water, dilute sodium hydroxide, dried, and concentrated *in vacuo*. The residue was treated with a mixture of 25 ml. of benzene and 50 ml. of hexane, and undissolved starting material was removed by filtration. The solution was then adsorbed on a column of 50 g. of activated alumina (Woelm, neutral, grade I) and the product eluted with benzene.[33] The combined benzene eluates were concentrated *in vacuo* and the residue crystallized.

Method U.—A 50% suspension of sodium hydride in heavy mineral oil, (0.13 mole) was added portionwise to a stirred solution of 1,3-dihydro-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one (0.12 mole) in 60 ml. of dimethylformamide. The mixture was stirred for 15 min. in the cold, then 0.142 mole of methyl iodide was added and the solution stirred for 20 min. more. The solvent was removed under reduced pressure to yield an oil which was partitioned between water and methylene chloride. The organic layer was washed, dried, and filtered. Removal of the solvent gave an oil which was taken up in ether and filtered through alumina (Woelm, Grade I). The colrrless filtrate was concentrated and the residue crystallized.

Acknowledgment.—We are indebted to Dr. L. O. Randall and his co-workers for the pharmacological information, to Dr. A. Motchane, and Mr. S. Traiman for the infrared spectra, to Dr. Al Steyermark and his staff for microanalyses, and to Mrs. B. Sluboski for the compilation of the tables. Mr. L. A. Dolan was helpful in preparation of larger amounts of starting materials and intermediates.

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[33] Further elution with benzene containing 5% ethanol gave unreacted starting material.

Borohydride Reductions of 8-Oxodecahydronaphthoic Acids and Esters[1]

D. M. S. WHEELER[2] AND MARGARET M. WHEELER[2]

Department of Chemistry, University of Nebraska, Lincoln 8, Nebraska, and
Department of Chemistry, University of South Carolina, Columbia 1, South Carolina

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The action of sodium borohydride on *cis*- and *trans*-8-oxodecahydronaphthoic acids and their methyl esters has been studied. The results suggest that a carboxylate ion can inhibit the attack of borohydride ion.

As part of a study of the stereochemistry of the lactone ring of marrubiin,[3] we wished to reduce the keto acid (Ia) stereospecifically to the alcohols (IIa) and (III) and then to observe the relative ease with which these hydroxy acids lactionized. The keto acid (Ia) has now been synthesized and reduced to the alcohol (IIa) but not to III. The work has been extended to include a study of the reactions of the keto acid (VIIIa) and the keto esters (Ib) and (VIIIb) with sodium borohydride.

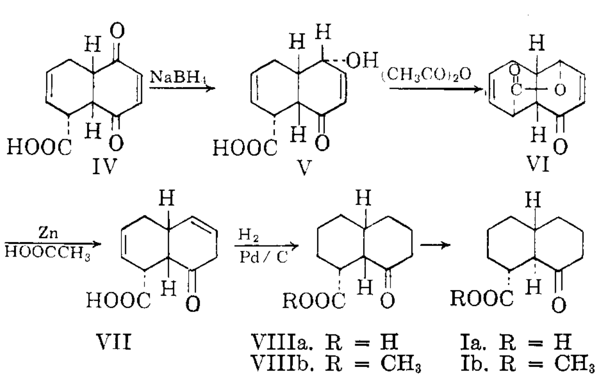

CHART I

The keto acid (VIIIa) was synthesized from the Diels-Alder adduct (IV, from pentadienoic acid and *p*-benzoquinone) by the route shown in Chart I. The stages IV–VII had previously been reported by Woodward and co-workers.[4] Some minor clarifications of their work are mentioned in the Experimental. In the presence of palladium VII took up two moles of hydrogen and yielded VIIIa. The stereochemistry of VIIIa follows from the stereochemistry of VI.[4] The possibility that the ring fusion had become *trans* during the conversion of VI to VIIIa was obviated when it was found that VIIIa, when heated with base, was isomerized to a new compound which was, therefore, assigned the structure Ia. Both Ia and VIIIa were converted to the corresponding methyl esters (Ib) and (VIIIb) by treatment with diazomethane. The infrared spectra and analyses of Ia, Ib, VIIIa, and VIIIb were all consistent with the assigned structures.

Reduction Studies.—The reduction of Ia was attempted under three sets of conditions, (a) sodium and propanol (b) lithium, methanol and liquid ammonia, and (c) sodium borohydride in bicarbonate solution at 0°. In all reactions only one product was isolated—a hydroxy acid—which, because it was formed under conditions (a) in 50% yield and under conditions (b) in 90% yield, was assigned the structure IIa,[5,6] in which the hydroxyl group is equatorial. As expected, the hydroxy acid (IIa) lactonized readily to yield IX.

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[1] For a preliminary account see D. M. S. Wheeler and M. Wheeler, *Chem. Ind.* (London), 463 (1961).

[2] Present address: Department of Chemistry, University of Nebraska, Lincoln 8, Nebraska.

[3] W. H. Castine, D. M. S. Wheeler, and M. Wheeler, *Chem. Ind.* (London), 1832 (1961).

[4] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

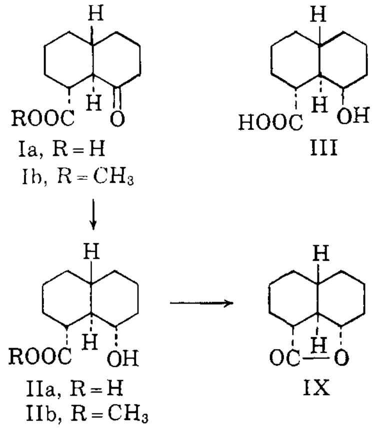

CHART II

The reduction of the methyl ester (Ib) by borohydride in methanol solution at 0° gave in 90% yield a hydroxy ester, which was assigned the structure IIb because it was also obtained by treating IIa with diazomethane.

When the keto acid (VIIIa) was treated with sodium borohydride in bicarbonate solution for periods up to twenty-five hours at 0°, no detectable reduction occurred and only starting material was isolated.

The keto ester (VIIIb) in methanol was reduced by sodium borohydride, which was added in aqueous solution. The reduction appeared to be complete within two hours. Chromatography on Florisil gave three fractions, an oil (A), b.p. 120–130°/0.3–0.4 mm. (infrared bands at 2.80 and 5.80 μ); a second oil (B), b.p. 82–89°/0.2 mm. (infrared band at 5.65 μ); and a solid (C), m.p. 75–77° (infrared bands at 2.74 and 2.84 μ, none in the carbonyl region). The spectrum of A indicated that it was a hydroxy ester formed by the reduction of the ketone group in VIIIb. This was confirmed by the hydrolysis of A to the corresponding hydroxy acid (D) with correct analysis, and infrared absorption in the hydroxyl region and at 5.80 μ. In the neutral fraction from the hydrolysis a product E (described below) was isolated. This indicates that the hydroxy ester (A) as obtained from the column is contaminated with about 20% of E. When A was treated with lithium aluminum hydride C was obtained. Oxidation of C gave VIIIa in small yield. The spectrum of B showed that it was a γ-lactone. Hydrolysis of the lactone gave an acid mixed with B. As neutral material had been extracted from the hydrolysis mixture before acidification, the result indicates that this hydroxy acid tends to recyclize very readily to the lactone B. The hydroxy acid (D) does not show this behavior. This suggests that the lactone (B) was not, as assumed earlier,[1] formed from A. The reduction of B with lithium aluminum hydride to yield the product E (m.p. 118–120°), which is isomeric with C, confirmed that A and B are not directly related. As indicated above E was also a product of the reaction of VIIIb with sodium borohydride. E is best obtained by the reduction of VIIIb with lithium aluminum hydride.

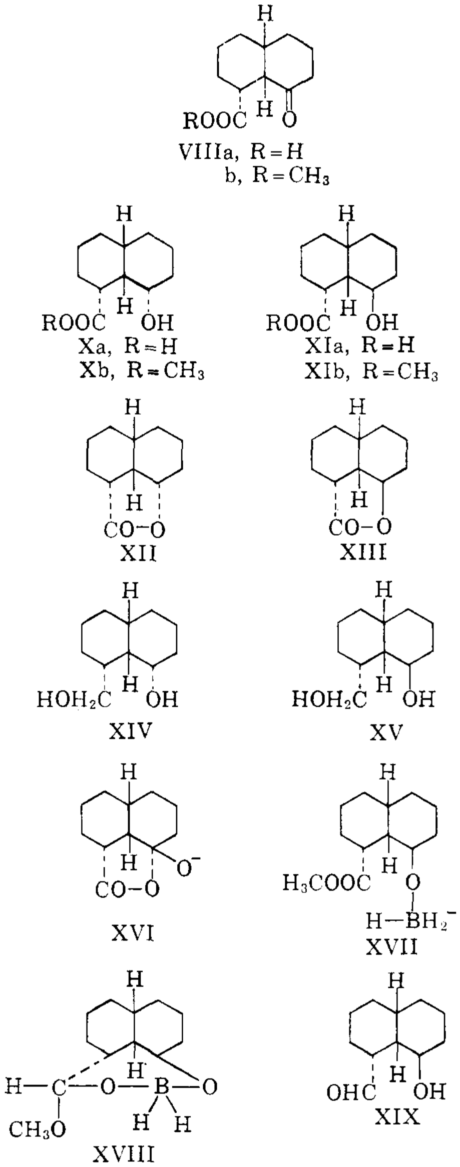

CHART III

The results indicate that the reduction of VIIIb gives two epimeric alcohols A and its epimer (Xb and XIb); the epimer is converted into the corresponding lactone B (XII or XIII); A is slowly reduced to the corresponding diol C (XIV or XV); the lactone is also slowly reduced to an isomeric diol E. General experience suggests that XII should be

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(5) G. Ourisson and A. Rassat, *Tetrahedron Letters*, **21**, 16 (1960).

(6) The sodium and propanol reduction is not as clear-cut as the lithium, ammonia, and methanol and appears to give additional products such as IX. We have also observed a variety of products by use of sodium–alcohol reductions in the marrubiin series.[7]

(7) W. H. Castine, D. M. S. Wheeler, and M. M. Wheeler, unpublished work.

more stable than XIII.[4] B is therefore assigned the structure XII; this leads to the structures XIb for A, XIa for D, XV for C, and XIV for E. Studies with Dreiding models indicate that to form XII one of the rings of Xb must take up a boat conformation. However, once this conformation is adopted, it appears that it is easier for the lactone (XII) to form from Xb than it is for XIII to form from XIb, although in the latter case both rings in the lactone can remain in the chair form. Use of close packed models (Fisher type) shows more definitely that XII can form more easily and is less strained than XIII. This evidence supports our assignments. However, since the choice of XII for B is not completely established, the interesting possibility that B has the structure XIII cannot be eliminated entirely. If this were so, then A would be Xb, D Xa, C XIV and E XV. Such a revision of the structures would not invalidate any of the main arguments presented in the next section.

In view of the complexity of the reaction of VIIIb with sodium borohydride, we have examined the infrared spectra of the crude products from reductions which were allowed run for different periods of time. We also have available the results of a number of chromatograms run on some of these crude mixtures. From these studies we have concluded that the reduction of VIIIb is complete within two hours; that the lactone formation has started within forty-five minutes; that after about fifteen hours or less the lactone formation appears to be complete; and that the diol (C) comprises about 10% of the material after four hours and rises to as much as 30% if the reaction is allowed run for fifteen hours. In the run described in the experimental the composition of the mixture after four hours was: A, 26%; B, 53%; C, 14%; and E, 7%.

Discussion of Results.—The failure of sodium borohydride to reduce VIIIa agrees with Woodward's result[4] that IV is reduced only to V, even when an excess of borohydride is used. Our result shows that, as implicity assumed by Woodward,[4] the double bonds and hydroxyl group in V are not involved in the failure of borohydride to reduce the ketone at C-8. Woodward suggested that this failure probably involves two factors: the usual lack of accessibility of the concave side of a *cis* decalin[4]; and the protection of the carbonyl group by the carboxyl, which prevents the attack on the convex face. He thought that steric factors could only play a minor part in this shielding and proposed two other possibilities: Either the carboxylate ion can exert an electrostatic repulsion on the borohydride ion, or it can interact electronically with the carbonyl group in such a way as to effect the virtual saturation of the latter (XVI). This latter type of interaction has been observed previously.[8] Since the carbomethoxy group in VIIIb is larger than the carboxyl group in VIIIa, if steric factors were important in the shielding of the ketone at C-8 in VIIIa, it would be expected that VIIIb would also be unaffected by sodium borohydride. The smooth reduction of VIIIb shows that, as expected,[4] steric factors are not important. Of the other possibilities we favor the electrostatic shielding over lactol formation for three reasons. (a) The ultraviolet spectra of Ia, Ib, VIIIa, and VIIIb in ethanol and of Ia and VIIIa in aqueous sodium bicarbonate show the normal absorption of ketones at about 285 $m\mu$ with ϵ varying from 21 to 29. A maximum of this sort would not be expected for compounds of the type XVI.[8] (b) The infrared spectra of Ia and VIIIa show no band at 5.65 μ corresponding to a γ-lactone. Further, the spectra show the normal hydroxyl absorption of a carboxyl group. (This is not a completely compelling reason, as the infrared spectra were run in different solvents from the borohydride reactions.) (c) The fact that the keto acid (Ia) reacts with sodium borohydride shows that the carboxyl can shield only one side of the carbonyl group. This is more consistent with the idea of electrostatic repulsion than that of lactol formation. In the latter case one would expect Ia, as well as VIIIa, to resist reduction.

The reduction of VIIIb with sodium borohydride gives a mixture of Xb and XIb; one of these hydroxy esters (probably Xb) is then converted to the corresponding lactone (XII), which is reduced slowly to a diol (XIV); the other hydroxy ester is reduced directly to the corresponding diol (probably XV). The formation of diols from the reaction of keto esters with sodium borohydride is discussed by Atwater.[9] Although his mechanism (*via* a lactone and a hemiacetal) probably applies in the reduction of XII, it cannot apply to the formation of XV. We suggest that the pathway in the latter case involves an intramolecular hydride transfer[10] in the complex XVII. This would lead to XVIII, then XIX, and finally XV.

On the present assignment of structures it can be seen that the reduction of VIIIb with lithium aluminum hydride involves attack of the reagent on the convex side of VIIIb.[4] The reduction with sodium borohydride occurs about equally from both sides (60% from convex side). The reduction of the keto ester (VIIIb) was carried out in aqueous methanol (over 80% of methanol). The results indicate that a reducing species was still present in the solution after four hours and perhaps for periods of as long as ten to fifteen hours. This is surprising in view of Brown's[11] work on the rate of reaction between methanol and borohydride. A possible explanation would be that there is a

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(8) D. H. R. Barton, P. de Mayo, and M. Shafiq, *J. Chem. Soc.*, 140 (1958).

(9) N. W. Atwater, *J. Am. Chem. Soc.*, **83**, 3071 (1961).

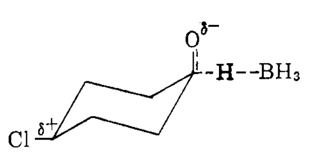
(10) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 4608 (1957), and D. S. Tarbell, *et al.*, *J. Am. Chem. Soc.*, **83**, 3096 (1961), suggest such transfers for certain reductions with lithium aluminum hydride.

(11) H. C. Brown and K. Ichikawa, *ibid.*, **83**, 4372 (1961).

rapid formation of a complex between the ketone and the hydride, with the actual reduction following more slowly.[12] The hydride tied up in the complex would not then be available for reaction with methanol[13].

The reductions of the keto acid (Ia) and the keto ester (Ib) with sodium borohydride lead to the corresponding hydroxy compounds (IIa) and (IIb). As the ketone groups in Ia and IIa are somewhat hindered, it might have been expected from Barton's rules,[14] that the axial alcohols (III) and its methyl ester would have been obtained. However, examination of models of Ia and Ib shows that in these compounds the carboxyl or carbomethoxy group shields the underside of the ketone. The shielding by the acid group is presumably mainly electrostatic in character; that by the ester mainly steric. Thus the reagents attack from the upper side of the ketone and produce equatorial alcohols (IIa and IIb). These reductions are examples of cases in which both the factors controlling the stereochemistry of the reduction (steric approach control and product development control[15]) operate to favor the same epimer. On this basis we have suggested[1] that Barton's generalization[14] concerning the reduction of hindered ketones should be modified to: Ketones are reduced by metallic hydrides to give mainly the axial alcohol if the approach of reagents along the axial direction is hindered.

After the publication of our preliminary note,[1] Combe and Henbest[16] demonstrated the existence of an electrostatic effect in the reduction of 4-chlorocyclohexanone with borohydride. They observed that this compound on reduction gave more *cis*-chlorocyclohexanol than the amount of *cis*-4-methylcyclohexanol formed by reduction of 4-methylcyclohexanone. Combe and Henbest explained their results by suggesting that the positive charge induced by the chlorine atom on C-4 of 4-chlorocyclohexanone stabilizes the transition state XX over XXI.



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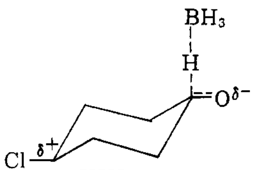
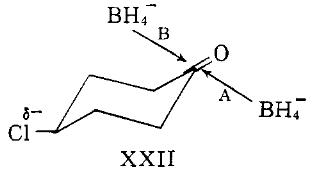


XXI



XXII

It should be pointed out that this picture is an oversimplification: Although the inductive effect dies away rapidly, it is clear that the positive charge on C-4 will be partially neutralized by movements of electrons in the adjoining bonds and that small positive charges will be induced on C-3, C-5, C-2, and C-6. However, there is a more fundamental objection to their theory. The theory implies that there has been a considerable development of negative charge on the oxygen of the carbonyl group in the transition state, which (as they write it) resembles the products rather than the reactants. In general, hydride reductions of ketones are exothermic reactions and take place easily and so application of the Hammond principle[17] suggests that the transition state of a borohydride reduction should resemble the reactants not the products.

We propose that a better explanation of Henbest's results is that the chlorine atom with its slight negative charge repels to some extent the approach of the borohydride ion along direction B (XXII, the approach of the borohydride is envisaged along a line perpendicular to the plane of the carbonyl group), and thus the ion attacks preferentially along the direction A.

Experimental

Boiling and melting points are uncorrected. Microanalyses are by Microtech, Skokie, Illinois, and Bernhardt, Mulheim (Ruhr), Germany. Ultraviolet spectra were measured on Cary spectrophotometers (Models 12 and 14). Infrared spectra were determined on Perkin-Elmer instruments (Model 21 and Infracord Model 137B). Unless otherwise specified ultraviolet spectra were measured in 95% ethanol; infrared spectra, in methylene chloride.

***cis*-1α-Carboxy-8-oxo-1,4,7,8,4a,8a-hexahydronaphthalene (VII).**[18]—This compound was prepared by Woodward's route,[4] which involves a four-stage synthesis starting from vinyl acrylic acid and *p*-benzoquinone. The following minor points are noted in clarification of Woodward's account. (a) It is essential that in the sodium borohydride reduction of *cis*-1α-carboxy-5,8-dioxo-1,4,5,8,4a,8a-hexahydronaphthalene (IV) the reaction mixture be cooled throughout the reaction. (b) The m.p. of the lactone of *cis*-1α-carboxy-5α-hydroxy-8-oxo-1,4,5,8,4a,8a-hexahydronaphthalene (VI) (after crystallization from ethyl acetate) was 149–151°.[19]

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[12] *Cf.* H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957).

[13] We thank Drs. F. McLafferty, and F. Johnson of the Dow Laboratory, Framingham, Massachusetts, for a stimulating discussion of this point.

[14] D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

[15] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

[16] M. G. Combe and H. B. Henbest, *Tetrahedron Letters*, **12**, 404 (1961).

[17] G. S. Hammond. *J. Am. Chem. Soc.*, **77**, 334 (1955).

[18] There appears to be no generally accepted system for specifying the stereochemistry of substituents on reduced naphthalene systems. We use the following rules: (i) The 8a-H is always up; (ii) the relation of the 4a-H to that at 8a is shown by the terms *cis* and *trans*; (iii) the stereochemistry of the substituents on the rings is specified by the use of the letters "α" and "β," which are used in the steroid sense; (iv) acids are named as carboxynaphthalenes rather than as naphthoic acids; this avoids the use of expressions such as . . . . -1α-naphthoic acid, which might be confusing as "1" and "α," are both used in the naphthoic acid series to designate positions in the ring. We wish to thank Professor W. G. Dauben for helpful suggestions on formulating the rules.

One difficulty with these rules is that using them in drawing structures obscures the relationship between the compounds in the *cis* and *trans* series. For this reason we have drawn the *trans* compounds with 8a-H down, although they are named in the experimental section on the basis that 8a-H is up.

(c) We were not able to duplicate the yield obtained previously by the zinc–acetic acid reduction of the lactone (VI). The major problem was contamination of the product with small traces of zinc acetate. The following is our best preparation:

A solution of the ketolactone (VI 25 g.) in glacial acetic acid (250 ml.) at 15° was treated with water (81 ml.). Zinc (dust 75 g. purified by washing in dilute hydrochloric acid and then water) was then added in five lots with vigorous stirring. During this addition the temperature of the reaction mixture rose to 25°. On completion of the addition stirring was continued for 30 min. The zinc was removed by filtration and was washed with aqueous acetic acid of the same composition as the reaction mixture. The combined filtrates were added to ethyl acetate (2 l.), and the precipitated zinc acetate was filtered off. The ethyl acetate solution was washed with water and saturated aqueous sodium chloride and was dried (Na_2SO_4). Evaporation of the warmed ethyl acetate in a stream of nitrogen yielded *cis*-1α-carboxy-8-oxo-1,4,7,8,4a,8a-hexahydronaphthalene (VII), which after crystallization from ethyl acetate had m.p. 156–160° [12.3 g., lit.[4] m.p. 155–158° and 152–159° (3.6 g.)].

***cis*-1α-Carboxy-8-oxodecahydronaphthalene (VIIIa).**[21]—A solution of VII (12 g.) in ethyl acetate (250 ml.) was shaken under hydrogen in the presence of prereduced palladized charcoal (5% 2 g.) until 2 moles of hydrogen per mole of VII had been consumed. The catalyst was removed by filtration through Celite; evaporation of the filtrate gave *cis*-1α-carboxy-8-oxodecahydronaphthalene (VIIIa, 12.5 g.), which crystallized from ethyl acetate in small prisms m.p. 148–151° (5.8 g.) and 145–150° (2.4 g.). Further crystallization from ethyl acetate and from ether raised the m.p. to 149–151.5°. The infrared spectrum had bands at 5.72 and 5.84 μ; in KBr bands were at 5.84 and 5.91 μ. The ultraviolet spectrum had λ_{max} 286 mμ (ϵ 21); in aqueous sodium hydrogen carbonate λ_{max} 285 mμ, (ϵ 22).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.37; H, 8.11.

The corresponding methyl ester (VIIIb) was prepared by the action of a slight excess of ethereal diazomethane on a solution of VIIIa (297 mg.) in ether. After 2 hr., the solvent was removed and the crude solid ester (VIIIb) crystallized from pentane in small prisms m.p. 63–65° (263 mg.) and m.p. 62–64° (40 mg.). Further crystallization from pentane gave VIIIb with m.p. 63–64.5°. The ester had infrared bands at 5.78 and 5.85 μ, and in the ultraviolet λ_{max} 284 mμ (ϵ 25).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.72; H, 8.60.

***trans*-1β-Carboxy-8-oxodecahydronaphthalene (Ia).**—A solution of the *cis* keto acid (VIIIa 1.5 g.) in methanolic potassium hydroxide (5%, 40 ml.) was heated under reflux for 1 hr. Water was added to the cooled mixture, which was acidified with concentrated hydrochloric acid. The crude product (1.24 g., m.p. 135.5–139.5°), which was isolated through extraction with ethyl acetate, crystallized from ethyl acetate in small prisms, m.p. 140–141° (0.99 g.). The m.p. was raised by further crystallizations from ethyl acetate and from methylene chloride–pentane to 142–144°. Addition of VIIIa depressed the m.p. to 106–136°.

The infrared spectrum of Ia had bands at 5.72 and 5.85 μ; in potassium bromide a band at 5.88 μ. The ultraviolet had λ_{max} 284 mμ (ϵ 24)[22]; in aqueous sodium hydrogen carbonate λ_{max} 283 mμ (ϵ 29).

The epimerization was also tried by refluxing a solution of VIIIa in methanolic hydrochloric acid (about 1*N*) for 3 hr. Since epimerization appeared to have taken place but was not complete, this method was not tried further.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.04.

The corresponding methyl ester (Ib) was prepared by treating a solution of the acid (Ia, 458 mg.) in ether with a slight excess of ethereal diazomethane. Next day the solvent was removed and the crude ester crystallized from pentane in small rhombs, m.p. 71–73° (425 mg.), which was raised by further crystallization from pentane to 72–74°.

The ester was also prepared in 75% yield (m.p. 71–73°) by refluxing a solution of the acid (Ia) in methanol with a little concentrated sulfuric acid and isolation of the product by extraction with ethyl acetate. The ester had infrared bands at 5.78 and 5.85 μ; the ultraviolet spectrum showed λ_{max} 283 mμ (ϵ 27).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.59; H, 8.58.

Attempted Reaction of VIIIa with Sodium Borohydride.—A solution of VIIIa (100 mg.) in aqueous sodium hydrogen carbonate (43 mg. in 2 ml. water) was treated at 0° with a solution of sodium borohydride (19 mg.) in water (1 ml.). The solution was kept for 4 hr. at 0°. The ultraviolet spectrum of the solution still showed a maximum at 285 mμ with ϵ 23. The mixture was acidified and the material isolated through extraction with ethyl acetate. The crude product (90 mg.) had m.p. 139–142.5° (raised to 145–147° on mixing with VIIIa) and its infrared spectrum was identical with that of the starting material. The crude compound crystallized from ethyl acetate–pentane to yield small prisms, m.p. 147.5–150° (65 mg.), undepressed by addition of VIIIa. Similar results were obtained when the reaction mixture was kept for 7 and 25 hr. at 0°. In these latter cases the m.p. of the crude recovered material was higher. A further attempt to reduce VIIIa (50 mg.) in aqueous sodium hydrogen carbonate was made using sodium borohydride (26 mg.). The reaction was kept at 0° for 15 hr. and the crude material had m.p. 125–140° raised to 133–145° by addition of VIIIa. The infrared spectrum of the product was the same as that of VIIIa and the material crystallized from ethyl acetate to yield starting material (29 mg.), m.p. 146–149°, not depressed on mixing with VIIIa.

It was found that a solution of VIIIa which had been kept in sodium hydrogen carbonate solution for periods up to 24 hr. also had m.p. 140–145° on recovery after acidification and extraction with ethyl acetate.

The conclusion from these experiments is that very little, if any, reduction of VIIIa occurs when it is kept with sodium borohydride at 0° for periods up to 25 hr.

Reduction of VIIIb with Sodium Borohydride.—A solution of sodium borohydride (502 mg.) in water (2 ml.) was added to a solution of the keto ester (VIIIb 1.006 g.) in methanol (10 ml.) at 0°. The mixture was kept at 0° for 4 hr. and was then acidified. Water (30 ml.) was added and the products were extracted with ethyl acetate. The combined ethyl acetate solutions were washed with water and saturated aqueous sodium chloride and were dried (Na_2SO_4). Removal

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(19) G. Muller, G. Nomine, and J. Warnant[20] report m.p. 150°.

(20) F. Muller, G. Nomine, and J. Warnant, *Chem. Abstr.*, **54**, 24613c (1960).

(21) (a) V. Georgian, U. S. Patent 2,858,314, reports the preparation of an 8-oxodecahydronaphthoic acid by hydrogenation of 8-hydroxynaphthoic acid followed by oxidation with chromic acid. His product is not described but is probably VIIIa. (b) J. O. Jílek, B. Kakáč, and M. Protiva, *Collection Czech. Chem. Commun.*, **26**, 2229 (1961), report a compound which is an 8-oxodecahydronaphthoic acid, but the stereochemistry was not established.

(22) When the ultraviolet spectrum of Ia was first measured, an additional peak was present at 240 mμ which had about twice the intensity of the ketone peak. This was attributed to the presence of about 0.5% of a conjugated ketone which had resulted from incomplete hydrogenation of VII followed by isomerization of the double bond during the epimerization reaction. This view was confirmed by shaking a solution of Ia under hydrogen in the presence of palladized charcoal; there was no visible uptake of hydrogen and the m.p. and infrared spectrum of the product were the same as the starting material. However, the ultraviolet spectrum no longer showed the extraneous peak at 240 mμ. The problem was encountered a number of times in this series of compounds. However, in every case the rehydrogenation process removed the extra ultraviolet peak without affecting the infrared spectrum or the melting point of the material.

of the solvent yielded an oil (845 mg.), which had an infrared spectrum containing bands indicating the presence of a γ-lactone (5.65 μ) and a hydroxy ester (2.80 and 5.80 μ). The oil was chromatographed on Florisil (30 g.).

The fractions (1–13) eluted in benzene and benzene–methylene chloride (3:1) totalled 442 mg.; infrared spectra indicated that 394 mg. were a γ-lactone and that the remaining 48 mg. were lactone containing traces of a hydroxy ester. The material (fractions 14–24) eluted in benzene–methylene chloride and the first two chloroform fractions (in all 179 mg.) contained mainly the hydroxy ester with traces of the lactone. Two chloroform fractions (25–26) contained hydroxy ester (113 mg.) and no lactone. Finally the material eluted in ethanol–chloroform (1:9) (Fraction 27) contained the diol, m.p. 75–77° (123 mg.).

The fractions 14–24 were rechromatographed on Florisil (8 g.). The material eluted in fractions 1–5 with benzene was mainly lactone (10 mg.). Fractions 6–8 eluted in benzene–methylene chloride (1:1) were a mixture of lactone and hydroxy ester (30 mg.). Fractions 9–22 (129 mg.) eluted in benzene–methylene chloride (1:1), methylene chloride and chloroform were hydroxy ester with a trace of lactone. The fractions 23–28 (21 mg.) eluted in chloroform contained hydroxy ester only.

In summary, the columns divided the product into three main fractions, the lactone (B, 450 mg.), the hydroxy ester (A, 280 mg.) and the diol, m.p. 75–77° (C, 123 mg.). Later it was shown that the hydroxy ester fraction also contained the diol, E, m.p. 118–120°.

These yields account for 94% of the starting material. The characterization of these fractions is described below.

Lactone of *cis*-1α-Carboxy-8α-hydroxydecahydronaphthalene (XII).—The oil obtained in the lactone fractions from the column distilled at 82–89°/0.2 mm. It had infrared bands at 5.65, 9.95, and 10.50 μ.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.74; H, 8.66.

Methyl Ester of *cis*-1α-Carboxy-8β-hydroxydecahydronaphthalene (XIb).—The oil obtained in the ester fractions from the columns distilled at 120–130°/0.3–0.4 mm. It had infrared bands at 2.80, 5.80, 9.95, and 11.75 μ. This material is contaminated with the diol E.

***cis*-1β-Hydroxy-8α-hydroxymethyldecahydronaphthalene (XV) (m.p. 75–77°).**—(i) Crystalline material (106 mg.) obtained in fraction 27 of the first column distilled at 120°/0.5 mm. to give a product with m.p. 65–73° (101 mg.), which crystallized from ethyl acetate in small rhombs m.p. 75° (74 mg.). For analysis the diol was recrystallized from ethyl acetate and sublimed in high vacuum, m.p. 75–77°.

(ii) A solution of the hydroxy ester (XIb, 60 mg.) in ether was stirred for 3 hr. with lithium aluminum hydride (78 mg.). The excess of hydride was decomposed with ethyl acetate (5 ml.) and water (5 ml.), and then 5% hydrochloric acid (20 ml.) was added. The crude product, which was isolated through an extraction with ether, crystallized from ethyl acetate in small rhombs, m.p. 74–76° (29 mg.) and 75–78° (9 mg.), not depressed by addition of authentic diol (XV).

The infrared spectrum had bands at 2.74, 2.84, 9.66, and 10.47 μ. The peak at 2.84 μ is more intense than that at 2.74 μ.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94; O, 17.37. Found: C, 71.58; H, 10.65; O, 17.58.

Oxidation of *cis*-8-Hydroxymethyldecalol (XV) (m.p. 74–76°).—A solution of the diol (XV, 100 mg.) in acetone (distilled from permanganate) was treated with a solution of chromium trioxide in sulfuric acid[23] (0.67 ml.). After 10 min. the reaction was worked up and divided into neutral (63 mg.) and acidic (18 mg.) fractions. The neutral material in acetone was treated with the chromic acid solution (0.7 ml.) and the mixture was kept for 4 hr. The second oxidation yielded further acid (17 mg.) and some neutral products (13 mg.). The infrared spectrum of the neutral fraction showed that it was a mixture, the major component of which was a γ-lactone. The infrared spectra of both acidic materials resembled closely the spectrum of VIIIa. The combined fractions were crystallized from ethyl acetate–petroleum ether, b.p. 30–60°, to yield material with m.p. 138–144° (9 mg.) raised on addition of authentic VIIIa. The infrared spectrum of the material 138–144° is identical with that of VIIIa.

***cis*-1α-Hydroxy-8α-hydroxymethyldecahydronaphthalene (XIV) (m.p. 118–120°).**—(i) A solution of VIIIb (99 mg.) in ether (15 ml.) was added to lithium aluminum hydride (100 mg.) in ether (10 ml.). After 1.75 hr. the mixture was worked up in the same way as in preparation (ii) of XV. The crude oily product (140 mg.) crystallized from ethyl acetate in rhombs, m.p. 119–121° (46 mg.). Further crystallization from ethyl acetate gave material with m.p. 118–120°, which sublimed at 0.4 mm. The sublimed material had m.p. 118–120°.

(ii) A solution of the lactone (XII, 96 mg.) in ether was stirred for 3 hr. with lithium aluminum hydride (99 mg.). The crude product (86 mg.), which was isolated as in the reduction of XIb with lithium aluminum hydride, crystallized from ethyl acetate to give the diol, m.p. 115–118° (46 mg.). The m.p. was raised by addition of the material prepared in (i) and was depressed by addition of diol m.p. 74–76°. The same product, m.p. 115–118°, was obtained when XII was reduced with lithium aluminum hydride in refluxing tetrahydrofuran.

The infrared spectrum had bands at 2.74, 2.83, 9.62, 9.90, and 10.60 μ. The band at 2.74 is more intense than that at 2.83 μ.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94; O, 17.37. Found: C, 71.77; H, 10.99; O, 17.41.

***cis*-1α-Carboxy-8β-hydroxydecahydronaphthalene (XIa).**—A solution of the hydroxy ester(XIb, 97 mg.) in alcoholic sodium hydroxide (0.8 g. in 8 ml., 1:1 water–ethanol) was refluxed for 1 hr. On next day water (50 ml.) was added, and the solution extracted with ethyl acetate. The ethyl acetate solutions were washed with water and saturated aqueous sodium chloride and were dried (Na_2SO_4). Removal of the solvent yielded neutral material (22 mg.) which solidified and was diol (XIV) (infrared spectra). This indicates that the hydroxy ester obtained from the column is contaminated to the extent of 20% by the diol, 118–120°.

The aqueous solutions were acidified to Congo Red and extracted with ethyl acetate. The combined ethyl acetate solutions were washed with saturated aqueous sodium chloride and were dried (Na_2SO_4). Removal of the solvent by evaporation yielded a solid, m.p. 135–137° (74 mg.), which crystallized from ethyl acetate in small prisms, m.p. 138–139° (52 mg.), and 140–142° (10 mg.). For analysis the compound was crystallized from ethyl acetate and ethyl acetate–pentane and had m.p. 138–139°. The infrared spectrum had a band at 5.80 μ.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.45; H, 9.44.

Infrared Study on the Course of the Reduction of VIIIb with Borohydride.—The course of the reduction of VIIIb with borohydride was studied in the following way: A series of seven reactions was run at 0° for different times: 15 min., 30 min., 45 min., 1 hr., 2 hr., 4.5 hr., and 48 hr. In each reaction a solution of sodium borohydride (24 mg.) in water (0.3 ml.) was added to a solution of the keto ester (VIIIb, 25 mg.) in methanol (2 ml.) at 0°. After the appropriate time, the mixture was acidified and the crude products isolated through extraction with ethyl acetate. The weights of products varied from 19 to 25 mg. The infrared spectra of the crude products were studied and an attempt was made to deduce approximately the composition of the mixture. The peaks used were those at 2.74, 2.85, 5.65, 5.78, 9.66, and 9.95 μ. In addition the presence of a peak at 11.95 μ served to detect the starting keto ester (VIIIb). These studies

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[23] C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

were supplemented by examination of the crude infrared spectra of other runs of the reaction, many of which were subsequently chromatographed. The results of these studies indicate that the reduction of the keto ester starts at once and is probably complete in 2 hr. Formation of the lactone (XII) becomes apparent after 45 min. After 4 hr. the ester peak is usually more intense than the lactone. After about 15 hr. the intensity of the lactone peak is about twice that of the ester. Because the diols have no strong characteristic peaks it is difficult to detect their first appearance. Usually XV is about 10% the mixture after 4 hr. and rises to about 25–30% overnight.

***trans*-1β-Carboxy-8β-hydroxydecahydronaphthalene (IIa).**—(i) Sodium (2 g.) was added over a period of 1.5 hr. to a refluxing solution of the *trans* keto acid (Ia, 200 mg.) in propanol (25 ml.). The refluxing was continued until all the sodium had reacted. Water (100 ml.) was added to the cooled solution, which was then acidified with concentrated hydrochloric acid. The solution was extracted three times with ethyl acetate, and the combined ethyl acetate solutions were washed with saturated aqueous sodium chloride and were dried (Na_2SO_4). Removal of the solvent by evaporation yielded a yellow oil (233 mg.), which after treatment in methylene chloride with charcoal, crystallized from ethyl acetate in small prisms, m.p. 155–157° (84 mg.) and m.p. 154–157° (9 mg.). The residue from these crystallizations was divided into a neutral fraction (10 mg.) and an acidic fraction (30 mg.) (by extraction of an ethyl acetate solution of the residue with dilute aqueous sodium hydrogen carbonate). The acidic fraction on crystallization yielded further IIa, m.p. 149–152° (16 mg.).

The m.p. 155–157° of the hydroxy acid was not depressed on addition of material prepared by the reduction of Ia either by sodium borohydride or by lithium, methanol, and ammonia.

(ii) Lithium (400 mg.) was added in small pieces over 45 min. to a stirred solution of the keto acid (Ia, 205 mg.) in methanol (10 ml.) and liquid ammonia (*ca.* 200 ml.). When the blue color resulting from the addition of the last piece of lithium had disappeared, ammonium chloride (10 g.) was added slowly. After the ammonia had evaporated water and ice (*ca.* 100 ml.) was added, and the mixture acidified with hydrochloric acid. The product was isolated by extraction with ethyl acetate. Removal of the solvent yielded crystalline IIa (187 mg.), m.p. 158.5–160.5°. The material recrystallized from ethyl acetate to give m.p. 159–161° (168 mg.), which was raised to 161–162° when mixed with IIa from method (i).

(iii) A solution of sodium borohydride (100 mg.) in water (1 ml.) was added to a solution of Ia (202 mg.) in aqueous sodium hydrogen carbonate (80 mg. in 4 ml.) at 0°. The mixture was kept at 0° for 24 hr. and was acidified with 20% sulfuric acid until acid to Congo Red. The precipitate (148 mg.) was removed by filtration. The filtrate was extracted with ethyl acetate (three times) and the combined ethyl acetate solutions were washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent yielded further product (40 mg.) which was combined with the precipitate. The hydroxy acid (IIa) was obtained by crystallization from ethyl acetate in small prisms, m.p. 157–159° (141 mg.). The m.p. was not depressed by addition of IIa prepared by method (i).

The hydroxy acid (IIa) showed an infrared peak at 5.83 μ. For analysis it was crystallized several times from ethyl acetate and had m.p. 160–162°.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.83; H, 9.37.

Lactone of *trans*-1β-Carboxy-8β-hydroxydecahydronaphthalene (IX).—A mixture of the hydroxy acid (IIa, 101 mg.), sodium acetate (21 mg.), and acetic anhydride (0.1 ml.) in benzene (2 ml.) was refluxed for 2 hr. The cooled mixture was added to water (8 ml.) which was then extracted with ethyl acetate. The combined ethyl acetate solutions were washed with water, dilute aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride and were dried (Na_2SO_4). The solvent was removed by evaporation and the lactone (79 mg., m.p. 95–100°) crystallized from ethyl acetate and from aqueous ethanol in plates, m.p. 98–99° (49 mg.), which crystallized again from aqueous ethanol, m.p. 98.5–101°. The infrared spectrum had a maximum at 5.60 μ.

The hydroxy acid (IIa) in a m.p. tube was heated at 160° for 10 min. The infrared spectrum of the cooled material when compared with that of IIa showed a decrease of intensity of the characteristic carboxyl absorption in the 3–4 μ region and of the peak at 5.83 μ. Peaks characteristic of the lactone (IX) had appeared at 5.65 and 10.48 μ.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.9. Found: C, 73.26; H, 9.15.

Methyl Ester of *trans*-1β-Carboxy-8β-hydroxydecahydronaphthalene (IIb).—(i) A solution of the *trans* keto ester (Ib, 99 mg.) in methanol (1 ml.) was treated at 0° with a solution of sodium borohydride (41 mg.) in water (1 ml.). When the mixture had been kept for 24 hr. at 0°, it was acidified with 20% sulfuric acid, and water (10 ml.) was added. The mixture was extracted with ethyl acetate and the combined ethyl acetate solutions were washed with water and saturated aqueous sodium chloride and were dried (Na_2SO_4). Evaporation of the solvent yielded the hydroxy ester (IIb), m.p. 71–74° (91 mg.), which after three crystallizations from pentane had m.p. 72–74° (small needles), which was depressed on addition of the starting keto ester (Ib).

(ii) A solution of *trans*-8-hydroxydecahydronaphthoic acid (IIa, 100 mg.) in ether was treated with excess of ethereal diazomethane. Next day the solvent was removed and the crude hydroxy ester crystallized from ethyl acetate in small needles, m.p. 66–69° raised to 67–70° on addition of hydroxy ester (IIb) prepared by method (i). The infrared spectra of the two materials were the same. The infrared spectrum of the hydroxy ester (IIb) had maxima at 2.78 and 5.80 μ.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.85; H, 9.23.

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