g.). The aqueous layer was acidified with hydrochloric acid, saturated with salt, and extracted exhaustively with ether. The residue, obtained on evaporation of the ether, was dissolved in 30 ml. of water and 3 ml. of concentrated hydrochloric acid, and heated on the steam-bath for 1 hr. to effect hydrolysis of the ketal residue. The solution was then saturated with salt and exhaustively extracted with ether. The combined ether extracts were washed once with a small volume of saturated brine and dried over anhydrous sodium sulfate.

The residue, obtained on evaporation of the ether, was reduced by the Wolff–Kishner method.[19] It was dissolved in 10 ml. of diethylene glycol, 1.1 g. of potassium hydroxide pellets in 2 ml. of water and 2.0 ml. of 85% hydrazine hydrate were added, and the mixture refluxed for 2 hr. The condenser was removed and the temperature was gradually raised to permit evaporation of the water and excess hydrazine; then the solution was heated at 195–200° for 4.5 hr. The solution was diluted with water, acidified with hydrochloric acid and extracted exhaustively with ether. The combined ether solutions were washed with saturated brine and dried over anhydrous sodium sulfate. The oily residue (0.569 g.), obtained on evaporation of the ether, crystallized on seeding with authentic *cis*-β-(2-carboxy-2-methylcyclohexyl)-propionic acid[7] and trituration with water to yield 0.412 g. (61%) of material, m.p. 92–103° (reported[40] 108–109°). Since this acid is difficult to purify by recrystallization, it was converted into the 8-methyl-1-hydrindanone by pyrolysis with lead carbonate.[3]

A mixture of 100 mg. of the crude diacid and 150 mg. of basic lead carbonate was pyrolyzed in a 9-mm. sublimation tube at 295–300°.[3] The colorless oily distillate, on treatment with 2,4-dinitrophenylhydrazine in 95% ethanol and hydrochloric acid, gave 0.116 g. of yellow needles of the 2,4-dinitrophenylhydrazone of 8-methyl-*cis*-1-hydrindanone, m.p. 140.5–141.8°, undepressed on admixture with authentic material,[7] m.p. 140.5–141°.

(b) **Of the *trans* Isomer.**—A 0.149-g. sample of 2-furfurylidene-6-ethylenedioxy-9-methyl-*trans*-1-decalone, m.p. 89.3–90.1°, was submitted to ozonolysis, hydrolysis and Wolff–Kishner reduction as described above for the *cis* isomer. The crude *trans*-β-(2-carboxy-2-methylcyclohexyl)-propionic acid amounted to 0.076 g., m.p. 167–174°. Recrystallizations from aqueous methanol and from ethyl acetate raised the melting point to 175.5–177.5° (with previous softening), undepressed on admixture with authentic material[7] (m.p. 175.5–177.5°).

1,4-Decalindione.—1,4-Naphthoquinone (Eastman Kodak Co., White Label grade) was dissolved in ether, treated with activated carbon, and crystallized from ether. A 10.0-g. sample of this material, m.p. 125–125.5°, in 150 ml. of 95% ethanol was hydrogenated over 0.2 g. of ruthenium oxide (Baker and Co., Inc.) at 60–80° and 2000 p.s.i. initial pressure. After 7 hr. the reaction was essentially over and 6 mole-equivalents of hydrogen had been absorbed. The mixture was filtered, and the filtrate concentrated, diluted with water, saturated with sodium chloride, and extracted thoroughly with ether. The combined ether layers were washed with 10% sodium hydroxide solution, water, saturated brine, and dried over anhydrous sodium sulfate. The oily residue, obtained upon evaporation of the solvent, was distilled at reduced pressure through a 3-in. Vigreux column to give 9.1 g. of yellow viscous oil, 1,4-decalindiol, b.p. 97–130° (0.6 mm). Determination of hydroxyl content[41] showed 92% of the amount calculated for the diol. The ultraviolet absorption, λ_{max}^{EtOH} 247 mμ (ε 350), indicated that the product contained about 1.6% of naphthoquinone.[42]

An 8.49-g. sample of 1,4-decalindiol in 100 ml. of benzene was oxidized with 11.9 g. of sodium dichromate dihydrate in 53 ml. of water, 16 ml. of concentrated sulfuric acid and 8.9 ml. of glacial acetic acid according to the procedure described for the 1,5-isomer.[38] The crude oily product, isolated as already described,[38] was crystallized from 60–68° petroleum ether. The yield of crude *cis*-1,4-decalindione was 5.5 g., m.p. 42–50° (reported[14] 49–50°). After two recrystallizations from petroleum ether and a third from ether, the m.p. was 42.5–48.5°. The dipole moment of this material, which may have been contaminated with some of the *trans* isomer, was determined by Flowers[16] and found to be 1.07 Debye units.

Isomerization of the crude *cis*-diketone to *trans*-1,4-decalindione was effected by vigorously stirring a solution of 32.8 g. of the former in 430 ml. of ether, with 140 ml. of 2% aqueous sodium hydroxide for 15 min. The aqueous layer was extracted with ether. The combined ether layers were washed well with water and dried over anhydrous sodium sulfate. After filtration, the solution was concentrated to a volume of about 400 ml. and allowed to stand at 0°. After 30 hr., 15.5 g. of the *trans*-diketone crystallized, m.p. 120.5–121.5° (reported[14] 122°). A further 6.3 g. of material of the same m.p. was obtained from the mother liquors, after recrystallization from ether. Pure *trans*-1,4-decalindione was obtained by recrystallization of the first crop material from ether, m.p. 121–121.6°, dipole moment[16] 1.19 Debye units.

***trans*-1,4-Bis-ethylenedioxydecalin.**[43]—A mixture of 5.0 g. of the aforementioned *trans*-diketone, m.p. 119–121°, 50 ml. of benzene, 0.1 g. of *p*-toluenesulfonic acid monohydrate and 10 ml. of ethylene glycol was refluxed in a system containing a water separator for 5.5 hr. A total of 1.5 ml. of water was collected. The mixture was cooled, 0.3 ml. of pyridine was added, followed by dilute sodium hydroxide solution and ether. After shaking, the organic layer was washed thoroughly with water, then with saturated brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 7.62 g. of crystalline residue, m.p. 61–75°. Crystallization from pentane gave 5.42 g. of colorless prisms, m.p. 76–78°. Recrystallization followed by sublimation at 60° (0.01 mm.) gave material melting at 76–77°.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.2; H, 8.6.

***trans*-4-Ethylenedioxy-1-decalone.**—This procedure was adapted from that of Szmuszkovicz and Sausen for the synthesis of 5-ethylenedioxy-1-decalone.[18] A solution of 6.20 g. of *trans*-1,4-bis-ethylenedioxydecalin, m.p. 72–78°, 4.05 g. of *trans*-1,4-decalindione, m.p. 119–121°, and 0.11 g. of *p*-toluenesulfonic acid monohydrate in 50 ml. of benzene was heated at reflux for 2 hr. After cooling, 0.3 ml. of pyridine was added and the mixture was then washed thoroughly with saturated sodium bicarbonate solution, followed by water and finally with saturated brine. The solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. A 2.0-g. portion of the reddish viscous oily residue was chromatographed on 50 g. of Alcoa alumina. The early fractions (no. 1–4) eluted with pentane consisted mainly of bis-ketal. Those (no. 5–11) eluted with up to 50% benzene in pentane consisted mainly of the desired mono-

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(40) V. C. E. Burnop and R. P. Linstead, *J. Chem. Soc.*, 720 (1940).

(41) S. Siggia, "Quantitative Organic Analysis Via Functional Groups," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 8.

(42) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, plate 254.

(43) *Cf.* E. J. Salmi, *Ber.*, **71**, 1803 (1938).

ketal. With the exception of no. 9, these fractions were combined and recrystallized from pentane to give 0.352 g., m.p. 55–60°. Fraction no. 9 (0.16 g.) was recrystallized twice to give 0.068 g. of colorless needles, m.p. 61–62.5°.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.8; H, 8.9.

Monoketal was isolated from the remainder of the crude oily product by fractional crystallization form petane. The first crop consisted of diketone. The second crop amounted to 1.68 g., m.p. 47–53°, and the third, after recrystallization, amounted to 0.84 g., m.p. 36–52°.

***trans*-4-Ethylenedioxy-1-*syn*[44]-decalol and *trans*-4-*syn*[44]-Hydroxy-1-decalone.** (a) **Reduction with Lithium and Alcohol in Ammonia.**[45]—To a stirred solution of 88 ml. of absolute ethanol in 1750 ml. of liquid ammonia was added about 5 g. of lithium wire (cut into small pieces) followed immediately by a solution of 1.59 g. of *trans*-4-ethylenedioxy-1-decalone, m.p. 57–62.5°, in 60 ml. of absolute ethanol. Additional lithium (to a total weight of 10.3 g.) was then added over a 13-min. period. After the blue color of the mixture had faded, the ammonia was evaporated with the aid of added ether at the later stages, ether and water were added, and the water layer was extracted with ether. The combined ether layers were washed thoroughly with saturated brine and dried over anhydrous sodium sulfate. The brown oily residue, obtained upon distillation of the solvent, crystallized on standing. Evaporative distillation at 100° (0.1 mm.) gave 1.55 g. of colorless prisms, m.p. 94–101°. Crystallization from pentane gave 1.39 g. of material, m.p. 99–100°. Recrystallization raised the m.p. to 100–101°.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.6; H, 9.25.

Acid hydrolysis of the hydroxy ketal according to the procedure described below gave, after recrystallization of the crude product from pentane, the hydroxy ketone in 85% yield, m.p. 94–96°, undepressed on admixture with the analytical sample (see below).

(b) **Reduction with Lithium Aluminum Hydride.**—A solution of 0.352 g. of *trans*-4-ethylenedioxy-1-decalone, m.p. 55–60°, in 3–5 ml. of ether was added slowly with stirring to a solution of 0.11 g. of lithium aluminum hydride in 15 ml. of ether. After stirring for 2 hr. at room temperature, the excess lithium aluminum hydride was decomposed with 0.1 ml. of ethyl acetate. The mixture was then cooled (ice-bath), 0.4 ml. of water was slowly added and the mixture stirred for 1 hr. The mixture was filtered, the filter cake was washed thoroughly with ether, and the filtrates and washings evaporated to give 0.355 g. of colorless solid, m.p. 88–97°. This was dissolved in 10 ml. of methanol, 5 ml. of water and 0.5 ml. of concentrated hydrochloric acid were added, and the mixture allowed to stand overnight at room temperature. Most of the methanol was evaporated, the aqueous residue was neutralized with 10% sodium hydroxide solution, and the solution was saturated with sodium chloride. The mixture, containing a colorless organic precipitate, was extracted with ether. The combined ether layers were dried over anhydrous sodium sulfate. The crystalline residue obtained on evaporation of the ether was recrystallized from ether–pentane to give 0.210 g. of the hydroxy ketone, m.p. 94–95°. A sample, twice recrystallized from pentane and sublimed at 70° (0.02 mm.), melted at 93.5–94°, $\lambda_{\max}^{\mathrm{KBr}}$ 3.02 μ (OH), 5.88 (C=O).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.1; H, 9.6.

Wolff–Kishner Reduction of *trans*-4-*syn*[44]-Hydroxy-1-decalone.[19]—A mixture of 0.243 g. of *trans*-4-*syn*-[44]-hydroxy-1-decalone, m.p. 94–96°, 2.5 ml. of 85% hydrazine hydrate-2.2 g. of potassium hydroxide and 16 ml. of ethylene glycol was heated at reflux under a nitrogen atmosphere for 70 min., then distilled until the internal temperature reached 200°. The distillate contained oily product which crystallized on cooling. The residue was heated for an additional 2.5 hr., 16 ml. of water was added and the mixture distilled to separate more of the decalol. This treatment was repeated thrice using 6 ml. of water each time. The crystalline product was separated from the combined distillates by centrifugation, and the mother liquor was extracted with benzene. The combined benzene layers were washed with dilute hydrochloric acid, water, saturated brine, and then dried over anhydrous sodium sulfate. The solvent was removed by distillation through a 6-in. Vigreux column, and the residual oil which crystallized on cooling amounted to 0.135 g., m.p. 59–60°. Recrystallization from pentane gave long flat colorless prisms, m.p. 60-61.5° (reported[20] 63°), undepressed on admixture with authentic material prepared by lithium aluminum hydride reduction of *trans*-1-decalone.

***trans*-2-Furfurylidene-4-*syn*[44]-hydroxy-1-decalone.**—A 0.200-g. specimen of crude *trans*-4-syn[44]-hydroxy-1-decalone was dissolved in 2 ml. of methanol, 2 ml. of water was added, followed by 0.12 ml. of furfural and 0.6 ml. of 10% sodium hydroxide. The oil which soon began to precipitate was easily induced to crystallize, and the mixture was allowed to stand at room temperature overnight. The yellow crystals, which were separated and washed with aqueous methanol, amounted to 0.217 g., m.p. 120-123.5°. A specimen twice recrystallized from aqueous methanol was obtained as pale yellow needles, m.p. 124–125°, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 325.0 mμ (ε 22,500).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.5; H, 7.5.

The acetate was prepared by the usual acetic anhydride–pyridine method. Recrystallization from methanol gave pale yellow elongated prisms, m.p. 133.5–135.5° with sintering at 126°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.7; H, 7.0.

Angular Methylation Experiments.—*trans*-2-Furfurylidene-4-*syn*[44]-hydroxy-1-decalone was converted to the tetrahydropyranyl ether as follows. A solution of 1.79 g. of the furfurylidene ketone, m.p. 121.5–126°, in 70 ml. of benzene was distilled, in order to remove traces of water, until 20 ml. of benzene was collected. The solution was cooled to room temperature, 3.7 ml. of anhydrous dihydropyran was added, followed by a solution of 0.047 g. of *p*-toluenesulfonic acid monohydrate in benzene which had been rendered anhydrous by concentration of the solution by distillation. After 2.5 hr. at room temperature, 0.2 ml. of pyridine was added, the mixture diluted with ether and washed with saturated sodium bicarbonate solution, water, and saturated brine. The organic solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield 2.40 g. of brown crystalline solid. Trituration with ether afforded 2.19 g. of colorless crystals, m.p. 135–149°, presumably a mixture of epimers.

A 2.15-g. specimen of the aforementioned tetrahydropyranyl ether was dissolved in 25 ml. of anhydrous *t*-butyl alcohol and 15 ml. of anhydrous benzene. Then 3.4 ml. of freshly distilled methyl iodide was added. This mixture was added under an atmosphere of nitrogen to a stirred and cooled (ice-water) solution of 1.30 g. of potassium in 28 ml. of anhydrous *t*-butyl alcohol. The mixture was stirred for 10 min., in the cold, followed by 3.5 hr. at room temperature. The mixture now containing suspended potassium iodide was concentrated under reduced pressure to a volume of about 20 ml., then 125 ml. of water was added and the product extracted with benzene and ether. The combined organic layers were washed with water, then with saturated brine and concentrated under reduced pressure. The residue was dissolved in 100 ml. of anhydrous methanol, 0.173 g. of *p*-toluenesulfonic acid monohydrate was added, then the resulting solution allowed to stand at room temperature overnight. Pyridine (0.6 ml.) was added, the solution concentrated to dryness under reduced pressure, water was added and the mixture was extracted with ether. The combined organic layers were washed with water, saturated brine, and then dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent under reduced pressure amounted to 1.82 g. of a red oil which could not be crystallized, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 325.5 mμ. This material was chromatographed on 105 g. of Florisil. After a small forerun eluted with benzene–pentane and pure benzene, a total of 1.56 g. of oily material corresponding to the angularly methylated substance was eluted with 1–10% ether in benzene. The early fractions (1.28 g. total) eluted with 1% ether in benzene proved to be (see below) mainly *cis*-2-furfurylidene-4-*syn*[44]-hydroxy-9-methyl-1-decalone, while the later fractions (0.15 g. total) corresponded to the *trans* isomer.

Acetylation of the *cis* isomer fraction described above by the acetic anhydride–pyridine method gave essentially one

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(44) The configuration of the hydroxyl group is denoted by relating it as *syn* or *anti* to the nearest bridgehead hydrogen atom.

(45) *Cf.* A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).

product (see below) which after crystallization successively from aqueous methanol, methanol and pentane was obtained as yellow prismatic crystals of **cis-2-furfurylidene-4-*syn*[44]-acetoxy-9-methyl-1-decalone**, m.p. 86–87.5°, $\lambda_{\max}^{95\%\ \text{EtOH}}$ 326.5 mμ (ε 22,000).

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.5; H, 7.3.

The acetate similarly obtained from the *trans* isomer fraction was repeatedly recrystallized from methanol to give pale yellow prisms of *trans*-2-furfurylidene-4-*syn*[44]-acetoxy-9-methyl-1-decalone, m.p. 135–137.5°, $\lambda_{\max}^{95\%\ \text{EtOH}}$ 324.5 mμ (ε 24,300).

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.4; H, 7.4.

From the acetylation reactions described above it was possible to isolate by a combination of crystallization and chromatography a total of 1.12 g. of the *cis* derivative melting in the range between 75 and 86°, and 0.095 g. of the *trans* derivative melting in the range between 124 and 134°.

The *p*-Toluenesulfonate of *cis*-2-Furfurylidene-4-*syn*[44]-hydroxy-9-methyl-1-decalone.—A solution of 0.87 g. of *cis*-2-furfurylidene-4-*syn*[44]-acetoxy-9-methyl-1-decalone, m.p. 68–85°, in 59 ml. of methanol and 9 ml. of 20% aqueous potassium carbonate was allowed to stand at room temperature for 2 days. The solution was neutralized with dilute hydrochloric acid, most of the methanol was evaporated at room temperature under reduced pressure, and the oily aqueous residue extracted with ether. The combined ether layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the ether was dried by adding benzene and distilling. The residue from this treatment was then treated with 12 ml. of dried pyridine and 1.24 g. of *p*-toluenesulfonyl chloride, and the solution allowed to stand at room temperature overnight. Excess dilute sodium bicarbonate solution was added, followed by water, and the mixture was extracted with ether. The combined ether layers were washed with dilute hydrochloric acid and water and then dried over anhydrous sodium sulfate. The dark semi-crystalline residue obtained on removal of the ether was triturated twice with small portions of methanol to yield 0.88 g. of tan crystals, m.p. 127.5–128.5° dec. Successive crystallizations from pentane, methanol and again from pentane yielded pale yellow needles m.p. 133.5–134.5° dec.; $\lambda_{\max}^{95\%\ \text{EtOH}}$ 225 mμ (ε 13,500), 327.5 (19,200).

Anal. Calcd. for $C_{23}H_{26}O_5S$: C, 66.64; H, 6.32. Found: C, 66.65; H, 6.2.

Lactone of *cis*-β-Hydroxy-β-(2-carboxy-2-methylcyclohexyl)-propionic Acid.—A solution of 0.504 g. of the aforementioned *p*-toluenesulfonate, m.p. 127.5–128.5°, in 300 ml. of ethyl acetate was treated with ozone at −70° until the solution became slightly blue in color, indicating an excess of ozone. During this treatment some of the starting material had crystallized; therefore the solution was allowed to warm until solution was complete, recooled to −70° and retreated with ozone as above. The dissolution and reozonization procedure was repeated once again to ensure complete reaction. The solution was concentrated to a volume of about 40–50 ml., and 1 ml. of 30% hydrogen peroxide solution, 10 ml. of water and 50 ml. of glacial acetic acid were added. The mixture was swirled to dissolve the precipitated oil, then allowed to stand at room temperature overnight. This mixture was then concentrated under reduced pressure to a volume of about 40 ml., water was added and the mixture extracted with ether. The combined ether layers were washed with water and dried over anhydrous sodium sulfate. A 0.105-g. sample of the oily crystalline residue (total 0.395 g.) obtained on evaporation of the solvent was recrystallized from benzene to give 0.050 g. of prisms, m.p. 158–164°. Further recrystallization from benzene followed by two more from water gave 0.033 g. of colorless prisms, m.p. 165.5–166.5°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.4; H, 7.7.

***cis*-β-(2-Carboxy-2-methylcyclohexyl)-acrylic Acid.**—A mixture of 0.148 g. of the crude lactone from the preceding experiment and 8 ml. of 1 *M* sodium carbonate solution was heated under reflux (nitrogen atmosphere) for 12 hr. The solution was acidified (to change congo red to blue) with concentrated hydrochloric acid. The crystalline precipitate was collected after chilling for 1.5 hr. and dissolved (with some difficulty) in ether. The filtered solution was evaporated, leaving 0.080 g. of brownish crystals, m.p. 145–148°. Repeated recrystallization from water gave colorless prisms, m.p. 150.5–152.5°, $\lambda_{\max}^{95\%\ \text{EtOH}}$ 211 mμ (ε 14,800).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.6; H, 7.7.

***cis*-β-(2-Carboxy-2-methylcyclohexyl)-propionic Acid.**—A solution of 0.021 g. of the aforementioned substituted acrylic acid, m.p. 153–159°, in 9 ml. of 95% ethanol was hydrogenated over 0.025 g. of 10% palladium-on-charcoal (American Platinum Works) at room temperature and atmospheric pressure. After 25 min., hydrogen uptake ceased. The mixture was filtered and the filtrate evaporated, leaving 0.021 g. of an oil which readily crystallized on trituration with water; m.p. 102–110°. Recrystallization from water gave colorless prisms, m.p. 109.5–111° (reported[40] 108–109°) undepressed on admixture with an authentic specimen obtained by the ozonization of *cis*-2-furfurylidene-9-methyl-1-decalone (m.p. 44–45).[46] The infrared spectra of the two specimens were identical.

***cis*-4-*anti*[44]-Hydroxy-1-decalone.**—*cis*-1,2-Decalindiol was prepared by hydrogenation of naphthoquinone according to the procedure described above for the hydrogenation of 1,6-dihydroxynaphthalene with the exception that the crude product was distilled under reduced pressure and the fraction, b.p. 145–160 (1 mm.), was dissolved in a mixture of benzene and ether and extracted with 10% aqueous sodium hydroxide. A solution of 4.3 g. of this crude diol in 60 ml. of benzene was oxidized with 2.51 g. of sodium dichromate in 11 ml. of water, 3.4 ml. of concentrated sulfuric acid and 1.87 ml. of glacial acetic acid according to the procedure already described for the 1,5-isomer.[38] The organic layer containing the crude reaction product was dried over anhydrous magnesium sulfate, and the solvent removed at reduced pressure. Trituration of the oily residue with ether gave 1.43 g. of tan crystals, m.p. 103–110°. Recrystallization from ether followed by sublimation at 100°(0.4 mm.) gave colorless needles, m.p. 113.5–115°; $\lambda_{\max}^{\text{KBr}}$ 2.97 μ (OH), 5.97 (C=O).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.4; H, 9.4.

***trans*-4-*anti*[44]-Hydroxy-1-decalone.**—A solution of 0.101 g. of the aforementioned *cis*-hydroxydecalone, m.p. 113.5–114°, in 3 ml. of methanol containing 0.14 ml. of 10% aqueous sodium hydroxide was heated under reflux for 30 min. on the steam-bath. Excess concentrated hydrochloric acid was added, and then the solution was neutralized with saturated aqueous sodium bicarbonate. The methanol was removed by distillation and the aqueous residue extracted with ether. The combined ether layers were washed with water and dried over anhydrous sodium sulfate. The oily residue obtained upon removal of the ether amounted to 0.095 g. and could not be crystallized. This oil was then retreated with 2 ml. of methanol and 2 ml. of 10% aqueous sodium hydroxide solution for 24 hr. at room temperature, and the product was isolated as described directly above. After standing for 2 days at 0°, the brown oil partially crystallized. Trituration with pentane containing a small amount of ether gave 0.022 g. of colorless crystals, m.p. 61–66°. Recrystallization from the same solvent system followed by sublimation at 60° (0.2 mm.) gave colorless prisms, m.p. 64.5–66°; $\lambda_{\max}^{\text{KBr}}$ 2.92 μ (OH), 5.97 (C=O).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.7; H, 9.3.

2-Furfurylidene-4-*anti*[44]-hydroxy-1-decalone.—A mixture of 0.74 g. of the aforementioned *cis*-4-*anti*[44]-hydroxy-1-decalone, m.p. 108–115°, 14.8 ml. of 50% aqueous methanol, 0.41 ml. of furfural and 2.2 ml. of 10% sodium hydroxide was allowed to stand at room temperature overnight. The yellow crystalline precipitate, which was collected and washed with aqueous methanol, amounted to 1.08 g., m.p. 153.5–160.5°. Recrystallization from methanol, then again from benzene, afforded 0.70 g. of yellow prisms, m.p. 165–166°. After sublimation at 150° (0.06 mm.), this material melted at 164–165.5°, $\lambda_{\max}^{95\%\ \text{EtOH}}$ 324.5 mμ (ε 19,950).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.7; H, 7.2.

Angular Methylation.—The tetrahydropyranyl ether of 0.81 g. of 2-furfurylidene-4-*anti*[44]-hydroxy-1-decalone, m.p. 165–166°, was prepared according to the procedure

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(46) *Cf.* reference 7.

described above for the epimeric alcohol using 22 ml. of benzene, 1.7 ml. of dihydropyran and 10 mg. of *p*-toluenesulfonic acid monohydrate. The crude product isolated as described above, after the addition of 0.1 ml. of pyridine, was dissolved in 20 ml. of benzene and 15 ml. of anhydrous *t*-butyl alcohol; then methylated with 1.7 ml. of methyl iodide and a solution of 0.70 g. of potassium in 15 ml. of anhydrous *t*-butyl alcohol. The reaction mixture was allowed to stir at room temperature overnight and the crude methylation product (0.156 g.) was isolated essentially as described above. Acid-catalyzed hydrolysis of the tetrahydropyranyl ether linkage as described above gave a hydroxy compound which could not be crystallized. Acetylation of this material afforded a hydroxy acetate which likewise could not be rendered crystalline.

A solution of 0.157 g. of the crude tetrahydropyranyl ether in 12 ml. of ethyl acetate was treated with ozone at −70° until the solution developed a pale blue color. The solvent was removed at room temperature under reduced pressure, 10 ml. of 2% aqueous sodium hydroxide and 0.4 ml. of 30% hydrogen peroxide were added to the oily residue, and the mixture stirred for 4.5 hr. at room temperature. Water was added and the mixture extracted with ether. The combined ether layers were washed with water and the combined aqueous layers, including the original alkaline solution, were acidified with concentrated hydrochloric acid and extracted with ether. (Extraction of the combined ether layers with saturated sodium bicarbonate revealed, after acidification, that there was only a small amount of acidic material present in the product. This acidic material was extracted with ether and recombined with the original ether solution.) The combined ether layers were washed with 3% aqueous ferrous sulfate solution, water, saturated brine, and then dried over anhydrous sodium sulfate. The colorless semi-crystalline residue obtained upon evaporation of the solvent amounted to 0.093 g. Trituration with 3 portions of ether left 0.047 g. of colorless crystals, m.p. 162–165°, undepressed on admixture with authentic lactone of *cis*-β-hydroxy-β-(2-carboxy-2-methylcyclohexyl)-propionic acid. The infrared spectra of the two specimens were identical. An additional 0.006 g. of lactone, m.p. 150–155.5°, was isolated from the mother liquors.

***cis*-2-Methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone.**—This procedure is a modification of that described by Chuang and Han.[47] To a mixture of 69.2 g. of toluquinone, m.p. 67.2–68.5°, and 70 ml. of benzene contained in a pressure bottle which was cooled in an ice-bath, was added 55 g. of liquid butadiene. The bottle was stoppered and allowed to come to room temperature with shaking. The resulting homogeneous solution was allowed to stand for 62 hr. at room temperature; then the solvent was removed by evaporation under a stream of air. Three recrystallizations of the residue from 60–80° petroleum ether gave 62.4 g. of pale yellow needles, m.p. 79–80.5° (reported[48] 80–81°).

***cis*-2-Methyl-Δ^6-octalin-1,4-dione.**[49]—Over a 25-min. period, 3.7 g. of zinc dust was added in portions to a vigorously stirred solution of 5.0 g. of the aforementioned tetrahydronaphthoquinone, m.p. 79–80.5°, in 50 ml. of 95% acetic acid while the temperature was maintained at 20–30° by means of an ice-bath. An additional 2.3 g. of zinc dust was then added and stirring continued for an additional 25 min. The mixture was filtered, concentrated under reduced pressure, and the solid residue was stirred with acetone and filtered again to remove insoluble inorganic material. The oily residue obtained upon evaporation of the solvent was crystallized from 60–80° petroleum ether to yield 3.8 g. (first crop) of slightly tan-colored plates, m.p. 84–85.3°, and 0.46 g. (second crop), m.p. 83.9–85°. The reported m.p. is 85–86°.[47]

***cis*-2-Methyldecalin-1,4-dione.**[49]—A solution of 9.0 g. of the aforementioned octalindione in 175 ml. of ether was hydrogenated at room temperature and atmospheric pressure over 0.5 g. of 10% palladium-on-carbon catalyst (American Platinum Works). After 24 min., 0.97 mole-equivalent of hydrogen was absorbed and uptake had ceased. The mixture was filtered and the solvent evaporated under reduced pressure to give 9.0 g. of almost colorless crystals, m.p. 41–45°. Recrystallization from ether at −70° and then again from 40–60° petroleum ether at 0° gave colorless prisms, m.p. 44–45°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.70; H, 8.95. Found: C, 73.6; H, 9.0.

***trans*-2-Methyldecalin-1,4-dione.**—A mixture of 50.3 g. of the crude *cis* isomer, described in the preceding experiment, 830 ml. of ether and 150 ml. of 0.5% aqueous sodium hydroxide solution was stirred vigorously for 6 hr. at room temperature; then the aqueous layer was extracted with ether. The combined ether layers were washed with water, dried over anhydrous magnesium sulfate, and concentrated until crystals began to separate. On cooling overnight there were obtained 25.0 g. (first crop) of fine colorless needles, m.p. 129–133°, and 8.8 g. (second crop), m.p. 111–126°.

A sample, m.p. 127–137°, obtained from a similar experiment was recrystallized twice from methanol, then sublimed at 150° (12 mm.) and crystallized once again from methanol to give colorless plates, m.p. 137–138.5°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.3; H, 8.8.

In another experiment the oily mother liquors were retreated, yielding additional *trans* isomer and bringing the total conversion to 88%.

***trans*-2-Methyl-4-ethylenedioxy-1-decalone.**—A solution of 0.5 g. of *p*-toluenesulfonic acid monohydrate in 450 ml. of benzene was dried by distillation of 100 ml. of the solvent. To this solution was added a mixture of 20.0 g. of the *trans*-decalindione, m.p. 129–133°, 200 ml. of dry benzene and 22.4 ml. of ethylene glycol. The mixture was refluxed (water separator) for 1.3 hr. druing which 1.9 ml. of water separated. The cooled solution was treated with 0.4 g. of solid sodium methoxide, then washed with saturated aqueous sodium bicarbonate followed by water. The dried (over anhydrous magnesium sulfate) solution was evaporated under reduced pressure to give 25.1 g. of semi-crystalline residue which was fractionally crystallized from 60–80° petroleum ether. The first crop amounted to 4.3 g. of starting material, m.p. 133–133.7°. Crops after recrystallization from aqueous ethanol amounted to 1.43 g. of colorless prisms, m.p. 82–83.2°, and 1.82 g., m.p. 80.3–82.4°.

A sample recrystallized successively from aqueous ethanol, aqueous methanol and finally 60–80° petroleum ether was obtained as colorless prisms, m.p. 85–86.1°.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.9; H, 9.1.

***trans*-2-Methyl-4-ethylenedioxy-1-decalol.**—To a vigorously stirred solution of 0.465 g. of the aforementioned monoketal, m.p. 79.2–83.4°, in 130 ml. of absolute ethanol and 1 l. of anhydrous ammonia was added in portions 7 g. of lithium wire over a period of 1 hr. After the blue color disappeared, the ammonia was evaporated, water was added, and the mixture extracted with ether. The combined ether layers were washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to give an oily product which after sublimation at 135° (0.2 mm.) amounted to 0.469 g. of colorless crystals, m.p. 107–119.5°. Crystallization from 90–100° petroleum ether gave 0.414 g. of colorless prisms, m.p. 123–124°. Two additional recrystallizations from the same solvent raised the m.p. to 126.5–127.5°.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.2; H, 9.7.

***trans*-3-Methyl-4-hydroxy-1-decalone.**—A solution of 0.330 g. of the aforementioned hydroxyketal, m.p. 123–124°, in 25 ml. of acetone containing 0.5 ml. of water and 4 drops of concentrated hydrochloric acid was heated under reflux for 1 hr. The mixture was evaporated under reduced pressure, water was added and the mixture extracted with benzene. The combined benzene layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 0.266 g. of colorless needles, m.p. 129.5–132°. Repeated recrystallization from benzene–petroleum ether (90–100°) gave colorless fluffy needles, m.p. 134.8–135.5°.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.7; H, 10.1.

***trans*-2-Furfurylidene-3-methyl-4-hydroxy-1-decalone.**—To a solution of 0.146 g. of the aforementioned hydroxy ketone, m.p. 131–132°, in 1.4 ml. of methanol, 0.09 ml. of furfuraldehyde and 1.0 ml. of water, was added 0.2 ml. of 25% aqueous sodium hydroxide solution. The mix-

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[47] C. K. Chuang and C. T. Han, *Ber.*, **68B**, 876 (1935).

[48] L. F. Fieser and F. C. Chang, *J. Am. Chem. Soc.*, **64**, 2043 (1942).

[49] *Cf.* the procedure of K. Alder and G. Stein, ref. 14.

ture was allowed to stand in an atmosphere of nitrogen overnight at room temperature. The oil which had separated was induced to crystallize by scratching. Trituration with 50% aqueous methanol gave 0.049 g. of pale yellow needles, m.p. 109.3–110°, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 323 mμ. The mother liquors afforded a second crop of 0.025 g., m.p. 109–110°, a third crop of 0.009 g., m.p. 109–110° and a fourth crop of 0.008 g., m.p. 107–109°. The first crop material, after one crystallization from methanol followed by two from benzene–petroleum ether (60–80°), gave colorless needles, m.p. 112.2–113.1°, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 323.0 mμ (ϵ 21,380).

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.0; H, 7.6.

In another experiment 4.00 g. of the monoketal, m.p. 80–82°, was reduced as described above, the crude product hydrolyzed, and this in turn was converted to the furfurylidene derivative without isolation of the intermediate products. The over-all yield of material, m.p. 107–109°, was 3.63 g.

Angular Methylation.—A 2.08-g. specimen of the aforementioned furfurylidene derivative, m.p. 107–109°, was converted to the tetrahydropyranyl ether by essentially the same procedure described above for the lower homolog. The following quantities were used: 50 ml. (after concentration) of benzene, 4.0 ml. of dihydropyran and 0.05 g. of *p*-toluenesulfonic acid in 10 ml. of benzene. The reaction was allowed to proceed for 2.5 hr. at room temperature. The crude oily product (3.36 g.) was dissolved in 15 ml. of dry benzene and 30 ml. of *t*-butyl alcohol, and methylated essentially by the procedure described above with a solution of 1.6 g. of potassium in 35 ml. of dry *t*-butyl alcohol and 4.2 ml. of methyl iodide. Reaction was complete after 2.5 hr. at room temperature. The crude product isolated as described above was dissolved in 100 ml. of methanol containing 0.10 g. of *p*-toluenesulfonic acid monohydrate, and allowed to stand at room temperature for 11 hr. in order to remove the tetrahydropyranyl ether group. The crude product isolated as described above amounted to 2.41 g. of red-brown oil. Chromatography on 110 g. of Florisil gave in the fractions eluted with 1% ether–benzene a total of 1.73 g. of non-crystalline *cis* isomer, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 317.5 mμ (e 20,900). Further elution with 1–2% ether in benzene gave a total of 0.230 g. of non-crystalline oily *trans* isomer, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 308 mμ.

The first eluates of the *cis* fraction, amounting to 1.01 g., were combined and dissolved in 20 ml. of dry pyridine containing 10 ml. of acetic anhydride. After 2 days at room temperature the solution was evaporated under a stream of nitrogen, benzene was added, and the solution washed with 2% aqueous hydrochloric acid followed by water, then dried over anhydrous sodium sulfate. The crude product obtained on evaporation of the solvent was triturated with ether to give 1.14 g. of brown crystalline solid, m.p. 127–134.5°. Crystallization from methanol afforded 0.71 g. (first crop) of almost colorless crystals, m.p. 135.5–137°, and 0.22 g. (second crop), m.p. 131.5–134.5°. Pure *cis*-**2-furfurylidene-3,9-dimethyl-4-acetoxy-1-decalone** was obtained by recrystallization of the first crop material from methanol, then again from ethyl acetate, in the form of colorless needles, m.p. 136.8–138°, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 318.5 mμ (ϵ 20,090).

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.3; H, 7.4.

The later eluates (0.114 g.) of the *trans* fraction from the chromatogram described above were combined and acetylated as described above. The product, after chromatography on 7.5 g. of Florisil, amounted to 0.093 g. of colorless oil, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 301.7 mμ (ϵ 8,128), which could not be induced to crystallize.

cis-α-**Methyl-**β**-acetoxy-**β**-(2-carboxy-2-methylcyclohexyl)-propionic Acid.**—A solution of 0.421 g. of the aforementioned *cis*-acetate, m.p. 135.5–137°, in 200 ml. of ethyl acetate was treated with ozone at −70° as described above. Acetic acid (25 ml.) was added, the solution concentrated under reduced pressure to a volume of about 50 ml., then 10 ml. of acetic acid, 5 ml. of 30% hydrogen peroxide and 5 ml. of water were added. After several days at room temperature the product was isolated essentially as described in preceding experiments, potassium bicarbonate being used to separate the acidic material which amounted to 0.323 g. of colorless solid, m.p. 163–167°. Crystallization from water afforded 0.241 g., m.p. 169–173°, neut. equiv. 149 (calcd. 143).

A sample from a similar experiment was recrystallized three times from water, then finally from benzene–ethyl acetate to give heavy, colorless prisms, m.p. 173–175°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.76 μ (ester C=O), 5.88 (COOH).

Anal. Calcd. for $C_{14}H_{22}O_5$: C, 58.73; H, 7.75. Found: C, 59.0; H, 7.8.

The mother liquors in a similar experiment yielded a small amount (13% yield) of the lactonic acid described below, m.p. 140–107°, undepressed on admixture with authentic material.

γ-**Lactone of** *cis*-α-**Methyl-**β**-hydroxy-**β**-(2-carboxy-2-methyl-cyclohexyl)propionic Acid.**—A solution of 0.118 g. of the aforementioned acetoxy diacid, m.p. 155–167°, in 10 ml. of 1 *N* aqueous sodium carbonate was heated under reflux (nitrogen atmosphere) for 36 hr. The solution was washed with ether, then made strongly acid with dilute hydrochloric acid, saturated with sodium chloride, and thoroughly extracted with ether. The combined ether layers were dried over anhydrous sodium sulfate and evaporated to give 0.100 g. of oily acid which exhibited strong end absorption in the ultraviolet spectrum and was therefore considered to consist mainly of *cis*-β-(2-carboxy-2-methylcyclohexyl)-acrylic acid. The material of this quality from another experiment was heated for 1 hr. at 80° (0.2 mm.). During this treatment the oil solidified to give, after crystallization from a small volume of benzene, fine colorless needles, m.p. 105–107°, in 92% yield based on the acetoxy diacid. Recrystallization from benzene and again from benzene–petroleum ether (60–80°) afforded fine colorless needles, m.p. 106–107.5°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.68 μ (γ-lactone), 5.86 (COOH).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.7; H, 8.0.

cis-**1-Methylcyclohexane-1,2-dicarboxylic Acid.**—A solution of 0.083 g. of the crude oily substituted acrylic acid described in the preceding section in 50 ml. of ethyl acetate was treated with ozone at −70° as described above. The solution was concentrated to a volume of 10 ml., an equal amount of acetic acid was added, followed by 5 ml. of 30% hydrogen peroxide and 2 ml. of water. After standing overnight at room temperature, 40 ml. of acetic acid was added, then the volume reduced to 5 ml. by evaporation under reduced pressure. The residue was dissolved in ether, washed with aqueous ferrous sulfate (acidified with concentrated hydrochloric acid before separation of the layers), saturated brine, and then dried over anhydrous magnesium sulfate. The pale brown oily residue obtained on evaporation of the solvent amounted to 0.068 g. Two crystallizations from benzene afforded 0.014 g. of prisms, m.p. 159.5–161°, undepressed on admixture with authentic material (see below).

Δ^6**-1-Octalone.**—A modification of the procedure of Nazarov and Bergel'son[50] was employed. A thick-walled Pyrex tube, which was cooled in a Dry Ice–trichloroethylene-bath, was charged with 48.1 g. of Δ^2-cyclohexenone, b.p. 66.9–67.2° (17 mm.), 13.5 g. of butadiene and 0.3 g. of hydroquinone. The tube was evacuated, filled with nitrogen, chilled and placed in a steel bomb. Pressure of 1500 p.s.i. of hydrogen was applied and the bomb heated at 205° for 45 hr. The reaction mixture was distilled through a 5-in. Vigreux column to give 7.75 g. of colorless oil, b.p. 77–84° (0.7 mm.).

trans-**2-Furfurylidene-**Δ^6**-1-octalone.**—To a solution of 4.61 g. of the aforementioned Δ^6-1-octalone in 35 ml. of 95% ethanol (nitrogen atmosphere) was added 13.5 ml. of a 15% solution of aqueous sodium hydroxide. After 20 min., 3.2 ml. of furfuraldehyde and 35 ml. of water were added and the mixture stirred for 3 hr. at room temperature with the exclusion of light. The crude crystalline product that separated amounted to 6.71 g. of bright yellow needles, m.p. 131–134°. Crystallization from methanol afforded 4.91 g. (first crop), m.p. 135.5–137.5°, and 0.87 g. (second crop), m.p. 136–137.5°. Sublimation of the second crop material at 100° (0.05 mm.) followed by crystallization from methanol gave pale yellow needles, m.p. 136–137.2°, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 327.0 mμ (ϵ 20,890).

Anal. Calcd. for $C_{15}H_{16}O$: C, 78.92; H, 7.06. Found: C, 78.6; H, 7.0.

Angular Methylation.—A solution of 2.28 g. of the aforementioned *trans*-2-furfurylidene-Δ^6-1-octalone, m.p. 135.5–137.5°, in 60 ml. of benzene was added to a solution of 4.0 g. of potassium in 125 ml. of anhydrous *t*-butyl alcohol.

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(50) I. N. Nazarov and L. D. Bergel'son, *Zhur. Obshchei Khim.*, **20**, 648 (1950).

The mixture was cooled to 2° and after the addition of 12.5 ml. of methyl iodide was stirred at room temperature for 12 hr. (exclusion of light). The crude product, which was isolated essentially as described above for other methylation experiments, was crystallized from methanol to give 1.02 g. (first crop) of pale yellow needles, m.p. 73–75°, and 0.33 g. (second crop), m.p. 72.5–75°. Sublimation at 100° (0.05 mm.) followed by three recrystallizations from methanol gave colorless plates of *trans*-2-furfurylidene-9-methyl-Δ^6-1-octalone, m.p. 75.7–76.5°, $\lambda_{max}^{95\%\ EtOH}$ 325.8 mμ (ε 21,180).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.2; H, 7.5.

Attempts to obtain further crystalline material by chromatography of the mother liquors failed.

***trans*-2-Carboxy-2-methyl-Δ^4-cyclohexenyl-β-propionic Acid.**[51]—A solution of 0.182 g. of *trans*-2-furfurylidene-9-methyl-Δ^6-1-octalone, m.p. 72–74°, in 40 ml. of methanol was added to a solution of 10 g. of sodium methoxide in 250 ml. of methanol contained in a Waring Blendor. Stirring was started and 40 ml. of 30% hydrogen peroxide was added, which resulted in a rise in temperature of the reaction mixture to 52–56°. After stirring for 5.7 hr., the peroxide had been consumed (starch-iodide test) and the ultraviolet absorption spectrum of an aliquot exhibited a maximum at 252 mμ with a slight shoulder at 333 mμ. The solution was concentrated, diluted with water and washed thoroughly with ether. The aqueous alkaline layer was acidified with concentrated hydrochloric acid, saturated with sodium chloride, and extracted thoroughly with ether. The combined ether layers were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give 0.197 g. of a dark brown oil which was chromatographed on 4.5 g. of silicic acid (Mallinckrodt 100 mesh). The fractions eluted with chloroform consisted mainly of furoic acid and those eluted with 1% methanol in chloroform consisted of an oily solid which on crystallization from benzene–petroleum ether (60–80°) gave 0.077 g. of colorless plates, m.p. 138–141°. Two recrystallizations from the same solvent pair raised the m.p. to 139.7–141.3°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.1; H, 7.6.

***trans*-2-Carboxy-2-methylcyclohexyl-β-propionic Acid.**—A solution of 0.029 g. of the aforementioned unsaturated dibasic acid, m.p. 138–141°, in 18 ml. of ethyl acetate was hydrogenated over 0.06 g. of 2% palladium-on-calcium carbonate catalyst[52] at room temperature and atmospheric pressure. After the cessation of hydrogen absorption the mixture was filtered and the filtrate evaporated under a stream of nitrogen to give 0.035 g. of a slightly oily solid. Trituration with a small amount of benzene afforded 0.023 g. of colorless prisms, m.p. 165–172°. Two recrystallizations from ethyl acetate gave material, m.p. 178.5–179.5°, undepressed on admixture with authentic material.[7]

***dl*-3β-(β-Carboxypropionyloxy)-11β-hydroxy-18-nor-D-homoandrostane-17a-one.**[53]—A solution of 2.04 g. of *dl*-3β,-11β-dihydroxy-18-nor-D-homoandrostane-17a-one,[5] m.p. 246–249°, and 3.34 g. of succinic anhydride, m.p. 119.5–120.5°, in 40 ml. of anhydrous pyridine was allowed to stand at room temperature for 5 days, then heated for 2 hr. at 90°. The solution was cooled, carefully acidified with 200 ml. of 10% aqueous hydrochloric acid and extracted thoroughly with chloroform. The combined chloroform layers were washed with water, dried over anhydrous sodium sulfate and evaporated under a stream of nitrogen to yield 2.76 g. of colorless crystalline needles, m.p. 199–202°. A sample crystallized from ethyl acetate–methanol and again from ethyl acetate alone was obtained as colorless needles, m.p. 211.1–213.2°.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.7; H, 8.4.

***dl*-3β-(β-Carbomethoxypropionyloxy)-11β-hydroxy-18-nor-D-homoandrostane-17a-one.**—A solution of 2.66 g. of the aforementioned half-succinate, m.p. 199–202°, in 200 ml. of methanol was treated with an excess of an ethereal solution of diazomethane. Evaporation of the solvent under a stream of nitrogen yielded 2.71 g. of colorless needles, m.p. 148–159°. Crystallization from benzene–petroleum ether (60–80°) gave 2.34 g. (first crop) of colorless needles, m.p. 157.5–161.2°, and 0.093 g. (second crop), m.p. 154–158.3°. Repeated recrystallization of the first crop material gave colorless needles, m.p. 168.3–169.5°.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.5; H, 8.6.

***dl*-3β-(β-Carbomethoxypropionyloxy)-9,11-dehydro-18-nor-D-homoandrostane-17a-one.**[54]—A solution of 1.10 g. of the aforementioned methyl ester, m.p. 157.5–161.2°, and 1.35 ml. of phosphorus oxychloride in 15 ml. of anhydrous pyridine was allowed to stand for 15 hr. at room temperature under an atmosphere of nitrogen. The reaction mixture was poured into 200 ml. of cold water and the solid product which precipitated was collected by filtration and washed thoroughly with water. The yield of crude product thus obtained was 1.00 g., m.p. 120–123°. Comparable material obtained from another experiment was recrystallized three times from benzene–petroleum ether (60–80°) to yield colorless needles, m.p. 126.5–127.5°.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.6; H, 8.5.

***dl*-3β-Hydroxy-9,11-dehydro-18-nor-D-homoandrostane-17a-one.**—A mixture of 1.00 g. of the aforementioned 9,11-dehydro ester, m.p. 120–123°, 15 ml. of a 10% solution of potassium hydroxide in methanol, 5 ml. of methanol and 1 ml. of water was heated at reflux (nitrogen atmosphere) for 2 hr. The cooled solution was diluted with water and extracted thoroughly with chloroform. The combined chloroform layers were washed with water, dried over anhydrous sodium sulfate and evaporated to give an oil which slowly crystallized. Recrystallization from 90–100° petroleum ether afforded 0.591 g. of colorless crystals, m.p. 139–145°. A comparable specimen from a similar experiment was sublimed at 130° (0.05 mm.) and recrystallized from 90–100° petroleum ether, then again from 60–80° petroleum ether–benzene to give colorless prisms, m.p. 144.2–145.4°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.2; H, 9.8.

***dl*-3β-Hydroxy-9,11-dehydro-17-furfurylidene-18-nor-D-homoandrostane-17a-one.**—To a solution of 0.586 g. of the crude 9,11-dehydroketone, m.p. 139–145°, prepared as described in the preceding experiments, in 20 ml. of methanol were added 4.0 ml. of a 30% solution of sodium hydroxide in water and 0.6 ml. of furfuraldehyde (nitrogen atmosphere). After 7 min. at room temperature, crystals began to separate. After 4 hr., 16 ml. of water was added and the mixture allowed to stand at room temperature in the dark for an additional 13 hr. The precipitate amounted to 0.683 g. of bright yellow plates, m.p. 181–185°. Three recrystallizations from ethyl acetate afforded pale yellow needles, m.p. 190–191.5°, $\lambda_{max}^{95\%\ EtOH}$ 328.0 mμ (ε 22,910).

Anal. Calcd. for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.8; H, 8.2.

Angular Methylation.—To a suspension of 0.530 g. of the aforementioned crude 9,11-dehydrofurfurylidene ketone, m.p. 181–185°, in 15 ml. of dry benzene containing 3.5 ml. of dihydropyran was added 0.01 g. of *p*-toluenesulfonic acid monohydrate. The mixture, which rapidly became homogeneous, was allowed to stand at room temperature for 1.5 hr., light and air being excluded. Two milliliters of a 1% solution of sodium methoxide in methanol was added and the resulting solution diluted with benzene, washed thoroughly with water followed by saturated brine, then dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 0.737 g. of pale yellow crystals, m.p. 144–155°. This crude tetrahydropyranyl ether was dissolved in 10 ml. of anhydrous benzene and added to a solution of 0.65 g. of potassium in 50 ml. of anhydrous *t*-butyl alcohol (nitrogen atmosphere). The resulting solution was cooled and treated with 2.4 ml. of methyl iodide as described above. After 11 hr. (exclusion of light) the solvent was removed by evaporation under reduced pressure, benzene was added and the mixture washed thoroughly with water followed by saturated brine. The combined aqueous layers were back-extracted with benzene and the combined benzene layers were dried over anhydrous sodium sulfate. The yellow oily residue obtained on evaporation of the solvent was dissolved in 70 ml. of methanol containing 0.025 g. of *p*-toluenesulfonic acid mono-

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(51) *Cf.* the procedure described in ref. 6.

(52) M. Busch and H. Stöve, *Ber.*, **49**, 1063 (1916).

(53) *Cf.* the procedure of R. Jeanloz, D. A. Prins and J. Fon Euw, *Helv. Chim. Acta*, **30**, 374 (1947).

(54) *Cf.* the procedure of S. Bernstein, R. H. Lenhard and J. A. Williams, *J. Org. Chem.*, **19**, 41 (1954).

hydrate and heated under reflux (nitrogen atmosphere) for 1 hr. in order to hydrolyze the tetrahydropyranyl ether. The solution was cooled, 1.6 ml. of 10% aqueous potassium bicarbonate was added, and the mixture concentrated under reduced pressure. The solid residue was dissolved in benzene and water, and the benzene layer was washed with water. The aqueous layers were back-extracted with benzene and the combined benzene extracts were dried over anhydrous sodium sulfate. The partially crystallized residue obtained upon evaporation of the solvent was triturated several times with ether to give 0.321 g. of *dl*-3β-hydroxy-9,11-dehydro-17-furfurylidene-D-homoandrostane-17a-one as pale yellow crystals, m.p. 119.5–202°, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 326.7 mμ (ϵ 20,890).

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.9; H, 8.3.

The non-crystalline residues from the above triturations were combined and chromatographed on 13 g. of Florisil (exclusion of light). Fractions eluted with 1–2% ether in benzene amounted to 0.082 g. of a yellow glass, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 326.0 mμ (ϵ 23,420), probably the 13-iso compound. Later fractions eluted with up to 20% ether in benzene on trituration with ether gave altogether 0.056 g. of additional *trans* isomer, m.p. 199–202°, making the total yield 69%.

***dl*-3β-Hydroxy-9,11-dehydroetioallohomobilianic Acid.**[55]—This procedure is a modification of that previously described.[6] To a solution of 0.198 g. of the aforementioned *trans*-methylated furfurylidene ketone, m.p. 199–201°, in 200 ml. of methanol was added with gentle stirring 10 g. of sodium methoxide and 40 ml. of a 30% solution of hydrogen peroxide. The mixture which now contained a thick white precipitate was heated under reflux for 3 hr. during which treatment the precipitate largely dissolved. An additional 30 ml. of 30% hydrogen peroxide was added and the mixture heated under reflux for 21 hr., then concentrated under reduced pressure to a volume of about 35 ml. Water (20 ml.) was added and the solution washed with ether. The aqueous layer was carefully acidified with 25 ml. of concentrated hydrochloric acid and thoroughly extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 0.198 g. of a brown glass.

Two additional oxidations using 0.219-g. and 0.216-g. samples of the *trans*-methylated furfurylidene ketone were performed exactly as described above and afforded yields of 0.230 g. and 0.231 g., respectively, of crude acidic material.

The crude products from all three oxidations were combined and triturated with acetone to give 0.149 g. of colorless crystals, m.p. 237–242°. Concentration of the mother liquors from the triturations gave an additional 0.083 g., m.p. 230–238.5°, and 0.43 g., m.p. 228–236.5°, of colorless crystals, making the total yield 47%. Two recrystallizations of the 237–242° material from ethyl acetate–methanol gave colorless prisms, m.p. 242–244°.

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.5; H, 8.65.

***dl*-3β-Hydroxy-9,11-dehydroandrostane-17-one.**—A solution of 0.250 g. of the aforementioned dibasic acid, m.p. 235–242°, in 10 ml. of methanol and 25 ml. of ether was treated with an excess of an ethereal solution of diazomethane. The crude product obtained on evaporation of the ether was chromatographed on 11 g. of Florisil. Elution with ether afforded 0.261 g. of a colorless oil which did not crystallize.

The Dieckmann cyclization was carried out by a modification of a previously described procedure.[4] A solution of 1.37 g. of potassium in *t*-butyl alcohol was treated as previously described[4] to effect complete removal of the *t*-butyl alcohol; then a solution of 0.251 g. of the oily dimethylbilianate in 110 ml. of benzene was added. The mixture was heated under reflux (nitrogen atmosphere) with stirring for 14 hr., then cooled and acidified with 5 ml. of glacial acetic acid. Water and benzene were added and the benzene layer washed with water followed by saturated brine, and finally dried over anhydrous sodium sulfate. The yellow oily residue obtained on evaporation of the solvent amounted to 0.244 g. which gave a deep violet color with ferric chloride solution.

Decarbomethoxylation was effected by heating a mixture of this oily keto ester, 10 ml. of acetic acid, 5 ml. of concentrated hydrochloric acid and 1 ml. of water for 1 hr. under reflux (nitrogen atmosphere). The brown oily residue obtained upon concentration of the mixture under reduced pressure was dissolved in 20 ml. of a 2.5% solution of sodium hydroxide in methanol and 2 ml. of water. The mixture was heated under reflux (nitrogen atmosphere) for 2 hr., most of the solvent was evaporated under reduced pressure, water and ether were added, and the aqueous layer was thoroughly extracted with ether. The combined ether layers were washed with water followed by saturated brine and dried over anhydrous magnesium sulfate. The yellow oily residue obtained on evaporation of the solvents under reduced pressure amounted to 0.233 g. and partially crystallized on standing. Chromatography on 6 g. of neutral alumina afforded in the fractions eluted with ether–benzene (concentrations from 10–100% ether) 0.149 g. of colorless glass which partially crystallized on trituration with 60–80° petroleum ether. Sublimation at 140° (0.01 mm.) gave 0.124 g. of colorless crystals, m.p. 152–160°. Two crystallizations from cyclohexane afforded colorless prisms, m.p. 160.2–162.3°.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 79.12; H, 9.79. Found: C, 79.0; H, 9.75.

The infrared spectrum of this specimen was identical with that of authentic naturally derived *dl*-3β-hydroxy-9,11-dehydroandrostane-17-one prepared according to a previously described method.[29]

***dl*-3α-(β-Carboxypropionyloxy)-11β-hydroxy-17-furfurylidene-18-nor-D-homoetiocholane-17a-one.**—Selective succinoylation of 1.55 g. of *dl*-3α,11β-dihydroxy-17-furfurylidene-18-nor-D-homoetiocholane-17a-one[56] was effected with 2 g. of succinic anhydride in 20 ml. of pyridine as described above. The crude product amounted to 1.88 g. of buff-colored needles, m.p. 186–196.5°. Crystallization from ethyl acetate afforded 1.21 g. (first crop), m.p. 195.3–198.5°, and 0.309 g. (second crop), m.p. 193–196.5°. The first crop material after two further recrystallizations from ethyl acetate was obtained as very pale buff-colored micro-needles, m.p. 198.1–199.3°, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 324.0 mμ (ϵ 21,880).

Anal. Calcd. for $C_{28}H_{56}O_7$: C, 69.40; H, 7.48. Found: C, 69.5; H, 7.5.

The methyl ester was obtained by the usual method with diazomethane. It crystallized from ethyl acetate in the form of colorless plates, m.p. 170–171.5°, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 324.5 mμ (ϵ 21,380).

Anal. Calcd. for $C_{29}H_{38}O_7$: C, 69.85; H, 7.68. Found: C, 69.6; H, 7.6.

***dl*-3α-(β-Carbomethoxypropionyloxy)-11-keto-17-furfurylidene-18-nor-D-homoetiocholane-17a-one.**—Sarett oxidation of 0.674 g. of the aforementioned ester, m.p. 170–171.5°, was effected by adding it to a suspension of 0.336 g. of dry chromium trioxide in 3.7 ml. of dry pyridine. The mixture was stirred at room temperature for 5 hr., filtered and diluted with water and ethyl acetate. The aqueous layer was thoroughly extracted with ethyl acetate, and the combined organic layers were washed thoroughly with water and then dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent amounted to 0.644 g. of tan needles, m.p. 200–207.5°. Crystallization from ethyl acetate afforded 0.434 g. (first crop) of pale yellow micro-needles, m.p. 208.5–211.5°, and 0.084 g. (second crop), m.p. 205.5–209.5°. The first crop material after two recrystallizations from ethyl acetate was obtained as very pale yellow micro-needles, m.p. 210.8–212.5°, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 325.0 mμ (ϵ 22, 910).

Anal. Calcd. for $C_{29}H_{36}O_7$: C, 70.14; H, 7.31. Found: C, 70.0; H, 7.3.

***trans*-2-Benzylidene-Δ^3-1-octalone.**—To a solution of 2.40 g. of *trans*-2-benzylidene-1-decalone,[7] m.p. 93.8–95°, in 25 ml. of dry carbon tetrachloride was added 1.78 g. of dry N-bromosuccinimide (nitrogen atmosphere). The mixture was heated to reflux with stirring and irradiated for 35 min. with a Hanovia ultraviolet lamp placed 8 in. from the flask. The mixture was cooled, filtered to remove succinimide, and concentrated under reduced pressure to give a pale yellow oil, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 279.7 mμ, which contained *trans*-2-benzylidene-3-bromo-1-decalone. Dehydrohalogenation of the oily bromo compound was effected by heating with 25 ml. of pyridine at reflux for 1 hr. (nitrogen atmosphere). Most of

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(55) *Cf.* W. A. Vredenburgh, Ph.D. Dissertation, University of Wisconsin, 1959.

(56) W. S. Johnson, J. C. Collins, Jr., R. Pappo and M. B. Rubin, *J. Am. Chem. Soc.*, **80**, 2585 (1958).

the solvent was evaporated at room temperature under reduced pressure, water and benzene were added, and the aqueous layer extracted with ether. The combined organic layers were washed with water, saturated brine and then dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent was freed of traces of pyridine by azeotropic distillation with toluene under reduced pressure. The crystalline residue was chromatographed on 100 g. of Florisil. The early fractions eluted with petroleum ether amounted to 1.08 g. of slightly oily crystalline solid, $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 316.2 mμ. Crystallization from 95% ethanol gave 0.505 g. (first crop) of colorless plates, m.p. 109–114°, and 0.029 g. (second crop), m.p. 109–113°. The first crop, after two recrystallizations from 60–80° petroleum ether and one from methanol, was obtained as colorless plates, m.p. 114–115°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 316.0 (ε 15,140), 227.3 (10,230).

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.5; H, 7.5.

From the later fractions of the above chromatogram a total of 0.623 g. of starting material was recovered. Crystallization from methanol gave pale yellow plates, m.p. 89–92°, undepressed on admixture with the benzylidene decalone.

Angular Methylation.—A solution of 0.201 g. of the aforementioned *trans*-2-benzylidene-Δ³-octalone, m.p. 113.5–114.5°, in 5 ml. of benzene containing 1.2 ml. of methyl iodide was treated as described above with a solution of 0.35 g. of potassium in 15 ml. of *t*-butyl alcohol. After 5 hr. at room temperature the product was isolated as described above. The pale yellow oily residue obtained on evaporation of the solvent at reduced pressure was crystallized from 40–60° petroleum ether, to give 0.168 g. of colorless rectangular prisms, m.p. 76–77°. The residue from the mother liquors was chromatographed on 1.3 g. of Florisil, and the early fractions eluted with petroleum ether yielded, after crystallization from 40–60° petroleum ether, 0.022 g. of additional material, m.p. 75–77°. The total yield of *cis*-2-benzylidene-9-methyl-Δ³-1-octalone (A isomer) was thus 0.190 g. or 89%. A sample of the 76–77.5° material after sublimation at 95° (0.2 mm.) and crystallization from methanol was obtained as colorless prisms, m.p. 77.5–78.5°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 319.0 mμ (ε 14,450), 229.5 (10,470).

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.4; H, 7.79.

The m.p. of the product obtained by the above procedure was depressed on admixture with the *cis*-2-benzylidene-9-methyl-Δ³-1-octalone, m.p. 82.5–83.5°, and the corresponding *trans* isomer, m.p. 101–102.5°, described below.

***cis*-2-Benzylidene-9-methyl-Δ³-1-octalone (B Isomer).**—A 5.0-g. sample of *cis*-2-benzylidene-9-methyl-1-decalone,[7] m.p. 103–104.8°, in 50 ml. of carbon tetrachloride containing 3.9 g. of N-bromosuccinimide was irradiated as described above for the lower homolog. The crude product was dehydrobrominated with pyridine and isolated as described above. Trituration with ether gave 2.7 g., m.p. 73–81°. Crystallization from methanol afforded 2.18 g., m.p. 81–84.5°.

Comparable material from another experiment was evaporatively distilled at 7.05 mm. (120°) and recrystallized from methanol to give colorless prisms, m.p. 86.5–87.5°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 315 mμ (ε 14,500), 228 (10,600).

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.6; H, 8.3.

***trans*-2-Benzylidene-9-methyl-Δ³-1-octalone.**—A 5.0-g. sample of *trans*-2-benzylidene-9-methyl-1-decalone,[7] m.p. 92–93.5°, was brominated and dehydrobrominated just as described in the preceding experiment for the *cis* isomer. The crude product amounted to 4.35 g., m.p. 91–99°. After sublimation as above and recrystallization from 95% ethanol, the pure material was obtained as thick colorless prisms, m.p. 105.5–106.5°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 317.5 mμ ε (16,500), 229.5 (11,400).

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.4; H, 7.9.

Ozonolysis of *cis*-2-Benzylidene-9-methyl-Δ³-1-octalone. (a) B Isomer.—A solution of 0.058 g. of this ketone (see above), m.p. 72–74°, in 10 ml. of ethyl acetate was treated with excess ozone at 0°; then 5 ml. of acetic acid and 2 ml. of 30% hydrogen peroxide were added. The mixture was allowed to stand overnight at room temperature and the product was isolated as described above for the oxidation of the substituted acrylic acid. Crystallization of the crude product from a small amount of benzene gave 0.005 g. of colorless prisms, m.p. 160–162°, undepressed on admixture with authentic *cis*-1-methylcyclohexane-1,2-dicarboxylic acid described immediately below.

(b) **A Isomer.**—A 1-g. specimen of this material was ozonized as described above. After crystallization of the crude product from benzene there was obtained 0.2 g. of *cis*-1-methylcyclohexane-1,2-dicarboxylic acid, m.p. 163–165°. The reported melting points are 160,[57] and 165°.[58] The anhydride was produced by heating the diacid at 180° for 10 min. Recrystallization from 65–68° petroleum ether afforded material, m.p. 64–65° (reported[57] 60–65°).

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[57] R. P. Linstead and A. F. Millidge, *J. Chem. Soc.*, 478 (1936).

[58] F. Vocke, *Ann.*, **497**, 247 (1932).

[CONTRIBUTION FROM THE ORGANISCH-CHEMISCHES INSTITUT DER UNIVERSITÄT MAINZ, GER., AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MASSACHUSETTS, AMHERST, MASS.]

Oxidation of N-Aminodihydroisoindoles. Synthesis of *cis*- and *trans*-1,2-Diphenylbenzocyclobutenes[1-3]

BY LOUIS A. CARPINO

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Oxidation of N-aminodihydroisoindole (II) by means of mercuric oxide in methylene dichloride or alkaline degradation of the corresponding *p*-toluenesulfonhydrazide (III) gave the dimer of *o*-quinodimethane, isolated as the corresponding dibromide. The related *cis*- and *trans*-1,3-diphenyl-2-aminodihydroisoindoles have been prepared from 1,3-diphenyl-1-hydroxyisoindole (XIII) by zinc–acetic acid and lithium aluminum hydride–aluminum chloride reduction, respectively. Conversion of each amine to the corresponding hydrazine through the nitroso compounds proceeded normally. Mercuric oxide oxidation of the *trans* isomer VIIb yielded the previously reported *trans*-1,2-diphenylbenzocyclobutene (XVII). Mercuric oxide oxidation of the *cis*-hydrazine VIIa was unsatisfactory, although the use of activated manganese dioxide led to isolation of the previously unknown *cis*-1,2-diphenylbenzocyclobutene (XVI) in 27% yield. N.m.r. spectral data as well as oxidation, reduction and isomerization studies support the assigned structure. A convenient synthetic route to alkyl *o*-cyanobenzoates by the one-step dehydration–esterification of phthalamic acid is reported utilizing an alkane- or arenesulfonyl chloride in the presence of pyridine and an alcohol.

Continuing a study of the oxidation of 1,1-disubstituted hydrazines, the oxidation and sulfonhydrazide degradation of N-aminodihydroisoindole and its 1,3-diphenyl derivatives is reported. It had been reported earlier[4] that the *p*-toluene-

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[3] For the previous paper in this series see L. A. Carpino, A. A. Santilli and R. W. Murray, *J. Am. Chem. Soc.*, **82**, 2728 (1960).

[4] L. A. Carpino, *ibid.*, **79**, 4427 (1957).