

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY, NEW YORK 27, N. Y.]

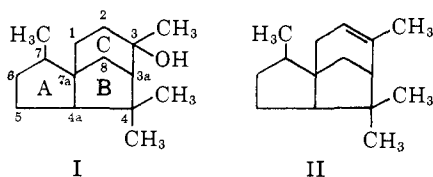
**Cedrol: Stereochemistry and Total Synthesis**

BY GILBERT STORK AND FRANK H. CLARKE, JR.

RECEIVED MARCH 4, 1961

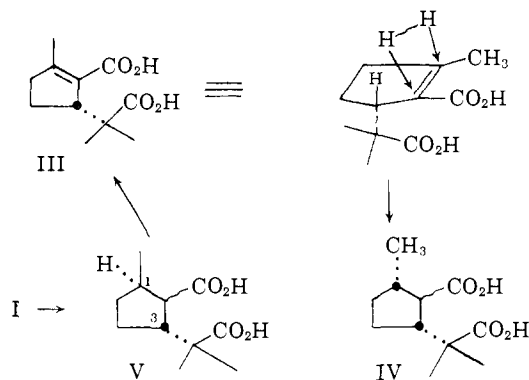
The total stereospecific synthesis of natural cedrol is described. This synthesis establishes the stereochemistry of cedrol as that shown in Ib.

We have outlined elsewhere<sup>1,2</sup> the chemical and spectral evidence which led us to the establishment of structure I for cedrol and, consequently, II for  $\alpha$ -cedrene, two sesquiterpenes which occur in "cedar wood oil," the essential oil of several juniper species.

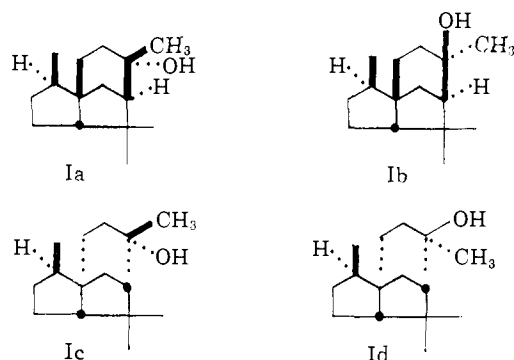


It will be noted that the solution of the structural problem is not completed with the establishment of structure I since there are five asymmetric centers in the cedrol molecule, and thus there exists the possibility of sixteen optical isomers (rather than thirty-two since the carbon-carbon bonds at 3-3a and 1-7a are necessarily *cis* to each other).

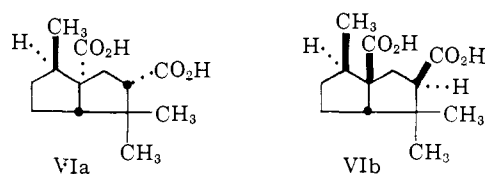
The available degradative evidence permits the conclusion that the hydrogens at position 7 and 4a must be *trans* to each other: It has been demonstrated by Plattner, *et al.*,<sup>3</sup> that catalytic hydrogenation of the olefinic acid III gives a saturated acid IV *different* from the acid V obtained by destruction of ring B and C of the cedrol molecule. Since the acids IV and V could be equilibrated without becoming interconverted, the non-identity came from the different relative stereochemistry at positions 1 and 3 of the two cyclopentane acids. As Plattner, *et al.*, have pointed out, the mode of formation of IV permits only a *cis* arrangement at these centers and consequently the hydrogens at C<sub>1</sub> and C<sub>3</sub> in the degradation acid V, and therefore the hydrogens at positions 4a and 7 in cedrol itself, must be *trans* oriented.

(1) G. Stork and R. Breslow, *J. Am. Chem. Soc.*, **75**, 3291 (1953).(2) G. Stork and R. Breslow, *ibid.*, **75**, 3292 (1953).(3) Pl. A. Plattner, A. Fürst, A. Eschenmoser, W. Keller, H. Kläui, St. Meyer and M. Rosner, *Helv. Chim. Acta*, **36**, 1845 (1953).

This leaves four possible relative arrangements of structure I, illustrated by Ia to Id.



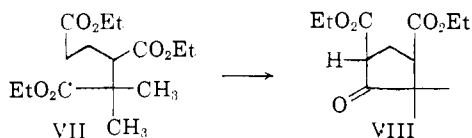
Cedrol has been transformed into "norcedrenedicarboxylic acid" (VI), with attendant destruction of ring C and of the center of asymmetry at C<sub>3</sub>. Since there are only two possible structures for norcedrenedicarboxylic acid and since such a substance appeared to us an ideal intermediate for a total synthesis of cedrol itself, we will turn our attention first to the synthesis of this dicarboxylic acid. We shall then return to the problem of the C<sub>3</sub> asymmetry and of the elaboration of the C ring of cedrol.



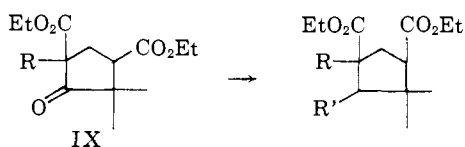
Of the two possibilities VIa and VIb, the latter appeared *a priori* rather more likely since the *trans* fusion of the A/B system in VIa, while not impossible, implies a degree of strain<sup>4</sup> which would be surprising on the basis of biogenetic speculations. We therefore turned our attention initially to the possible stereospecific synthesis of the dicarboxylic acid VIb. As will become apparent, the synthesis was accomplished and VIb proved identical with norcedrenedicarboxylic acid from natural cedrol.

For a variety of reasons, some of which will become apparent, we chose to start with ring B and proceed with the attachment of ring A. For this purpose the cyclopentanone diester VIII appeared suitable. This had been prepared previously by Simonsen, *et al.*,<sup>5</sup> from diethyl 2,2-dimethyl-3-carbethoxyadipate (VII), an improved synthesis of which is given in the Experimental section of this

(4) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 436 (1935).(5) C. S. Gibson, K. V. Hariharan and J. L. Simonsen, *ibid.*, 3009 (1927).

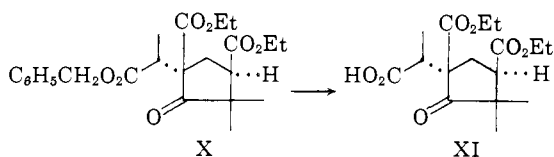


paper. A possibility for the construction of ring A involves attachment of a carbon chain, R, at the  $\beta$ -keto ester carbon (*cf.* IX) and of another, R', at the carbonyl center followed by ring formation between R and R'. The degree of anticipated



steric hindrance of the cyclopentanone carbonyl in IX, however, makes it extremely dubious that addition of an external reagent to the carbonyl group could be successfully carried out. It is therefore R itself which must be so constructed as to permit intramolecular formation of the carbon-carbon bond at the carbonyl center.

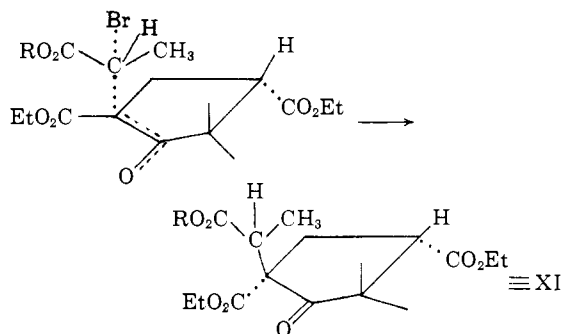
It is these considerations which led to the choice of benzyl  $\alpha$ -bromopropionate as the alkylating agent: Alkylation of VII was carried out by letting its sodium salt, prepared with sodium hydride, react for several days at *ca.* 50° in a medium of benzene-dimethylformamide with the bromo ester. The resulting alkylated substance was then purified by distillation under high vacuum and the benzyl ester (X, 90% yield) was transformed into the corresponding free acid by hydrogenolysis in ethyl acetate in the presence of palladium-on-charcoal. The resulting monocarboxylic acid XI was obtained in 45% yield as colorless rectangular prisms, m.p. 113-115° after recrystallization from cyclohexane. In the acid XI, the chain which is to be used to construct ring A has now been differentiated from the two other carboxyl functions and is ready for further elaboration.



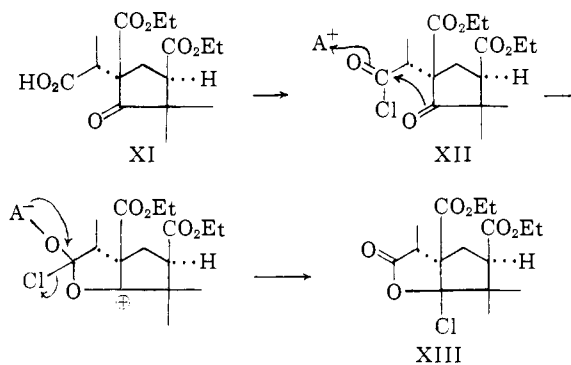
Before proceeding with this, we would like to remark on the stereochemistry indicated in XI. Two new asymmetric centers have been introduced with a remarkable degree of stereospecificity. One of these, at the methyl-bearing carbon alpha to the free carboxyl group of XI, is of no concern to us at this point. The stereochemical arrangement at this center will not become fixed until the final removal of the carbonyl function adjacent to it. What is, however, of considerable moment at this stage is that the *cis* arrangement of the two carboxyl functions at C<sub>1</sub> and C<sub>3</sub> in XI, which is that present in norcedrenedicarboxylic acid VIIb, has now been established.

The lower energy transition state for the alkylation of VII must involve approach of the bulky benzene  $\alpha$ -bromopropionate fragment from the side away from that carboxyl group which remains

out of the plane in the enolate ion (hindrance by the *gem*-dimethyl grouping can be assumed to be substantially identical on either side of that plane).<sup>6</sup>



The internal aldol cyclization which we wished to use to complete the attachment of ring A now requires the transformation of the free carboxyl in XI into a methyl ketone grouping. This simple change is complicated here because the acid chloride XII, derived from XI, is readily transformed into the isomeric—and unreactive—chlorolactone XIII. Thus, although XII can be prepared by the reaction of the dry sodium salt of XI and oxalylchloride, reaction with dimethylcadmium is unsuccessful (MgX<sub>2</sub> presumably catalyzing the XII-XIII transformation).



It was therefore necessary to employ a method which would not only allow the survival of the  $\beta$ -keto ester system but would also avoid any acid reagent which could catalyze the XII $\rightarrow$ XIII transformation: reaction of XII with excess diazomethane<sup>7</sup> produced the diazoketone XIV, neutrality being maintained by the instantaneous reaction of the liberated hydrogen chloride and diazomethane. The crystalline diazoketone was converted with anhydrous hydrogen chloride<sup>8</sup> in ether into the chloromethyl ketone XV, m.p. 72-73°, and the latter was finally reduced with zinc dust and acetic acid in the presence of potassium iodide<sup>9</sup>

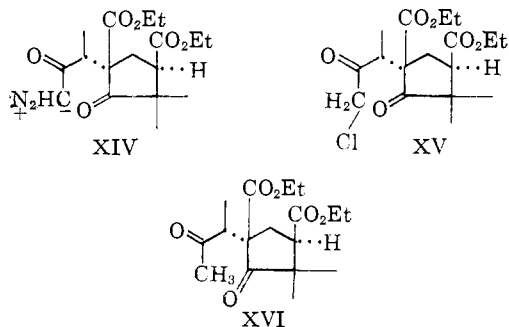
(6) The same stereochemical result would be obtained if the transition state for the alkylation looked very much like the product because the bulk of the alkylating agent is greater than that of the carboxyl group present at the alkylation site and XI would be the less hindered of the two possible products.

(7) Cf. A. L. Wilds and T. L. Johnston, *J. Am. Chem. Soc.*, **70**, 1166 (1948).

(8) Cf. Ch. R. Engel and G. Just, *ibid.*, **76**, 4909 (1954).

(9) Cf. A. Grüssner, J.-P. Bourquin and O. Schnider, *Helv. Chim. Acta*, **28**, 617 (1945).

to the desired methyl ketone XVI, a low melting solid which was further characterized as its semicarbazone, m.p. 191–193°.



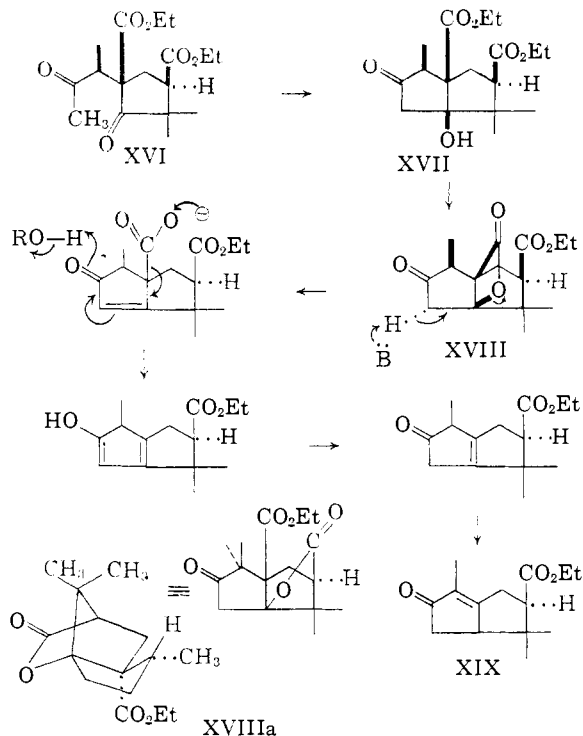
The remarkable efficiency of this sequence of steps is illustrated by the 79% over-all yield of crystalline methyl ketone XVI obtained from the sodium salt of the acid XI. The methyl ketone is undoubtedly a mixture of epimers at the center next to the side chain carbonyl. This is reflected in the fact that XVI gave analytical values in excellent agreement with the expected structure, although its melting point remained at 55–60° after several crystallizations.

We were now in position to complete the construction of the A/B skeleton by aldol cyclization of XVI to the important intermediate XX.

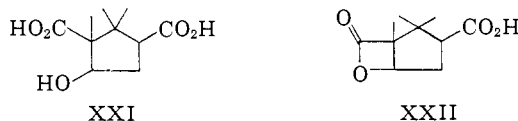
Attempts to effect this apparently simple step by treatment with *p*-toluenesulfonic acid in hot benzene or with aluminum *t*-butoxide in boiling toluene remained without effect. Treatment with potassium *t*-butoxide in boiling *t*-butyl alcohol appeared to produce cyclization and dehydration: It was possible to obtain from one such experiment, followed by careful chromatography on alumina of the neutral products, a trace of crystalline material, m.p. 65–66°, which had the expected absorption in the ultraviolet:  $\lambda_{\max}^{\text{EtOH}}$  228 m $\mu$ , log  $\epsilon$  4.1. The main product of such experiments, however, was clearly a different cyclopentenone system than XX: the crude material had  $\lambda_{\max}^{\text{EtOH}} \sim 240$  m $\mu$  while the infrared spectrum, although different from that of XX nevertheless clearly revealed by its intense  $\sim 6.1$   $\mu$  band coupled with the carbonyl absorption at  $\sim 5.82$   $\mu$  its cyclopentenone nature. The position of the ultraviolet absorption band (corresponding to one more degree of substitution than is present in XX) together with the isolation from the crude material of a crystalline semicarbazone, m.p. 174–176° which analysis showed to be that of a decarboxy derivative of XX, leaves no doubt that this product has the structure shown in XIX.

A likely reaction sequence for the surprising formation of XIX from XVI is outlined.

The main point of interest here is the postulated participation of a  $\beta$ -lactone XVIII rather than the possible  $\gamma$ -lactone XVIIIa involving the other carboxyl group. This is not as unlikely as might initially appear because the rigid system present in XVII removes most of the entropy difficulties which serve to explain the very slow formation of four-membered compared to three-membered rings. For instance, the rather closely

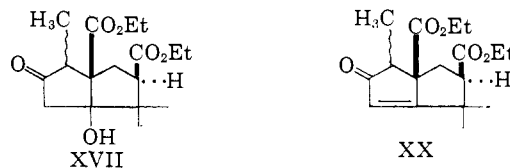


related  $\beta$ -lactone XXII has been shown to form easily when the hydroxy acid XXI is treated with acetic anhydride.<sup>10</sup> An important additional factor here is that the  $\gamma$ -lactone XVIIIa not only has the rather strained bicyclo[1,2,2]heptane



system, but additionally the equivalent of a diaxial methyl/methyl interaction, and consequently  $\gamma$ -lactone formation is here much less favorable than usual.

A successful solution of the vexing problem of achieving a satisfactory transformation of XVI into the bicyclic enone XX was reached by noting that the step XVII  $\rightarrow$  XVIII must be considerably slower than the formation of the aldol XVII from the methyl ketone XVI: Treatment of XVI for ten minutes at room temperature with potassium *t*-butoxide in *t*-butyl alcohol led to almost complete transformation into XVII as shown by infrared spectra (disappearance of bands due to XVI; appearance of hydroxyl absorption; no cyclopentenone peaks). The aldol XVII could then be dehydrated to the desired bicyclic enone XX by refluxing for one hour with *p*-toluenesulfonic acid in benzene solution.

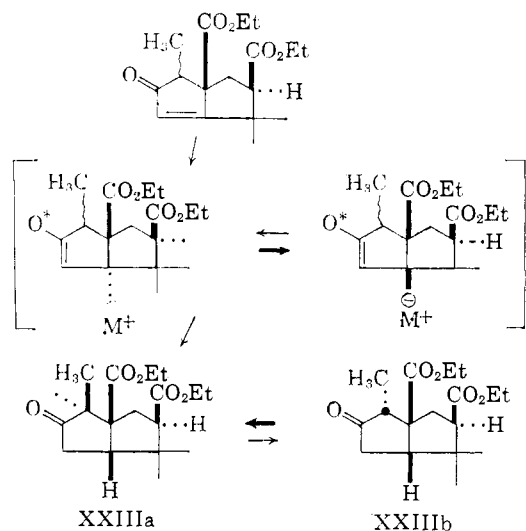


(10) N. J. Toivonen, P. Hirsjärvi, A. Melaja, A. Kainulainen, A. Halonen and E. Pulkkinen, *Acta Chem. Scand.*, **3**, 991 (1949).

The numerous difficulties we had encountered with the XVI  $\rightarrow$  XX conversion made the almost 80% yield of crude crystalline XX a source of considerable satisfaction.

We are now ready to consider the establishment of the *cis* fusion of rings A and B. Two methods come into consideration in this particular case: Reduction of XX can be carried out either catalytically or chemically. The stereochemical course of the catalytic hydrogenation of a system such as XX is not easily predictable because catalyst-substrate hindrance appears considerable on either side of the molecule. Such hindrance as exists would seem to favor adsorption from the side opposite the two carbethoxyl groups and might then lead to a *trans* A/B junction, but the considerably higher energy of the *trans* form of the [0,3,3] bicyclo-octane system than that of the *cis* isomer<sup>4</sup> might well raise the energy of the hydrogenation transition state leading to the *trans* system to a higher value than that leading to the *cis*.

Chemical reduction of the bicyclic enone XX with lithium-liquid ammonia would, on the other hand, be expected to lead to the desired *cis* A/B stereochemistry<sup>11</sup>: Of the two products in which the 4a-hydrogen is axial to ring A, the isomer with the *cis* A/B system is certainly the more stable. It was of course necessary to carry out the reduction without much excess lithium to prevent as much as possible reduction of the ester functions. Under such conditions the saturated ketodiester XXIIIa was obtained and characterized as its 2,4-dinitrophenylhydrazone, m.p. 152–154°, after crystallization from ethyl acetate-ethanol



With the authentic *cis*-bicyclic ketone XXIIIa in hand, it was now possible to investigate the course of the *catalytic* hydrogenation of XX: with palladium-charcoal as a catalyst, in ethanol solution, a saturated ketone was obtained as a crystalline solid, m.p. 33.5–35°. This was converted into a dinitrophenylhydrazone melting at 160–161° after recrystallization from ethanol. The same dinitrophenylhydrazone was obtained from the

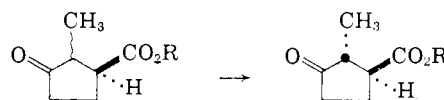
(11) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **82**, 1512 (1960). The bracketed structures in which O\* means either O- or O<sup>-</sup> illustrate the two conformations of the transition state for protonation.

oily mother liquors which remained after separation of the crystalline ketodiester. This ketodiester is correctly represented by XXIIIa and is identical with that from lithium-ammonia reduction: the disparity in melting points of the dinitrophenylhydrazones from the two sources was due to dimorphism. Recrystallization of the 160–161° form from ethyl acetate-ethanol converted it to the allomorph, m.p. 152–154°, undepressed on admixture with the product from the lithium-ammonia reduction.

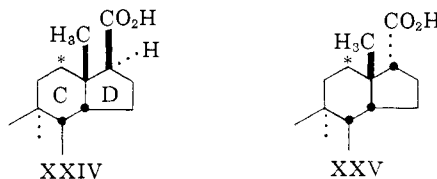
The demonstration that catalytic hydrogenation of XX gives the *cis*-bicyclic ketodiester XXIIIa substantiated our speculations on the possible stereochemical results of this particular reaction and greatly simplified the preparation of XXIIIa. In the latter, three of the asymmetric centers of norcedrenedicarboxylic acid have now been introduced while the fourth center—that bearing the methyl group in ring A—will now be considered: We will show that the more stable arrangement at the methyl-bearing carbon coincides in fact with that which exists in the norcedrenedicarboxylic acid molecule itself, *i.e.*, that the more stable arrangement of the methyl group is *cis* to the angular carboxyl group.

Such a conclusion is of some practical importance since the methyl group, being adjacent to the ketonic function in ring A, is readily equilibrated to the more stable arrangement, but it is also of considerable interest from a conformational analysis point of view.

We first point out that a conclusion opposite to that we have just mentioned above for XXIIIa would be reached by consideration of the simple "model" 2-methyl-3-oxocyclopentanecarboxylic acid which is certainly more stable with the methyl and carboxyl groups in *trans* relationship,<sup>12</sup> but it is immediately evident that this situation—which would be unfortunate for our purposes—



need not apply in the more complex case which concerns us here. A more closely related model is available in the 14-iso steroid series, for instance the pair of acids XXIV and XXV. Here again, the known position of equilibrium which is in

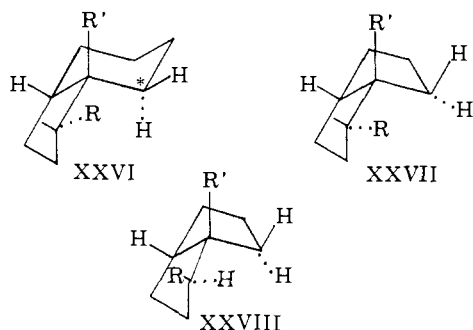


favor of XXV<sup>13</sup> might seem an unfavorable omen. We must, however, realize that the energy differences which will dictate which of the two isomers XXIIIa and XXIIIb is the more stable are quite

(12) Cf. A. P. Arendaruk, E. I. Budovskii, B. P. Gottikk, M. Y. Karpeiskii, L. I. Kudryashov, A. P. Skoldinov, N. V. Smirnova, A. Y. Khorlin and N. K. Kochetkov, *Zhur. Obshchei Khim.*, **27**, 1312 (1957).

(13) See, for instance, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **41**, 904 (1958).

small (of the order of one kilocalorie) and that consequently even as close a model as XXIV may be an improper one. Specifically, we can predict that the undesired *trans* arrangement of the methyl and carboxyl groups should be considerably *less* favorable in the *cis* five-five system than in a six-five model such as XXIV: Contraction from a six to a five-membered ring imposes a rotation on the starred carbon atom (*cf.* XXVI) such that the group R which in XXVI is staggered between the two hydrogens on the starred carbon is now opposed to one of them as in XXVII and the equilibrium should now be in favor of XXVIII.

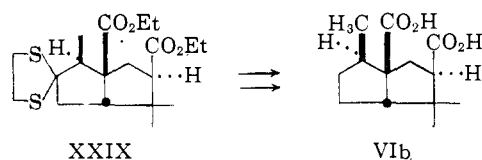


These considerations convinced us that in the particular system at hand the desirable stereochemical situation in which the 7-methyl group is *cis* to the angular carboxyl group (XXIIIa) would probably be favored if the methyl group were allowed to equilibrate to the more stable arrangement. The validity of the assumption was in any event soon verified by transformation to norcedrenedicarboxylic acid.

Before proceeding with the removal of the ketonic function of XXIIIa, it was necessary to establish whether the methyl group in XXIIIa was already in the more stable configuration: Prolonged refluxing of the ketodiester XXIIIa with 20% aqueous alcoholic potassium hydroxide led to a ketodiacid which was converted into its crystalline anhydride, m.p. 171–173°, on refluxing with acetic anhydride. Hydrolysis of the anhydride by refluxing with aqueous dioxane and esterification with diazoethane produced a ketodiester which had the same infrared spectrum as the original diester and which gave the same 2,4-dinitrophenylhydrazone (m.p. 159–161° from ethanol, alone or mixed with an authentic sample). This result establishes that the C<sub>7</sub>-methyl already possesses the more stable conformation in XXIIIa itself and confirms (reformation of XXIIIa from the anhydride) the *cis* disposition of the two carboxyl groups.

We now had to remove the carbonyl group of XXIIIa: Treatment of XXIIIa with ethanedithiol in the presence of anhydrous hydrogen chloride gave the crystalline thioketal XXIX, m.p. 75–76°, which was desulfurized by hydrogenolysis with Raney nickel. Saponification of the diester gave a crystalline diacid VIb, m.p. 221–223° after recrystallization from ether–pentane. This substance gave the analytical values expected for *dl*-norcedrenedicarboxylic acid and its infrared spectrum was indistinguishable from a sample of (–)-norcedrene-

dicarboxylic acid prepared from natural (+)-cedrol.



The conclusion that the dicarboxylic acid VIb was actually *dl*-norcedrenedicarboxylic acid was substantiated by the resolution of our synthetic acid. This proved remarkably easy: Slow evaporation of a solution of *dl*-norcedrenedicarboxylic acid and one equivalent of quinine in acetone produced a crop of crystals which after one recrystallization had the same rotation,  $[\alpha]^{27D} -123^\circ$ , as that of the quinine salt of authentic (–)-norcedrenedicarboxylic acid and did not depress its melting point. Regeneration of the resolved acid from its salt gave synthetic (–)-norcedrenedicarboxylic acid, m.p. 212–213°, undepressed by mixing with authentic material.<sup>14</sup> The rotation of the synthetic acid was  $[\alpha]^{27D} -38.9 \pm 1.5^\circ$  in acetone. The authentic (–)-acid has a rotation  $[\alpha]^{27D} -38.3 \pm 1.0^\circ$ .<sup>14</sup> Infrared spectra were, of course, also identical.<sup>15</sup>

We now have an extremely valuable synthetic intermediate for the further construction of the cedrol molecule and have incidentally established the position of the XXIIIa → XXIIIb equilibrium to be, as we had surmised, in favor of XXIIIa.

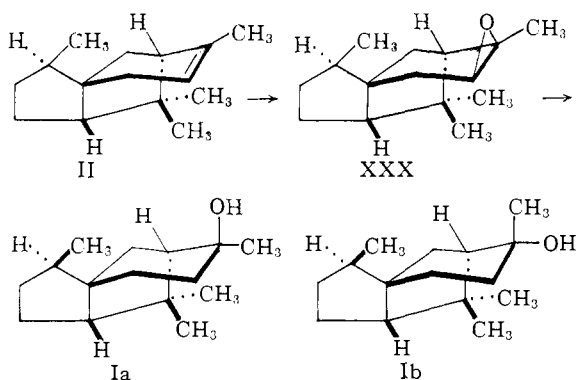
Before proceeding with the elaboration of ring C, it is necessary to settle the remaining stereochemical uncertainty. The synthetic route to norcedrenedicarboxylic acid establishes that cedrol is correctly represented by either Ia or Ib and rules out the other two possibilities which existed *a priori*.

A decision between Ia and Ib can be reached by noting that in Ia the tertiary hydroxyl group is axial while it is equatorial in Ib. We were able to show that Ib is the correct representation of the cedrol molecule in the following manner: Epoxidation of cedrene (II) can only take place from the side of ring C opposite the *gem*-dimethyl group which effectively blocks approach to the side of ring C facing it. The resulting epoxide XXX could be reduced with lithium aluminum hydride with the formation of an alcohol which was not oxidized by chromic acid and was therefore tertiary. This alcohol, which must be Ia, was not cedrol and the latter must then be represented by Ib.

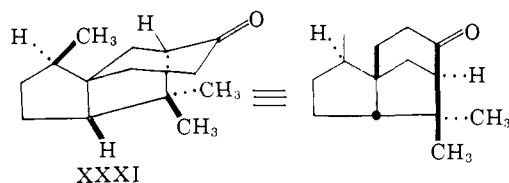
This conclusion not only settles the stereochemistry of the cedrol molecule, it also has definite synthetic implications. It would not be easily feasible, for instance, to synthesize cedrol *via* cedrene since direct hydration or, as we have just seen, epoxidation followed by reduction would lead to the epimeric axial alcohol. In fact the

(14) Norcedrenedicarboxylic acid from natural (+)-cedrol is reported to have m.p. 209° and  $[\alpha]^{14D} -39.4^\circ$  (in CHCl<sub>3</sub>); *cf.* ref. 16.

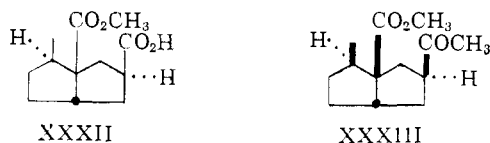
(15) The identity of our *cis* fused bicyclic diacid with norcedrenedicarboxylic acid from cedrol proves the *cis* fusion of the two 5-membered rings in cedrol itself. That equilibrium in the pair XXIIIa → XXIIIb is in favor of XXIIIa then follows from the fact that the experiments of Plattner, *et al.*,<sup>3</sup> rigorously establish that the C<sub>7</sub>-methyl must be *cis* to the 4a-hydrogen as discussed at the beginning of this paper.



stereochemistry of Ib strongly suggests that the desired result should be obtained by Grignard reaction on the ketone XXXI which thus became our next synthetic objective.



The half-methyl ester XXXII of norcedrenedicarboxylic acid was prepared, essentially as described previously by Plattner, *et al.*,<sup>16</sup> by the partial saponification of the dimethyl ester; the free carboxyl group was then transformed into a methyl ketone by either of two routes. The acid chloride prepared by reaction of XXXII with oxalyl chloride could be treated, as mentioned in an earlier paper,<sup>1</sup> with dimethylcadmium or the sequence acid chloride  $\rightarrow$  diazoketone  $\rightarrow$  chloromethyl ketone  $\rightarrow$  methyl ketone which we used for the conversion of XI into XVI could be employed. In spite of the number of steps, the efficiency of the latter sequence is extremely high and the crude methyl ketone XXXIII is thus obtained in 95% yield from the half-acid. The methyl ketone ester was characterized by its 2,4-dinitrophenylhydrazone, m.p. 140–142°. The same dinitrophenylhydrazone was obtained from the methyl ketone made by either route. Treatment of the crude ketoester XXXIII with potassium *t*-butoxide in



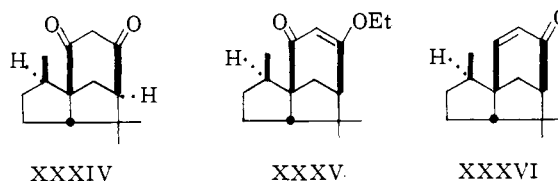
*t*-butyl alcohol resulted in cyclization in high yield to the  $\beta$ -diketone XXXIV, m.p. 202–204°.

In the  $\beta$ -diketone XXXIV we have built up the skeleton of the desired ketone XXXI and it is only necessary to remove the extra carbonyl group. Reduction with lithium aluminum hydride of the enol ether mixture prepared from the  $\beta$ -diketone was initially considered a plausible route to the cyclohexenone XXXVI<sup>17</sup> on the assumption that the

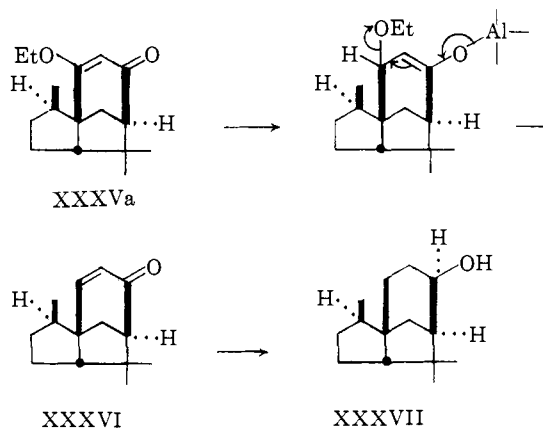
(16) Pl. A. Plattner, G. W. Kusserow and H. Kläui, *Helv. Chim. Acta*, **25**, 1345 (1942).

(17) Cf. R. L. Frank and H. K. Hall, Jr., *J. Am. Chem. Soc.*, **72**, 1645 (1950).

major enol ether should be XXXV. Remarkably, the only crystalline product isolated from the re-



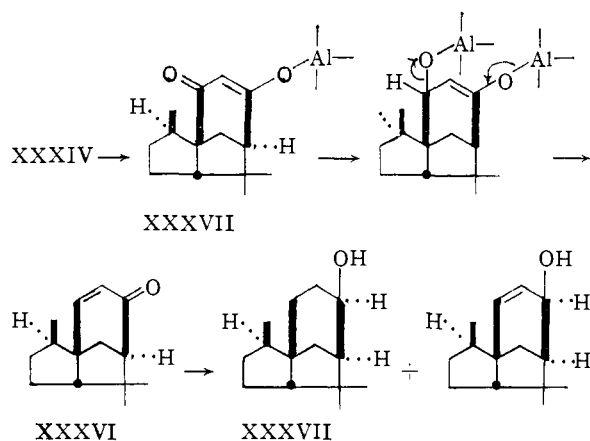
duction was a small (*ca.* 18%) yield of a saturated alcohol, m.p. 120–121°, later identified (see below) as the alcohol XXXVII. Its formation, while surprising, can be rationalized from the isomeric enol ether XXXVa undoubtedly present in the mixture. The structure of the alcohol XXXVII follows



from an unambiguous synthesis: Reduction of the ketoester XXXIII with lithium aluminum hydride followed by oxidation with chromic acid-pyridine<sup>18</sup> led to the crude related ketoaldehyde. This was cyclized with aqueous base to the cyclohexenone XXXVI which was characterized as its 2,4-dinitrophenylhydrazone, brilliant red prisms, melting at 164–167°. Reduction of the crude cyclohexenone with palladium-charcoal to the corresponding saturated ketone and treatment of the latter with lithium aluminum hydride gave the crystalline alcohol XXXVII, m.p. 120–121° alone or mixed with the previously obtained sample.

Although we had thus available the alcohol corresponding to the ketone which was our immediate synthetic objective, the yields in either sequence were low and it seemed desirable to find a better route. The course of the reduction of the enol ether of the  $\beta$ -diketone XXXIV suggested that the latter substance itself should result in the formation of the alcohol XXXVII or of the corresponding cyclohexenol: Salt formation on addition of lithium aluminum hydride to the  $\beta$ -diketone XXXIV should lead predominantly to the structure XXXVIII since the aluminum is thus attached to the less hindered oxygen (see selective formation of the half-ester XXXII). Further reduction would then result in the cyclohexenone XXXVI. It might be expected that XXXVI would then be reduced to the unsaturated alcohol, but the reduction product was mainly saturated alcohol: Oxida-

(18) Cf. G. I. Poos, W. F. Johns and L. H. Saret, *ibid.*, **77**, 1026 (1954).



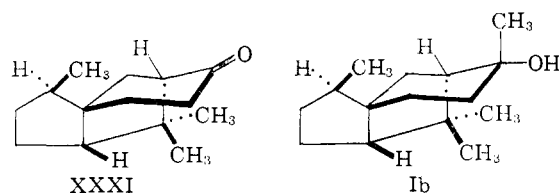
tion of the alcohol mixture gave ketones, the ultra-violet spectrum of which indicated only 10–15%  $\alpha,\beta$ -unsaturated carbonyl. The main constituent of the alcohol mixture was in fact the same crystalline alcohol XXXVII, m.p. 120–121°, which we had obtained previously. Whether the saturated alcohol comes from 1,4-reduction of the enone XXXVI followed by reduction of the ketone, liberated from its enolate during work-up, by excess hydride, or whether the saturated alcohol is produced by hydride reduction of the double bond of initially formed unsaturated alcohol is not known. In either case the facile reduction of the double bond implies unusual reactivity presumably because of the strain involved in putting a double bond in this particular position.<sup>19,20</sup>

Oxidation of the now readily available alcohol XXXVII with chromic acid gave the ketone XXXI, characterized as its 2,4-dinitrophenylhydrazone, m.p. 146–147°. Addition of the ketone to a solution of methyl lithium in ether followed by refluxing gave, as anticipated, (+)-cedrol (Ib), m.p. 86–87° after recrystallization from aqueous methanol. The melting point of the mixture with natural cedrol, m.p. 86–87°, was undepressed. The infrared spectrum of the synthetic material was identical with that of natural cedrol. Finally, the rotation of the synthetic cedrol in chloroform was  $[\alpha]_D^{25} +10.5 \pm 0.8^\circ$  and that of natural cedrol was  $[\alpha]_D^{25} +9.9 \pm 0.4^\circ$ .<sup>21</sup> The stereospecific

(19) The reduction of a *symmetrical*  $\beta$ -diketone with lithium aluminum hydride has been reported by A. S. Dreiding and J. A. Hartman, *ibid.*, **75**, 3723 (1953), and was shown to proceed, essentially as we have outlined here, to the allylic alcohol. The above results suggest that the reduction of *unsymmetrical*  $\beta$ -diketones in which one of the carbonyls is considerably more hindered than the other might generally result in the removal of the more hindered oxygen function. This could be of considerable synthetic utility but would have to be examined in further cases before any confidence could be placed in the anticipated result.

(20) The spectrum of the crude enone XXXVI from the cyclization of the ketoaldehyde had  $\lambda_{\text{max}}^{\text{EtOH}}$  243  $m\mu$  (see Experimental). This indicates considerable strain in the ground state (expected  $\lambda_{\text{max}}$  227  $m\mu$ ) thus resulting in lower energy for the transition to the excited state. It is presumably this strain which causes the easy reduction of the double bond of XXXVI or the corresponding allylic alcohol during the lithium aluminum hydride reaction.

(21) The melting point of natural cedrol is reported to be 86–87° while the rotations include  $[\alpha]_D +9^\circ 31'$  and  $+10^\circ 31'$  (in chloroform). See E. Guenther, "The Essential Oils," Vol. II, D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 284. The rotation reported here was obtained by us on a sample of the natural crystalline substance.



synthesis of cedrol is thus complete and its stereochemistry is established as Ib.<sup>22,23</sup>

### Experimental

Ethyl 2,3-dicyano-3-methylbutyrate was prepared according to Smith and Horwitz.<sup>24</sup> Yields of 76% to 82% were obtained; b.p. 99–114° (ca. 0.01 mm.). When the product was distilled at a higher pressure, b.p. 120–127° (4 mm.) with a bath temperature of 165–170° some decomposition took place and the infrared spectrum of the product showed a double bond band at 6.18  $\mu$  which was lacking in the spectrum of the product obtained by distillation at the lower pressure.

Ethyl 2-methylpentane-2,3,4-tricarboxylate (VII) was prepared in the following manner. Ethyl 2,3-dicyano-3-methylbutyrate was cyanoethylated with acrylonitrile in *t*-butyl alcohol using choline as a catalyst. The crude product was isolated and hydrolyzed to the triacid without purification. After removal of water and ammonium chloride from the hydrolysis mixture, the triacid was esterified with alcohol and sulfuric acid to give the triester VII. The following details are typical of the procedure used.

Ethyl 2,3-dicyano-3-methylbutyrate (250 g.) was dissolved in 232 g. of *t*-butyl alcohol, and 87 g. of acrylonitrile and 5.0 ml. of a 40% solution of choline in methanol were added. The reaction mixture was surrounded with ice for 6 hours, then left at room temperature for 18 hours and finally at 50° for 40 hours. The reaction mixture was then poured into a separatory funnel and cooled until crystals of *t*-butyl alcohol began to appear in the upper layer. The top layer was then separated and the solvent removed on the steam-bath under reduced pressure. The residue was combined with the bottom layer, ether was added and the solution was washed 5 times with a cool solution of sodium chloride. The aqueous layer was washed once with ether, the ether layers were combined and the solvent was removed on the steam-bath under reduced pressure.

The combined residues from two batches (638 g.) were dissolved in 1300 ml. of concentrated hydrochloric acid and 1300 ml. of water was added. The solution was refluxed for 48 hours and then evaporated to near dryness in two large evaporating dishes left on steam-baths overnight. In the morning the mixture was cooled and the ammonium chloride collected by suction filtration. The filtrate was taken to dryness on the steam-bath, under reduced pressure, to give an oily solid. The ammonium chloride was washed thoroughly with absolute alcohol and the oily solid was dissolved in the alcohol washings and filtered from ammonium chloride.

To the filtrate (3500 ml.) was added 700 ml. of concentrated sulfuric acid while stirring in an ice-bath. The solution was refluxed for 4.5 days. Then about 1 l. of the alcohol was distilled off and the remainder of the solution was cooled and poured (in three portions), into saturated sodium chloride solution. The ester, which separated as an oil, was washed with fresh sodium chloride solution and the aqueous washings were extracted with ether. The ether extract was dried (sodium sulfate) and the solvent removed

(22) The *absolute* configuration, now that the relative configuration is known, can be shown to be as implied in all the structures used in this paper: Ozonization of the exocyclic double bond isomer of cedrene, obtained by pyrolysis of the acetate of natural (+)-cedrol gave (+)-norcedranone (XXXI). This showed a positive Cotton effect curve and therefore the absolute configuration shown in XXXI (see C. Djerassi "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960). The same conclusion as to absolute configuration has recently been reached on a different basis by Büchi, *et al.* (G. Büchi, R. E. Erickson and N. Wakabayashi, *J. Am. Chem. Soc.*, **83**, 927 (1961)).

(23) A preliminary report of this synthesis has been published: G. Stork and F. H. Clarke, Jr., *ibid.*, **77**, 1072 (1955).

(24) P. A. S. Smith and J. P. Horwitz, *ibid.*, **71**, 3418 (1949).

to give more of the triester. Distillation of the ester gave a small forerun and a main fraction (480 g.), b.p. 134–160° (ca. 0.01 mm.), with a residue of 158 g. Redistillation of the main fraction gave 410 g., b.p. 154–156° (ca. 0.01 mm.). The residues from the distillations were hydrolyzed and reesterified to give more of the triester.

Ethyl 3,3-dimethylcyclopentan-3-one-1,4-dicarboxylate (VIII) was prepared according to Gibson, *et al.*,<sup>5</sup> using powdered sodium in benzene. The sodium was powdered with fast stirring in boiling toluene. An oversize reaction flask was necessary because the reaction once started was vigorous. Usually a few drops of ethanol was added to the boiling benzene solution to initiate the reaction. After the vigorous reaction had subsided the mixture was refluxed for 3 hours and worked-up as described.<sup>5</sup> The product was distilled through a Vigreux column, under good diffusion pump vacuum, at 132–133° to give the cyclic keto-diester in 64% yield.

Benzyl  $\alpha$ -bromopropionate was prepared by dissolving 34.0 g. of benzyl alcohol, 48.0 g. of  $\alpha$ -bromopropionic acid and about 0.5 g. of *p*-toluenesulfonic acid in 150 ml. of benzene and refluxing the solution for 18 hours with a water separator. To the cooled benzene solution ether was added and the solution was washed three times with ice-cold 5% sodium hydroxide solution, dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was distilled at 139–141° (7 mm.) to give 55.5 g. of ester (73% yield).

Alkylation of the Cyclic Keto-diester.—The cyclic keto-diester VIII was converted to its sodium salt and alkylated with benzyl  $\alpha$ -bromopropionate as follows. To 6.0 g. of sodium hydride and 100 ml. of dry benzene was added 50.0 g. of the cyclic keto-diester VIII in 80 ml. of dry benzene. The solution was refluxed until hydrogen evolution had ceased and was then decanted from unreacted sodium hydride. The latter was washed with 30 ml. of dry benzene and the combined benzene solutions were distilled until 155 ml. of distillate had been collected. To the residual solution of the sodium salt 47.5 g. of benzyl  $\alpha$ -bromopropionate and 100 ml. of dry dimethylformamide (dried by azeotropic distillation with 10% of benzene; b.p. 148–153°), was added and the mixture was heated at 50° under a nitrogen atmosphere. A second batch of 71.1 g. of the cyclic keto-diester was alkylated simultaneously using proportionate amounts of reagents. At the end of 1 week the solutions were combined and poured into ether. The ether solution was washed three times with ice-cold 5% sodium hydroxide solution and three times with water, then dried over anhydrous sodium sulfate and the solvent distilled. A short-path distillation of the residue using good diffusion pump vacuum gave 179 g. (90% yield) of the triester X boiling at 175–192° at a bath temperature of 200–205°.

Hydrogenolysis of the Benzyl Ester.—The benzyl ester X (77.0 g.) was hydrogenolyzed with 8.0 g. of 10% palladium-on-charcoal catalyst in 150 ml. of ethyl acetate, using a Parr shaker. The pressure fell from 50.0 lb. to 33.0 lb. in 12 minutes and to 32.6 lb. in 35 minutes when the hydrogen uptake ceased. The palladium-charcoal was collected on Celite and washed with dry ether. The ether and most of the ethyl acetate were removed on the steam-bath under reduced pressure. The residue was poured into an erlenmeyer flask and boiling petroleum ether (b.p. 30–60°) was added until an oil precipitated out of solution. The oil crystallized on seeding and 47.0 g. of oily crystals was collected. Three recrystallizations from cyclohexane gave 27.0 g. (45% yield) of the acid XI as colorless rectangular prisms, m.p. 113–115°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>24</sub>O<sub>7</sub>: C, 58.52; H, 7.37. Found: C, 58.47; H, 7.43.

Preparation of the Chloromethylketone XV.—The crystalline acid XI was transformed first to the dry sodium salt, and then to the acid chloride with oxalyl chloride. Treatment of the acid chloride with diazomethane gave a crystalline diazoketone which was transformed directly into the chloromethyl ketone with hydrogen chloride in ether solution.

To prepare the sodium salt, the crystalline acid XI was powdered in a mortar and mixed with a 5% excess of sodium bicarbonate. The mixture was placed in an oversize flask, water was added, and the mixture was stirred until the solid had all dissolved. The water was then removed under vacuum at room temperature or lower.

For the preparation of the acid chloride XII the dry sodium salt (11.6 g.) was powdered and covered with 100 ml. of dry benzene which contained 1.0 ml. of pyridine. The mixture was cooled until the benzene was partly frozen and 15 ml. of oxalyl chloride was added. The benzene melted from the heat of reaction and the mixture was left at room temperature for an hour and a half. The mixture was then cooled in ice and the oxalyl chloride and benzene were removed under vacuum at room temperature or lower. Traces of oxalyl chloride were removed by adding fresh benzene and removing it under reduced pressure as before. The residue was taken up in benzene and the precipitated salts were removed by filtration through Celite.

To form the diazoketone, the benzene solution of the acid chloride was poured slowly into an excess of diazomethane in ether (previously prepared from 45 g. of nitrosomethylurea and dried for several hours at 0° over potassium hydroxide pellets). The solution was left in an ice-bath for an hour and a half and then the diazomethane and ether were removed on the steam-bath in the hood. The residual benzene solution was taken to dryness under reduced pressure to give an orange colored oil which crystallized on standing or seeding.

The crude diazoketone XIV was converted to the chloromethylketone by dissolving it in 150 ml. of dry ether and passing an excess of dry hydrogen chloride into the ice-cooled solution. The solution was filtered through cotton and evaporated under reduced pressure. The crude oil which remained after removal of the ether crystallized exothermally on seeding. The solid chloromethylketone was dissolved in cyclohexane and most of the color was removed with activated charcoal. Concentration of the solution and seeding gave 10.7 g. (90% yield) of the chloromethyl ketone XV as yellow crystals, m.p. 65–70°. A portion of the chloromethylketone, after several recrystallizations from cyclohexane, melted at 72–73°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>26</sub>O<sub>6</sub>Cl: C, 56.58; H, 6.98. Found: C, 56.41; H, 7.08.

Reduction of the Chloromethylketone XV.—The chloromethylketone XV (19.2 g.) and 20 g. of powdered potassium iodide were dissolved in 250 ml. of glacial acetic acid. Zinc dust (100 g.) was then added slowly with stirring at 25° and stirring was continued for 6 hours. Water (50 ml.) was then added and stirring was continued overnight. The solids were filtered off and washed with 80% acetic acid. The combined washings and filtrate were taken to dryness on the steam-bath under reduced pressure and the residue was taken up in water and ether. The ether solution was washed with water, then three times with aqueous potassium carbonate solution containing some sodium thiosulfate. Finally, the ether solution was again washed with water, then dried over anhydrous potassium carbonate and the ether was removed to give an oily residue which crystallized on standing to give 17.1 g. (m.p. 50–57°). The solid was dissolved in petroleum ether (b.p. 30–60°) and the solution was treated with activated carbon, then concentrated and cooled. Colorless crystals of the methyl ketone XVI were obtained which melted at 55–60°, yield 15.3 g. (88%). A portion of the methylketone was distilled twice in high vacuum at 105° for analysis.

*Anal.* Calcd. for C<sub>17</sub>H<sub>26</sub>O<sub>6</sub>: C, 62.56; H, 8.03. Found: C, 62.34; H, 7.92.

The semicarbazone formed in poor yield either in pyridine-ethanol or with sodium acetate in aqueous ethanol. Colorless crystals, m.p. 191–193°, were obtained after recrystallization from ethanol-water and drying for analysis in a high vacuum at the temperature of boiling methanol.

*Anal.* Calcd. for C<sub>18</sub>H<sub>28</sub>O<sub>6</sub>N<sub>2</sub>: C, 56.38; H, 7.62. Found: C, 56.41; H, 7.91.

Cyclization of the Methylketone XVI.—Repeated attempts to obtain the cyclopentenone XX directly from the methylketone XVI using potassium *t*-butoxide in refluxing *t*-butyl alcohol gave only low yields of the desired product. A considerable quantity of the cyclopentenone monoester XIX was formed simultaneously: To a solution of 0.7 g. of potassium in 70 ml. of dry *t*-butyl alcohol was added 4.3 g. of the crude methyl ketone XVI in 30 ml. of dry *t*-butyl alcohol and the mixture was refluxed for 3 hours under nitrogen. Addition to cold water, extraction with ether, followed by washing of the ether extracts twice with cold 5% sulfuric acid, twice with water, six times with 5% sodium hydroxide, drying over sodium sulfate and removal of



solvent gave 1.47 g. of a neutral fraction with an ultraviolet maximum at 237  $m\mu$ . Distillation under diffusion pump vacuum gave a mobile oil at a temperature of 100–110° which still showed  $\lambda_{\max}^{\text{EtOH}}$  237  $m\mu$ .

A mixture of 0.4 g. of the above oil, 0.4 g. of semicarbazide hydrochloride, 1.65 ml. of pyridine and 8 ml. of ethanol was refluxed for 1.5 hours and allowed to stand overnight. Removal of the solvent under reduced pressure and trituration with ether gave an ether extract which left a gum after evaporation. Crystallization was effected from benzene-cyclohexane to give the semicarbazone of the cyclopentanone monoester XIX. After three recrystallizations from ethyl acetate-cyclohexane the semicarbazone melted at 174–176°.

*Anal.* Calcd. for  $C_{15}H_{23}O_3N_3$ : C, 61.41; H, 7.90; N, 14.33. Found: C, 61.51; H, 8.12; N, 14.80.

It was eventually found that if the *t*-butoxide reaction was carried out for a short time at room temperature the intermediate aldol could be isolated in high yield and this could easily be dehydrated with acid catalysis to give the cyclopentenone XX.

Potassium (3.0 g.) was dissolved with refluxing in 150 ml. of dry *t*-butyl alcohol. The solution was cooled to room temperature and added to a solution of 20.1 g. of the methyl ketone XVI (m.p. 55–60°) in 150 ml. of dry *t*-butyl alcohol. The resulting deep red solution was left at room temperature for 10 minutes and then poured into a mixture of ether and water. The aqueous layer was separated and washed twice with ether. The ether extracts were washed repeatedly with sodium chloride solution until the aqueous layer was colorless and neutral. The ether solution was dried over anhydrous sodium sulfate and the solvent was removed on the steam-bath, finally under reduced pressure. The crude aldol (18.6 g.) was a mobile yellow oil, the infrared spectrum of which possessed a strong hydroxyl band at 2.8  $\mu$ .

The aldol was dehydrated without purification by dissolving it with 2.0 g. of *p*-toluenesulfonic acid monohydrate in 400 ml. of benzene and refluxing for 1 hour. After cooling, the benzene solution was washed three times with potassium carbonate solution and the aqueous solutions were washed twice with ether. The organic layers were combined, dried over anhydrous potassium carbonate and the solvent was removed under reduced pressure. Petroleum ether (b.p. 30–60°, *ca.* 30 ml.) was added to the oily residue and, after seeding, the mixture was left in the refrigerator for several days. The crystalline cyclopentenone XX was collected to give 15.2 g., m.p. 46–56° (80% yield),  $\lambda_{\max}^{\text{EtOH}}$  228  $m\mu$ ,  $\log \epsilon$  4.06.

Crystalline cyclopentenone preparations melting over the range of 46–60° were obtained from a total of 32.1 g. of the methylketone and combined to give 23.6 g. These were recrystallized from petroleum ether (b.p. 30–60°) to give a first crop of 11.4 g. of large crystals, m.p. 63–66°, and a second crop of 8.0 g., m.p. 48–58°. Recrystallization of the first crop using charcoal gave 10.8 g. of colorless crystals, m.p. 65–67°. The yield of this isomer was 35%. A sample was evaporatively distilled in high vacuum at 90° for analysis.

*Anal.* Calcd. for  $C_{11}H_{20}O_2$ : C, 66.21; H, 7.85. Found: C, 66.06; H, 7.87.

Attempts to purify a second isomer of the cyclopentenone XX by recrystallization from petroleum ether were unsuccessful.

**Reduction of the Cyclopentenone XX.**—The cyclopentenone XX (m.p. 65–67°, 504 mg.) was dissolved in 16 ml. of absolute ethanol and hydrogenated at atmospheric pressure using 136 mg. of 10% palladium-on-charcoal catalyst. The uptake of hydrogen was 38.7 ml. in 20 minutes at 25.4° (calculated uptake: 40.0 ml.). The palladium-charcoal was collected on a mat of filter-aid and washed well with alcohol. The solvent was removed on the steam-bath under reduced pressure to give 486 mg. of a colorless oil. The oil crystallized on cooling in ice and the solid was collected and recrystallized once from petroleum ether (b.p. 30–60°) to give 325 mg. of colorless crystals of the keto diester XXIIIa, m.p. 33.5–35.0°. The oil obtained from the mother liquors was converted to the 2,4-dinitrophenylhydrazone. After two recrystallizations from ethanol the melting point was constant at 160–161°. The same 2,4-dinitrophenylhydrazone (same melting point and mixture melting point) was obtained from the crystalline keto diester.

*Anal.* Calcd. for  $C_{23}H_{30}O_8N_4$ : C, 56.32; H, 6.17. Found: C, 56.26; H, 6.04.

The 2,4-dinitrophenylhydrazone was peculiar in that when recrystallized from ethyl acetate-ethanol it formed matted needles which slowly changed to hard compact prisms on standing in the solution.

**Lithium-Liquid Ammonia Reduction of the Cyclopentenone XX.**—The cyclopentenone XX (307 mg.) was dissolved in 2 ml. of dry tetrahydrofuran and the solution added to 15 ml. of anhydrous liquid ammonia. With vigorous stirring 15 to 20 mg. of lithium was added and the color changed to yellow, pink, blue and finally the solution became colorless in about 10 seconds. Ammonium chloride (0.6 g.) was then added and, after stirring for a short time, the ammonia was allowed to evaporate. The residue was taken up in ether and water and the ether solution, after washing several times with water, was dried over anhydrous sodium sulfate and evaporated. The residue, 271 mg., was a yellowish oil. It was mostly dissolved in petroleum ether (b.p. 30–60°) and chromatographed on Merck alumina. The first eluates, using benzene-petroleum ether (1:1), were yellowish and contained some enone (as judged from the infrared spectra). Later fractions were colorless, however, and these were combined (115 mg.) and converted to the 2,4-dinitrophenylhydrazone (134 mg., m.p. 115–125°). The crystals of the 2,4-dinitrophenylhydrazone which were dimorphic from ethyl acetate-ethanol, melted at 152–154° after three recrystallizations from this solvent mixture. The mixture melting point with the 2,4-dinitrophenylhydrazone prepared from the palladium-charcoal reduced keto diester (also dimorphic crystals from ethyl acetate-ethanol; m.p. 152–154°) was not depressed. It is concluded that the more stable *cis* ring junction of the five-membered rings is present in the keto diester XXIIIa prepared by palladium-charcoal reduction of the cyclopentenone XX.

**Stereochemistry of Substituents in the Reduced Keto diester XXIIIa.**—The stereochemical relationship of the secondary methyl, and of the secondary ester to the tertiary ester in the reduced keto diester XXIIIa was deduced from the following series of experiments. The keto diester XXIIIa (655 mg.) was hydrolyzed by dissolving it in 10 ml. of 80% ethanol containing 2.0 g. of potassium hydroxide and refluxing for 36 hours under nitrogen. The solution was poured into water and the aqueous solution was washed twice with ether. The aqueous solution was then acidified with concentrated hydrochloric acid and the precipitate was removed by ether extraction. The ether solution was dried over anhydrous sodium sulfate and evaporated to give a gummy residue (528 mg.) which would not crystallize. The residue was therefore converted directly to the anhydride by refluxing for 3 hours in 6 ml. of acetic anhydride. The solvent was removed in a stream of nitrogen, finally on the steam-bath under reduced pressure. The brown residue solidified and was sublimed in high vacuum at 160–170° to give a colorless sublimate of oily crystals. Trituration with ether gave 174 mg., m.p. 154–172°. One recrystallization from ether gave 117 mg. of the anhydride as colorless prisms, m.p. 171–173° (infrared: 5.55 and 5.66  $\mu$ ).

The anhydride was hydrolyzed by dissolving it in 6 ml. of 50% aqueous dioxane and refluxing the solution for 20 hours. Removal of the solvent, first under nitrogen and finally on the steam-bath under reduced pressure, gave a viscous oil. The oil was dissolved in ether and added to an ethereal solution of diazoethane (prepared from 5 ml. of *N*-nitroso-*N*-ethyl carbamate) and the solution was left at room temperature for 1 hour. The solvent was removed under reduced pressure, then toluene was added and removed three times on the steam-bath under reduced pressure. The residue was taken up in petroleum ether (b.p. 30–60°) and the solution was filtered and evaporated. The residual yellow oil was evaporatively distilled at 100–110° in a high vacuum. The infrared spectrum of the distillate (102 mg.) was the same as that of the starting keto diester XXIIIa. The 2,4-dinitrophenylhydrazone was prepared, and after four recrystallizations from ethanol the melting point was constant at 159–161°. The mixture melting point with the 2,4-dinitrophenylhydrazone of the starting keto diester XXIIIa (m.p. 159–161° from ethanol) was not depressed.

Since the methyl group alpha to the carbonyl was not isomerized by the treatment with strong base, it must already be in the more stable configuration in the keto diester XXIIIa.

***dl*-Norcedrenedicarboxylic Acid (VIb).**—This diacid could be obtained from the keto-diester XXIIIa by Raney nickel desulfurization of the corresponding thioketal followed by alkaline hydrolysis. To form the thioketal the keto-diester XXIIIa (m.p. 31–34°, 1.03 g.) was dissolved in 10 ml. of chloroform and 1.0 ml. of ethane dithiol was added. The solution was then cooled, saturated with dry hydrogen chloride and left at 0° overnight. The solvent was then removed on the steam-bath under reduced pressure and toluene was added and removed in this manner three times. The residue was a colorless oil which crystallized on standing. The solid thioketal was collected and washed with petroleum ether (b.p. 30–60°) to give 0.86 g. of colorless crystals, m.p. 72–75°. After several recrystallizations from pentane the pure thioketal XXIX melted at 75–76°.

*Anal.* Calcd. for  $C_{10}H_{18}O_4S_2$ : C, 59.05; H, 7.83. Found: C, 59.23; H, 7.77.

For the desulfurization the thioketal (1.32 g., m.p. 72–75°) was dissolved in 125 ml. of absolute ethanol in which was suspended Raney nickel prepared according to Pavlic and Adkins<sup>28</sup> from 50 g. of Raney nickel alloy. The mixture was refluxed with stirring for 15 hours. After cooling, the Raney nickel was collected on filter aid and washed well with ethanol. The solvent was removed on the steam-bath under reduced pressure. The residue was taken up in ether and the solution was filtered and evaporated to give 0.86 g. of the diester of *dl*-norcedrenedicarboxylic acid as a colorless mobile oil.

The diester (0.82 g.) was hydrolyzed in 10 ml. of 95% ethanol containing 2.0 g. of potassium hydroxide by refluxing the solution for 24 hours. After cooling, the mixture was poured into water and the aqueous solution was washed well with ether and acidified with 10 ml. of concentrated hydrochloric acid. The precipitated diacid was removed by ether extraction. The ether solution, after drying over anhydrous sodium sulfate, was evaporated to give 0.62 g. of *dl*-norcedrenedicarboxylic acid (VIb) as a colorless crystalline solid, m.p. 210–215°. One recrystallization from ether–pentane gave 454 mg., m.p. 219–221°. Further recrystallizations from ether–pentane did not raise the melting point above 221–223°. The infrared spectrum was the same as that of (–)-norcedrenedicarboxylic acid from natural cedrene.

*Anal.* Calcd. for  $C_{18}H_{20}O_4$ : C, 64.98; H, 8.39. Found: C, 65.02; H, 8.36.

**Resolution of *dl*-Norcedrenedicarboxylic Acid.**—To a hot solution of 410 mg. (1.0 equiv.) of quinine in acetone was added a solution of 300 mg. of *dl*-norcedrenedicarboxylic acid in acetone. No precipitate appeared when the stoppered flask was allowed to stand at room temperature for 24 hours, but when the flask was left open to permit slow evaporation of the solvent colorless crystals formed and were collected after one day. This first crop, m.p. 204–206°, weighed 156 mg. Concentration of the mother liquor and seeding with the first crop gave more crystals. There was obtained a total of 252 mg. (71% of theory) which melted above 204°. One recrystallization from chloroform–acetone gave 210 mg., m.p. 209–210°,  $[\alpha]_D^{25} -123^\circ$  ( $c$  1.04, chloroform). One more recrystallization from chloroform–acetone did not change the melting point or rotation and there was no depression of the melting point of the mixture with the quinine salt of natural norcedrenedicarboxylic acid, m.p. 209–210°,  $[\alpha]_D^{25} -122^\circ$  ( $c$  1.00, chloroform).

*Anal.* Calcd. for  $C_{22}H_{24}O_6N_2$ : C, 70.18; H, 7.85. Found: C, 70.13; H, 8.18.

To obtain the free acid, the quinine salt (121 mg.) was shaken for 15 minutes with 5 ml. of 6 *N* hydrochloric acid and the solid was collected and washed with 6 *N* hydrochloric acid. The free acid weighed 46 mg. (89% yield), m.p. 212–213°. One recrystallization from ether–pentane did not change the melting point and the mixture melting point with natural norcedrenedicarboxylic acid (m.p. 213–214°<sup>14</sup>) was not depressed. The optical rotation of the resolved diacid in acetone solution,  $[\alpha]_D^{25} -38.9 \pm 1.5^\circ$  ( $c$  1.08), is the same as the rotation of the natural (–)-norcedrenedicarboxylic acid,  $[\alpha]_D^{25} -38.3 \pm 1.0^\circ$  ( $c$  1.09), in acetone.<sup>14</sup>

**Monomethyl ester of (–)-norcedrenedicarboxylic acid (XXXII)** was prepared according to Plattner, Kusserow and Kläui<sup>16</sup> by the half hydrolysis of NCDA dimethyl ester.

The latter was prepared by adding solid VIb to an excess of diazomethane in ether solution. From 10.00 g. of NCDA (m.p. 212–213°) a yield of 10.59 g. of the dimethyl ester (b.p. 95–132° (1 mm.)) was obtained.

For the hydrolysis, 10.5 g. of NCDA dimethyl ester was dissolved in 35 ml. of absolute ethanol containing 2.4 g. of potassium hydroxide and the solution was refluxed for 2 hours. The solution was cooled, poured into water and the aqueous solution washed three times with ether to remove unchanged diester (*ca.* 2 g.). After acidification with hydrochloric acid the NCDA monomethyl ester XXXII was removed by ether extraction. The ether extract was dried over anhydrous sodium sulfate and concentrated in an erlenmeyer flask. As the volume became small, petroleum ether was added slowly to the boiling solution to displace the ether. When crystals appeared the mixture was cooled and the colorless crystals were collected to give 6.20 g. of XXXII, m.p. 129–132° (reported<sup>16</sup> m.p. 130–131°).

The methylketone methyl ester XXXIII was prepared from NCDA monomethyl ester XXXII via the acid chloride, diazoketone and chloroketone by a procedure similar to that used in the preparation of the methylketone XVI.

The NCDA monomethyl ester XXXIII (8.05 g.) was converted to the acid chloride by dissolving it in 20 ml. of oxalyl chloride. The solution was left at room temperature for 1.5 hours and then excess oxalyl chloride was removed under reduced pressure. Dry benzene was then added and removed under reduced pressure three times.

The acid chloride was dissolved in dry ether and the solution poured into a solution of diazomethane in ether (prepared from 45 g. of *N*-nitroso-*N*-methylurea and dried over potassium hydroxide pellets). The solution was left at room temperature for 1 hour and then the excess diazomethane and the ether were removed on the steam-bath, finally under reduced pressure.

The crude diazoketone was dissolved in 50 ml. of dry ether and the solution was saturated at 0° with dry hydrogen chloride. The solvent was then removed on the steam-bath under reduced pressure.

The crude chloromethyl ketone was dissolved with 9 g. of potassium iodide in 100 ml. of 80% acetic acid, and 45 g. of powdered zinc was added slowly with stirring and cooling in ice. The mixture was stirred overnight at room temperature. The solids were then collected and washed well with 80% acetic acid. The solution was evaporated to dryness on the steam-bath under reduced pressure and the residue taken up in water and ether. The ether layer was washed several times with water, then with aqueous potassium carbonate solution containing some sodium thiosulfate and finally dried over anhydrous potassium carbonate and evaporated to give the crude methylketone methyl ester XXXIII (7.73 g., 96% yield).

The 2,4-dinitrophenylhydrazone of the methyl ketone methyl ester XXXIII was prepared; m.p. 140–142° from cyclohexane. The same 2,4-dinitrophenylhydrazone (m.p. 138–139°, mixture melting point 139–141°), and hence the same ketone, was obtained previously by Stork and Breslow<sup>1</sup> by the reaction with dimethylcadmium of the acid chloride prepared from XXXII.

*Anal.* Calcd. for  $C_{21}H_{28}O_3N_4$ : C, 58.32; H, 6.53. Found: C, 58.46; H, 6.63.

**Cyclization to the  $\beta$ -Diketone XXXIV.**—The crude methylketone methyl ester XXXIII (7.73 g.) was dissolved in a solution of 3.0 g. of potassium in 120 ml. of dry *t*-butyl alcohol and the solution was refluxed for 3 hours. The cooled solution was poured into water and the aqueous solution was washed four times with ether, then acidified (ice cooling) with concentrated hydrochloric acid and the colorless precipitate was removed by chloroform extraction. Removal of the chloroform on the steam-bath under reduced pressure gave the  $\beta$ -diketone XXXIV as a solid residue which was triturated with ether and collected to give 6.49 g. (83.5% yield), m.p. 199–201°. One recrystallization from dioxane gave 4.90 g., m.p. 200–202°. Further recrystallization from dioxane did not raise the melting point above 202–204°. The crystals were sublimed in high vacuum at 160–170° for analysis.

*Anal.* Calcd. for  $C_{14}H_{20}O_2$ : C, 76.32; H, 9.15. Found: C, 76.66; H, 9.07.

**Preparation of the Secondary Alcohol XXXVII from the  $\beta$ -Diketone XXXIV.**—Direct reduction of the  $\beta$ -diketone XXXIV with lithium aluminum hydride gave a solid mix-

(25) A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).

ture of saturated and unsaturated alcohols from which the pure saturated alcohol XXXVII could be separated by chromatography. The same saturated alcohol was also isolated when the mixture of enol ethers formed from the  $\beta$ -diketone with ethyl alcohol and a trace of acid was reduced with lithium aluminum hydride.

(a) **Reduction of the  $\beta$ -Diketone XXXIV.**—The  $\beta$ -diketone XXXIV (m.p. 200–202°, 2.00 g.) was added with stirring to an ice-cooled suspension of 2.0 g. of lithium aluminum hydride in 50 ml. of dry ether. The mixture was refluxed with stirring for 17 hours, then cooled and the excess lithium aluminum hydride was decomposed with saturated aqueous sodium sulfate solution. Anhydrous sodium sulfate was added and the solids were collected and washed well with ether. Removal of the ether gave 1.91 g. of colorless crystals, m.p. 95–110°. Trituration of the crystals with boiling pentane, then cooling and filtering gave colorless needles (1.27 g.), m.p. 114–116°. Further recrystallizations from cyclohexane failed to raise the melting point of the product above 117–118°. However, chromatography on alumina of solids obtained from the mother liquors resulted in the separation of the saturated alcohol on elution with 1:1 petroleum ether–benzene. After several recrystallizations from petroleum ether the saturated alcohol XXXVII melted at 120–121° and the melting point was not depressed on admixture with the alcohol of the same melting point obtained by reduction of the enol ether mixture from XXXIV (see below).

*Anal.* Calcd. for  $C_{14}H_{24}O$ : C, 80.71; H, 11.61. Found: C, 80.65; H, 11.58.

The crude alcohol, m.p. 114–116°, gave a mixture of saturated and unsaturated ketone on oxidation with chromic acid–pyridine complex (for procedure, see below). The ultraviolet absorption spectrum in 95% ethanol had  $\lambda_{max}$  243  $\mu$ ,  $\log \epsilon$  3.22, (estimated 10–15% unsaturated ketone). The saturated ketone XXXI was separated by chromatography on alumina by elution with petroleum ether. The 2,4-dinitrophenylhydrazone was prepared and it was identical (melting point and mixture melting point 146–147°) with that of the ketone prepared by reduction of the cyclohexenone XXXVI or from the pure alcohol XXXVII (see below).

(b) **Reduction of the Enol Ether(s) of XXXIV.**—The  $\beta$ -diketone XXXIV (2.84 g.) was dissolved in 50 ml. of absolute ethanol and 0.10 g. of *p*-toluenesulfonic acid monohydrate was added.<sup>26</sup> The mixture was distilled during 4 hours through a 24-cm. column of glass helices; 53 ml. of distillate was collected. The residue was dissolved in ether and the solution was washed twice with aqueous sodium bicarbonate and once with water, then dried over anhydrous sodium sulfate. The oil remaining after removal of the solvent was dissolved in petroleum ether and filtered to remove a few crystals of unchanged  $\beta$ -diketone (m.p. 198–200°). Removal of the solvent from the filtrate gave 2.82 g. of a mobile, nearly colorless oil (presumably a mixture of both possible enol ethers XXXV and XXXVa).

The crude mixture of enol ethers was dissolved in 25 ml. of dry ether and added over a 10-minute period to a stirred suspension of 1.0 g. of lithium aluminum hydride in 150 ml. of ether at 0°. The mixture was stirred at room temperature for 15 minutes, then under reflux for 15 minutes and finally left standing overnight at room temperature. In the morning, water was added, with stirring but without external cooling, followed by 3 *N* sulfuric acid. The ether layer was separated, washed twice with dilute sulfuric acid, three times with water, dried over anhydrous potassium carbonate and evaporated. The residue (2.45 g.) was a nearly colorless crystalline solid. The infrared spectrum showed a hydroxyl band at 2.9  $\mu$  and carbonyl bands at 5.9 and 6.1  $\mu$ . It seemed likely that the carbonyl band at 5.9  $\mu$  and the hydroxyl band corresponded to a  $\beta$ -hydroxyketone which on dehydration should give a cyclohexenone with a carbonyl band at 6.1  $\mu$ . Accordingly, the crude mixture was dissolved in 50 ml. of benzene containing 0.20 g. of *p*-toluenesulfonic acid monohydrate and the solution was refluxed for 1.5 hours. The cooled solution was washed with aqueous sodium bicarbonate, aqueous sodium hydroxide and then several times with water. After drying over anhydrous potassium carbonate, the solvent was removed under reduced pressure. The crystalline residue (2.18 g.) had a

weaker hydroxyl band and only one carbonyl band at 6.1  $\mu$ . One recrystallization from pentane gave 347 mg. of colorless needles, m.p. 120–121°. Chromatography of the residue from the mother liquor gave more solid (282 mg., m.p. 110–116°) on elution with benzene. Two recrystallizations from petroleum ether gave 161 mg. of colorless crystals, m.p. 120–121°. This compound (total 508 mg.) was identical in all respects (infrared spectra, melting point and mixture melting point) with the alcohol XXXVII obtained by direct reduction of the  $\beta$ -diketone XXXIV and also by reduction of the saturated ketone XXXI. Other fractions obtained by chromatography of the mother liquors included the fraction eluted first with petroleum ether (infrared spectrum lacks carbonyl bands; ultraviolet spectrum in ethanol had  $\lambda_{max}$  225  $\mu$ ,  $\log \epsilon$  3.3; decolorizes bromine in carbon tetrachloride) and a fraction eluted with a 1:1 mixture of petroleum ether and benzene (infrared had sharp band at 6.1  $\mu$ ; ultraviolet in ethanol had  $\lambda_{max}$  241  $\mu$ ,  $\log \epsilon$  4.0).

**Preparation of the Cyclohexenone XXXVI.**—The methylketone methyl ester XXXIII was reduced to the corresponding diol which was then oxidized to the ketoaldehyde, and the latter on treatment with aqueous base gave the cyclohexenone XXXVI. Intermediate compounds were not purified.

The methylketone methyl ester XXXIII (5.21 g.) was dissolved in dry ether and the solution was added slowly to a stirred, ice-cooled suspension of 7.77 g. of lithium aluminum hydride in 250 ml. of anhydrous ether. The mixture was stirred under reflux for 2 hours and at room temperature overnight. Excess lithium aluminum hydride was decomposed by adding a saturated aqueous solution of sodium sulfate to the ice-cooled mixture. Anhydrous sodium sulfate was added and the solids were collected and washed well with ether. Removal of the ether gave a colorless foam (4.11 g.) which had a strong hydroxyl band in the infrared spectrum but lacked carbonyl bands.

A suspension of chromic acid–pyridine complex<sup>18</sup> was prepared by adding 8.43 g. of chromic anhydride to 84 ml. of pyridine with cooling. To this was added a solution of the crude diol (4.11 g.) in 75 ml. of pyridine and the mixture was left at room temperature overnight (17 hours). The mixture was then poured into 750 ml. of ether and the solids were collected and washed well with 250 ml. of ether. The filtrate was concentrated on the steam-bath to about half its volume and was then washed three times with water, three times with 200 ml. of 5% aqueous potassium hydroxide, once with water, twice with dilute hydrochloric acid, and finally twice with water. The ether solution was then dried over anhydrous magnesium sulfate and the solvent was removed to give 2.81 g. of a pale yellow oil. The infrared spectrum had aldehyde and ketone bands.

For the cyclization a solution of 12.5 g. of potassium hydroxide in 500 ml. of water was first boiled under reduced pressure for a short time to remove oxygen. The alkaline solution was then added to 2.50 g. of the crude aldehyde-ketone. The mixture was stirred under reflux at 90 mm. pressure (about 50°) for 14.5 hours using a mercury trap.<sup>18</sup> The mixture was cooled and washed twice with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate and evaporated to give 2.02 g. of the crude cyclohexenone XXXVI as a mobile yellow oil. Most of the crude product (1.99 g.) was purified by chromatography on alumina. Eluates with petroleum ether, benzene–petroleum ether and benzene which appeared to give only the cyclohexenone carbonyl band at 6.1  $\mu$  in the infrared spectra were combined to give a total of 1.47 g. (39% over-all yield) of purified cyclohexenone XXXVI. The product was evaporatively distilled at 140–150° at 1 mm. ( $\lambda_{max}$  243  $\mu$ ,  $\log \epsilon$  3.91 in 95% ethanol). The 2,4-dinitrophenylhydrazone was prepared and recrystallized from methanol to give brilliant red prisms, m.p. 164–167°.

*Anal.* Calcd. for  $C_{10}H_{16}O$ : C, 62.48; H, 6.29. Found: C, 62.19; H, 6.33.

**Preparation of the Saturated Ketone XXXI.** (a) **Reduction of the Enone XXXVI.**—The cyclohexenone XXXVI (527 mg.) was reduced with 108 mg. of 10% palladium-on-charcoal catalyst in 10 ml. of absolute ethanol. The hydrogen uptake was 64.3 ml. in 20 minutes at 23° and atmospheric pressure. There was no further uptake of hydrogen after 1 hour. The calculated uptake is 63.8 ml. The catalyst was collected and washed with ether. Removal of

(26) Cf. E. D. Bergmann and J. Szmuzkovicz, *J. Am. Chem. Soc.*, **75**, 3226 (1953).

solvent from the filtrate gave the saturated ketone XXXI (524 mg.) as a colorless oil. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from methanol to give a mat of fine yellow needles which changed to stout prisms on standing in the solution; m.p. 146–147°.

*Anal.* Calcd. for  $C_{20}H_{26}O_4N_4$ : C, 62.16; H, 6.78. Found: C, 62.20; H, 6.95.

(b) Oxidation of the Alcohol XXXVII.—A solution of 219 mg. of the saturated alcohol XXXVII (m.p. 120–121°) in 2.2 ml. of pyridine was added to a suspension of the chromic acid-pyridine complex prepared by adding 224 mg. of chromic anhydride to 2.2 ml. of pyridine. The mixture was left at room temperature for 23 hours and dry ether was then added. The solids were collected and washed with dry ether. The filtrate was washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate and gave, after removal of the solvent, 190 mg. of the ketone XXXI as a yellowish oil. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from methanol; m.p. 146–147°. The melting point was not depressed on admixture with the 2,4-dinitrophenylhydrazone of the ketone obtained by reduction of the enone XXXVI.

Reduction of the Ketone XXXI.—The saturated ketone XXXI (164 mg.) was added in ether solution to a stirred suspension of 0.40 g. of lithium aluminum hydride in ether (total volume 30 ml.). The mixture was stirred under reflux for 17 hours and then cooled. Excess lithium aluminum hydride was decomposed with an aqueous sodium sulfate solution and anhydrous sodium sulfate was added. The solids were collected and washed with dry ether and the filtrate was evaporated to give 140 mg. of a colorless solid, m.p. 118–120°. One recrystallization from petroleum ether gave 96 mg. of colorless needles, m.p. 120–121°. One

further recrystallization from petroleum ether did not raise the melting point. The melting point was not depressed on admixture with the saturated alcohol XXXVII obtained from the  $\beta$ -diketone XXXIV and the infrared spectra were identical.

Preparation of Cedrol from the Ketone XXXI.—Methyl-lithium was prepared by adding 6 ml. of methyl iodide to 1.8 g. of lithium (in 6 pieces) in 40 ml. of dry ether, with stirring and cooling in ice. When the initial vigorous reaction had subsided the mixture was refluxed with stirring for 4 hours. The mixture was then cooled and the unreacted lithium (0.90 g.) was removed (calculated amount of methyl-lithium: 0.06 mole).

The ketone XXXI (446 mg., 0.0021 mole) in dry ether was added slowly to the solution of methyl-lithium and the mixture was refluxed with stirring for 18.5 hours. Excess methyl-lithium was decomposed by adding aqueous sodium sulfate solution containing some sodium thiosulfate to the stirred, ice-cooled solution. Water was added and the ether layer was separated and washed well with water, dried over anhydrous sodium sulfate and evaporated to give 480 mg. of crude cedrol as a solid residue. The crude product was recrystallized from methanol-water four times to give colorless needles: 1. obtained 380 mg., m.p. 80–81°; 2. obtained 340 mg., m.p. 83–87°; 3. obtained 284 mg., m.p. 85–87°; 4. obtained 215 mg., m.p. 86–87°.

Natural cedrol was also recrystallized from methanol-water to give colorless needles, m.p. 86–87°. The mixture melting point of natural and synthetic cedrol was 86–87° and the infrared spectra were identical. The rotations were measured in chloroform solution: natural cedrol:  $[\alpha]^{25}_D$  9.9  $\pm$  0.4 (*c* 5.00); synthetic cedrol:  $[\alpha]^{25}_D$  10.5  $\pm$  0.8 (*c* 5.00); reported<sup>20</sup> values include +9° 31' and +10° 30' in chloroform solution.

[CONTRIBUTION NO. 600 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO., WILMINGTON 98, DEL.]

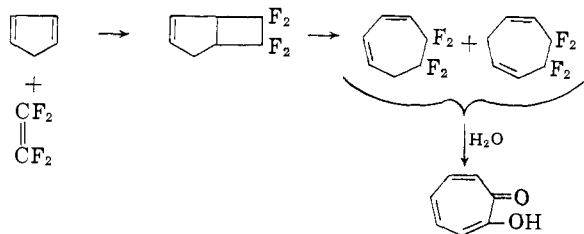
## N,N'-Disubstituted-1-amino-7-imino-1,3,5-cycloheptatrienes, a Non-classical Aromatic System

BY W. R. BRASEN, H. E. HOLMQUIST AND R. E. BENSON

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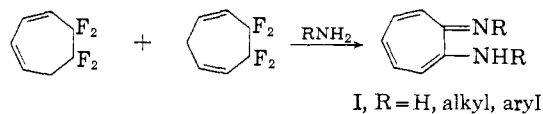
N,N'-Disubstituted-1-amino-7-imino-1,3,5-cycloheptatrienes are stable, highly colored compounds that are readily accessible from the tetrafluorocycloheptadienes derived from tetrafluoroethylene and cyclopentadiene. Chemical studies of these aminoimines have established that they have appreciable aromatic character. Although structurally related to tropolone, the reasons for aromaticity in these two systems appear to be fundamentally different. Whereas aromaticity in tropolone has been attributed to resonance forms containing the sextet, n.m.r. and infrared spectral data together with dipole moment studies of the aminoimines clearly rule out a major contribution from sextet forms. The evidence appears more consistent for a peripheral 10  $\pi$ -electron system involving hybridization of the two non-bonding electrons on nitrogen of the NHR substituent with the 8  $\pi$ -electrons of the double bonds.

A new synthesis of tropolone recently was reported from these laboratories, based on the hydrolysis of the tetrafluorocycloheptadienes accessible from cyclopentadiene and tetrafluoroethylene.<sup>1</sup>



The tetrafluorocycloheptadienes are also intermediates for the synthesis of the 1-amino-7-imino-1,3,5-cycloheptatrienes (I),<sup>2</sup> a little-studied class of

compounds that is not conveniently accessible from tropolone or its derivatives. The disubstituted aminoimines are stable, highly colored compounds



that exhibit aromatic reactivity similar to that of tropolone itself.<sup>3</sup> It appears, however, that the reasons for aromaticity in these two systems are fundamentally different.<sup>4</sup> The present paper describes additional studies of the aminoimines.

The previously reported examples of 1-amino-7-imino-1,3,5-cycloheptatrienes are the compounds II-IV.

(3) Excellent reviews of the chemistry of tropolone include (a) P. L. Pauson, *Chem. Revs.*, **55**, 9 (1955); (b) T. Nozoe, *Fortschr. Chem. Org. Naturstoffe*, **13**, 232 (1955); and (c) T. Nozoe in "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Editor, Interscience Publishers, Inc., New York, N. Y., 1959.

(4) R. E. Benson, *J. Am. Chem. Soc.*, **82**, 5948 (1960).

(1) J. J. Drysdale, W. W. Gilbert, H. K. Sinclair and W. H. Sharkey, *J. Am. Chem. Soc.*, **80**, 3672 (1958).

(2) W. R. Brasen, H. E. Holmquist and R. E. Benson, *ibid.*, **82**, 995 (1960).