Stereochemistry of the Tetrahydroabietic Acids[1]

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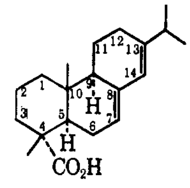
Three of the four possible abietanoic acids have been prepared by methods which unambiguously define their configuration. The results necessitate revision of some previously made assignments and provide several examples of epimerization which occur during Wolff–Kishner reduction and thioketal formation.

In order to continue work on some aspects of resin acid chemistry now being studied in our laboratories, it became necessary to have on hand abietanoic (tetrahydroabietic) acids of established configuration. Since the reduction of abietic acid has been reported to yield various tetrahydro derivatives of uncertain stereochemistry,[6-9] we decided to study the preparation of abietanoic acids from abietic or levopimaric acid by routes which would allow unambiguous assignment of configuration to the new asymmetric centers at C-8 and C-13. In the following we describe our results. These amplify and partially correct conclusions reached by Burgstahler and Marx[10] which were communicated in preliminary form while our work was in progress.



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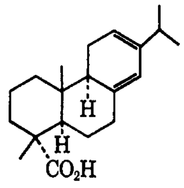

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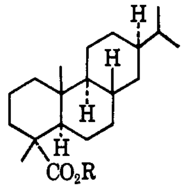

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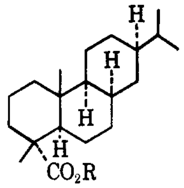
b, R = CH_3



4a, R = H
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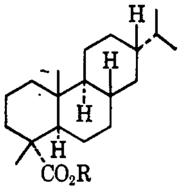
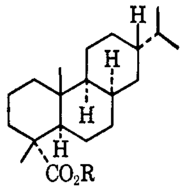
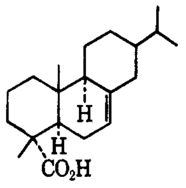


5a, R = H
b, R = CH_3



6a, R = H
b, R = CH_3



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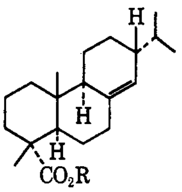
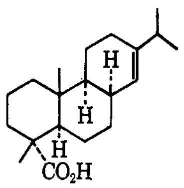


8a, R = H
b, R = CH_3



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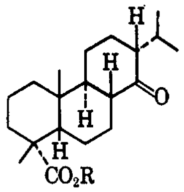
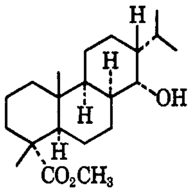


10a, R = CH_3
b, R = H



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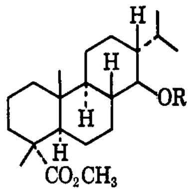

12a, R = H
b, R = Ts

On the basis of reasonable, but not unequivocal arguments, Velluz and co-workers[8] had assigned formulas **3a** and **4a** to two tetrahydroabietic acids, mp 168°, [α] +23° (A), and mp 202°, [α] +7° (B), respectively. The postulated configuration at C-13 (13α H) was strongly supported by later work,[11,12] but the assignments at C-8 remained unproved. Somewhat later, Royals and co-workers obtained an apparently new tetrahydroabietic acid, mp 186°, [α] −2° (C), by catalytic hydrogenation of an acid of presumed formula **7**, which in turn had been prepared by lithium–liquid ammonia reduction of abietic acid. More recently, Burgstahler and Marx[10a] revised the structure of the Royals dihydro acid from **7** to **8a**[13] and reported its conversion to a fourth tetrahydroabietic acid, mp 179°, [α] +10° (D), presumably identical with material isolated earlier,[6] to which they assigned formula **5a**. The Kansas group[10b] agreed with the conclusions of Velluz, *et al.*,[8] and suggested that acid C should be represented by **6a**.

Although Burgstahler's route[10a] from **8** to D appeared to be stereospecific, since it involved hydroboration–oxidation and conversion to the thioketal of the stable *trans*-keto ester **10a** followed by desulfurization and hydrolysis, some questions remained concerning the stereochemistry of the product presumed to be **5a**. First we had observed that Wolff–Kishner reduction of **10a**, generally thought to proceed without epimerization at the adjacent asymmetric centers,[14] resulted in

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[1] Work at Florida State University supported in part by a grant from the National Science Foundation (GP-1962). Work at Clemson University supported in part by grant GM-07817 and Career Development Award K3-GM5433, both from the National Institutes of Health.

[2] Clemson University. Paper III in a series "Studies on Resin Acids." Previous paper: J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965).

[3] Abstracted in part from a thesis presented by L. H. Wright in partial fulfillment of the requirements for the M.S. degree, Clemson University, May 1964.

[4] Florida State University. Paper X in a series "Resin Acids." Previous paper: W. Herz, A. R. Pinder, and R. N. Mirrington, *J. Org. Chem.*, **31**, 2257 (1966).

[5] To whom inquiries should be addressed.

[6] For a review of the literature through 1950, see J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. 3, Cambridge University Press, 1952, pp 374–445.

[7] R. Lombard and J. Ebelin, *Bull. Soc. Chim. France*, 930 (1953).

[8] L. Velluz, G. Muller, A. Petit, and J. Mathieu, *Bull. Soc. Chim. France*, **21**, 401 (1954).

[9] E. E. Royals, W. C. Bailey, and R. W. Kennedy, *J. Org. Chem.*, **23**, 151 (1958).

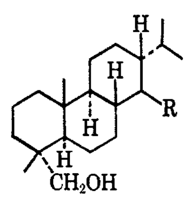
[10] (a) A. W. Burgstahler and J. N. Marx, *Tetrahedron Letters*, 3333 (1964); (b) A. W. Burgstahler and J. N. Marx, Abstracts of Papers presented at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 5–9, 1965.

[11] J. Minn, T. F. Sanderson, and L. C. Subluskey, *J. Am. Chem. Soc.*, **78**, 630 (1956).

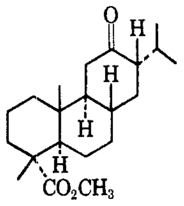
[12] L. Gough, T. F. Sanderson, V. Stenberg, and E. Wenkert, *J. Org. Chem.*, **25**, 1269 (1960).

[13] The material was contaminated with *ca.* 15% of a $\Delta^{13(14)}$ isomer of unspecified configuration at C-8 (**9**), but will be referred to subsequently as the $\Delta^{8(14)}$ isomer since in most cases the only isolable product is that derived from **8**.

[14] See the following references to formation of a less stable isomer during Wolff–Kishner reductions: (a) C. Djerassi, T. T. Grossnickle, and L. B. High, *J. Am. Chem. Soc.*, **78**, 3166 (1956); (b) N. S. Crossley and H. B. Henbest, *J. Chem. Soc.*, 4413 (1960); (c) R. L. Clark, *J. Am. Chem. Soc.*, **83**, 965 (1961).



13a, R = OH
b, R = H



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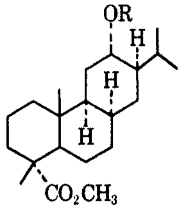
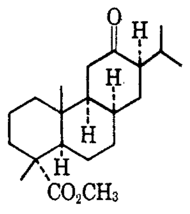


15a, R = H
b, R = Ts



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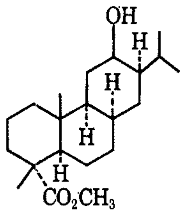

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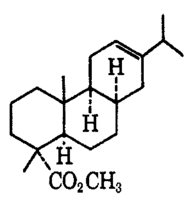

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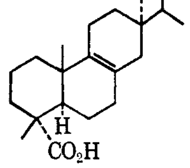

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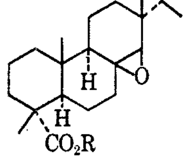
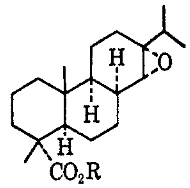
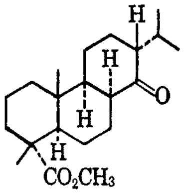


20a, R = H
b, R = CH_3



21a, R = H
b, R = CH_3



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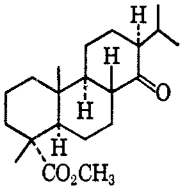

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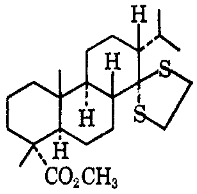

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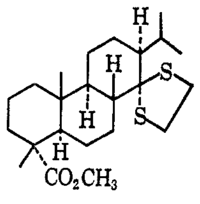

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the abietanoic acid of mp 202° (B, *vide infra*) rather than the acid of mp 179° (D). Secondly, in our hands catalytic hydrogenation of **8** furnished D[15] rather than the material reported by Royals, and, since examination of molecular models suggested that the α side of **8** was less hindered than the β side, it seemed possible that D was in fact the $8\alpha,9\alpha,13\beta$H isomer **6a**.[16] Thirdly, although it is usually assumed that conversion of a ketone to the thioketal does not affect the configuration of an adjacent asymmetric center, there is precedent for epimerization during thioketal formation.[18]

Two unambiguous syntheses of **5a** were therefore carried out. The first sequence began with **8b** which on hydroboration–oxidation afforded two products. The material formed in larger yield was a hydroxy ester which in view of the well-known *cis* addition of diborane and the nmr spectrum (H-14 signal broadened overlapping pair of doublets at 2.95 ppm, $J_{8,14} = J_{13,14} = 8$ cps, characteristic of two axial–axial splittings) was assigned formula **12a** rather than **11**.[19] The assignment was confirmed by oxidation of **12a** to the stable keto ester **10a** under conditions which have been shown not to cause deuterium exchange at positions adjacent to a carbonyl group[20] and by sodium–propanol reduction of **10b** followed by esterification which gave **12a** exclusively. The minor product from the hydroboration was the diol **13a**.[10] Conversion of **12a** to the 14-tosylate **12b** followed by reduction with lithium aluminum hydride and reoxidation gave $8\beta,9\alpha,13\beta$H-abietanoic acid (**5a**), mp 179°, identical with the substance previously prepared by the thioketal route[10a,21] and by catalytic hydrogenation of **8a**.

Although it had been assumed that the $\Delta^{8(14)}$-abietenoic acid prepared by lithium–liquid ammonia reduction of **1** had the indicated configuration at C-13,[10a] no evidence has heretofore been presented to confirm this assignment.[22] The properties of **12** require an α configuration for the isopropyl side chain, and since hydroboration will not alter the configuration at C-13 the isopropyl group of the precursor **8** must also be α.

A second series of transformations utilized the keto acid **14**[24] whose stereochemistry is now securely established.[25] Wolff–Kishner reduction of **14** or desulfurization of the thioketal yielded the 179° acid exclusively. Since the asymmetric center at C-8 cannot be affected during these processes, the result, in conjunction with the previous evidence, fully confirms the assigned stereochemistry **5a**.

We next describe the preparation of authentic $8\alpha,9\alpha,13\alpha$H-abietanoic acid (**4a**) for which **15a**[25] served as starting material. Either Wolff–Kishner reduction of ketone **16** of authenticated stereochemistry (isopropyl side chain equatorial and β)[25] or desulfurization of the corresponding thioketal followed by hydrolysis resulted in formation of an acid, mp 164°, [α] +21°, which was identical with the 168° acid A. This clearly defines the configuration of A at C-8 as enantiomeric with that previously postulated,[8,10] but leaves a grain of doubt, for reasons discussed in the preceding paragraphs, about the stereochemistry at C-13 which could conceivably have been inverted during Wolff–Kishner reduction and thioketal formation. However, this doubt was dispelled when it was found that lithium

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[15] This observation, and the preceding one, has been confirmed by Professor Burgstahler (private communication). The acid, mp 186°, reported by Royals[9] is actually a mixture of **5** and **8**, not **6**.

[16] We and others have since established the conditions which lead to formation of an $8\beta,9\alpha$ isomer from pimaric acid which is comparable with **8**.[17]

[17] (a) W. Herz and R. N. Mirrington, *J. Org. Chem.*, **30**, 3198 (1965); (b) J. W. ApSimon, P. V. DeMarco, and J. Lempe, *Can. J. Chem.*, **43**, 2793 (1965).

[18] (a) R. Stevenson and L. F. Fieser, *J. Am. Chem. Soc.*, **78**, 1409 (1956); (b) C. Djerassi and M. Gorman, *ibid.*, **75**, 3704 (1953).

[19] N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp. 49–52. For **11**, $J_{8,14} \sim 8$ cps, $J_{13,14} \sim 2$ cps which should give rise to a rather sharp doublet of doublets.

[20] E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).

[21] We wish to thank Professor Burgstahler for samples of **5**, **10a**, and **10b**.

[22] Actually, on the basis of previously published results an excellent case against this assignment could be made. The $\Delta^{8(14)}$ acid has been isomerized to a $\Delta^{8(9)}$ acid, mp 178°, [α] +8°, which has in turn been converted into a mixture of lactones from which was isolated a γ-lactone, mp 131°.[9] Since this lactone must have a β-isopropyl group,[11,12,23] one would have to attribute a β-isopropyl group to the Royals acid as well. In point of fact, the isolated yield of lactone from the $\Delta^{8(9)}$ acid derived from the Royals acid was very small (R. W. Kennedy, Ph.D. Thesis, Emory University, 1956). Repetition of this work showed that the $\Delta^{8(9)}$ acid is actually a mixture (*ca.* 1:1) of two acids, presumably the 13α and 13β isomers. Hydrogenation (100°, 60 psi) of the mixture gave a mixture of acids B and D (glpc analysis) from which D could be isolated in crystalline form.

[23] W. Herz and H. J. Wahlborg, *J. Org. Chem.*, **30**, 1881 (1965).

[24] W. G. Dauben and R. Coates, *ibid.*, **28**, 1698 (1963).

[25] W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *ibid.*, **30**, 3190 (1965).

aluminum hydride reduction of **15b** and subsequent reoxidation again furnished A to which formula **4a** must therefore be assigned.[26]

Although the hydroxyl group of **15a** is equatorial, the tosylate **15b** on standing underwent a spontaneous elimination reaction which resulted in a mixture containing **18** and the Δ^{11} isomer. This is clearly a reflection of the conformational distortion present in this system which we have commented upon earlier. Nevertheless the nmr spectrum of **15a** exhibited an ill-defined multiplet ($w_{1/2} \sim 26$ cps) near 3.85 ppm typical of an axial proton at C-12. By contrast, the C-12 epimer **17** which was prepared by sodium borohydride reduction of **16**, on treatment with toluenesulfonyl chloridepyridine underwent immediate dehydration to **18** and displayed a considerably narrower H-12 signal (broadened quadruplet at 4.00 ppm, $w_{1/2} \sim 11$ cps) characteristic of an equatorial proton. Catalytic hydrogenation of **18** furnished **4b** exclusively as could be predicted from the model. Since A and B can be prepared[8] by hydrogenation of the $\Delta^{8(9)}$-abietenoic acid **19**[27] for which the configuration at C-13 has now been established unambiguously through the conversion of **15a** to A, B must be the C-8 epimer of A or 8β,9α,13αH-abietanoic acid (**3a**). Similar apparent *trans* hydrogenations are now known.[17]

That ring C or **15a** and **17** possesses unusual properties is also indicated by measurements of the rates of oxidation.[28] The results are presented in Table I.

TABLE I

RATES OF OXIDATION

Compd	Rate in 90% acetic acid[a]	Rate in 90% acetic acid and 10^{-2} mole/H NaOAc
15a	30 ($t^{1/2} \sim 30$ min)	0.8
17	Too fast ($t^{1/2} \sim 20$ sec)	80 ($t^{1/2} \sim 10$ min)
5α-Cholestan-3α-ol	36.0	
5α-Cholestan-3β-ol	9.8	
2α-Methyl-5α-cholestan-3β-ol	12.0	

[a] Rates in mole^{-1} min^{-1}; conditions, 6 μmole ROH + 12 μequiv of CrO_3 in 90 ml of solvent at 25°.

The reaction rate of **15a** is about three times as fast as expected (compared with 2α-methyl-5α-cholestan-3β-ol) which suggests that there is additional Pitzer strain in the molecule. The dramatic speed of oxidation of **17**, which is comparable to that of 5α-cholestan-11β-ol must be due to a very large amount of strain. The results again indicate that ring C is distorted from the normal chair form and much more so in **17** than in **15a**.

We now return to our study of the further transformations of **8a**. Reaction of **8a**[13] with *m*-chloroperbenzoic acid gave a mixture of two isomeric epoxides in a ratio of 12 to 1, the physical constants of the major isomer corresponding to those reported by Royals.[9] The nmr spectrum of this substance exhibited H-14 as a slightly broadened singlet at 2.50 ppm, which indicates that $J_{13,14}$ is very small and that the H-13–H-14 dihedral angle must be close to 90°. Models show that this is consistent with formula **20a**, but not the α-epoxide. This also accounts for the appearance of the C-10 methyl resonance at a relatively deshielded 1.00 ppm and is confirmed by subsequent reactions.

The nmr spectrum of the minor product also had a broadened singlet at 2.95 ppm. Inspection of epoxide models derived from $\Delta^{8(14)}$-13βH- and $\Delta^{13(14)}$-abietenoic acid and consideration of the reaction of this substance with boron trifluoride to be discussed subsequently indicated that it must be 13α,14α-epoxy-8αH-abietanoic acid (**21a**). Consequently the contaminant in **8a** must be **9**.

Treatment of either **20b** or **21b** with boron trifluoride etherate in benzene furnished a ketone which was isomeric with **10a**,[10,21] and was quantitatively converted to the latter by treatment with base. Since the isopropyl group of **20a** is α and since inversion of a center adjacent to a carbonyl group in the boron trifluoride rearrangement of epoxides seems to be precluded,[29] the newket one must be methyl 8α,9α,13βH-14-oxoabietanoate (**22**). The *cis*-B/C ring fusion was confirmed by the nmr spectrum which exhibited a shielded C-10 methyl resonance at 0.72 ppm due to the location of the methyl group in the shielding cone above the plane of the carbonyl. By contrast the C-20 protons of **10a** lie in the plane of the carbonyl group and are somewhat deshielded as evidenced by a singlet at 0.96 ppm.

The rotatory dispersion curve of **22** has an extremely strong positive Cotton effect ($a = 171$).[30] While the octant rule predicts a strongly positive Cotton effect, the exceedingly large amplitude suggests that the C ring is in the twist conformation.[31] Examination of models of **22** with ring C in the twist conformation indicates that in various pseudo-rotational forms the rather large C-14-angular methyl interactions are minimized and the interactions related to the axial isopropyl group present in the chair form of **22** are relieved.

When the mixture of epoxy acids **20a** and **21a** was rearranged with boron trifluoride prior to separation, the only product which could be obtained was **10b**. Although the unstable acid corresponding to **22** was undoubtedly formed initially, the carboxyl group apparently catalyzed its epimerization to the stable isomer **10b**. The ORD curve of **10b** exhibited a negative Cotton effect of moderate amplitude which was consistent with the assigned stereochemistry.[32] Wolff–Kishner reduction of **10b** furnished B (**3a**), an observation which requires continuous removal of the less stable ketone **23**, apparently present in small amount at equilibrium, through the hydrazone.[33]

Treatment of **22** with boron trifluoride etherate and ethanedithiol yielded a mixture of thioketals one of which was identical with the previously reported[10]

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[26] This acid has also been prepared by Sanderson from dehydroabietic acid (T. F. Sanderson, private communication). We would like to thank Dr. Sanderson for a sample which allowed us to establish the identity.

[27] This has been verified (see the Experimental Section).

[28] J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955). We are greatly indebted to Dr. J. Schreiber, ETH, Zurich, for carrying out these determinations. The differences in the rates of oxidation were so great that it was necessary to measure rates in two systems.

(29) N. L. Wendler, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 1035–1037, Vol. 2. This article cites a number of instances where rearrangement of steroidal epoxides leads to a thermodynamically unstable ketone.

(30) We are grateful to Dr. P. Crabbé of Syntex S.A. for making this measurement.

(31) C. D. Beard, C. Djerassi, T. Elliot, and R. C. C. Tao, *J. Am. Chem. Soc.*, **84**, 874 (1962).

(32) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962).

(33) Ketone **23**, with an axial isopropyl side chain, must be less stable than **10a**, but is certainly more stable than **22**.

thioketal of **10a**. The principal product was an isomeric thioketal which on desulfurization and hydrolysis again produced B (**3a**). Obviously then, thioketal formation from **22** had resulted in epimerization at C-8 leading to **24** and in epimerization at C-8 and C-13 leading to **25**. In keeping with this observation, repetition of the reaction of **10a** with boron trifluoride etherate–ethanedithiol revealed formation of a mixture of **24** and **25**, contrary to the previously published report.[10]

That **24** and **25** possess the same configuraton at C-8 (8β H) and differ at C-13 is further indicated by the nmr spectra which exhibit the C-10 methyl resonances at 0.84 and 0.86 ppm typical of a B/C-*trans* fusion, but differ from each other in the greater deshielding experienced by the isopropyl methyls of **24** as required by the models. Compilation of a large body of published and unpublished data suggests that a chemical shift of 0.85–0.92 is characteristic of B/C-*trans*-fused (8β,9α) abietanes, pimaranes, and isopimaranes, while in the *cis*-fused derivatives (8α,9αH) the C-10 methyl signal is found at 1.0–1.10 ppm when no shielding influences come into play. As an illustration of this we cite the C-10 methyl signals of **3a**, **4a**, and **5a** which are found at 0.86, 1.07, and 0.86 ppm, respectively.

Furthermore, oxidation of **24** and **25** to the corresponding bissulfones produced no significant shift in the frequency of the C-10 methyl resonance such as would have been expected if either or both had retained the *cis*-B/C ring fusion of **22**. On the other hand, the oxidation produced changes in the chemical shifts of the isopropyl methyls, as required by the allocated configurations.

Experimental Section[34]

$\Delta^{18(14)}$-9α,13βH-Abietenoic Acid (8a).—The conditions used for the preparation of this substance were essentially those of Royals, Bailey, and Kennedy.[9] From 145 g of the diamylamine salt of abietic acid[35] there was obtained 77 g of crude dihydro acid, mp 150–175°. Fractional recrystallization from acetone gave 27.6 g (29%) of the mixture of **8a** and **9** used in subsequent experiments. This material had mp 187–194°; $[\alpha]^{23}\mathrm{D}$ −20° (*c* 0.822); nmr signals at 5.37 m (H-14 of **8a**), 5.10 m (H-14 of **9**, ∼15%), 1.20 (C-4 methyl), and 0.80 d (isopropyl superimposed on C-10 methyl). The methyl ester **8b** prepared by treatment with ethereal diazomethane, was an oil.

Methyl 14β-Hydroxy-8β,9α,13βH-abietanoate (12a).—To a solution of 3.00 g of **8b** in 30 ml of diglyme was added 0.60 g of sodium borohydride. The reaction was cooled in an ice bath and 2.5 g of freshly distilled BF_3 etherate was added in the course of 1 hr. The reaction mixture was allowed to warm up to room temperature and stirred for 2.5 hr. A few drops of water, followed by 15 ml of 10% sodium hydroxide and 15 ml of 30% hydrogen peroxide solution, was added cautiously. The mixture was stirred overnight and extracted with methylene chloride. The washed and dried extract was evaporated *in vacuo*, and the residue (3.00 g) was dissolved in hexane–benzene (1:4) and chromatographed over acid-washed alumina (Merck). Elution with hexane–benzene (1:4) gave first 0.17 g of **8b**, then 1.28 g (40%) of **12a**. Recrystallization from hexane furnished pure **12a**: mp 134–135°; $[\alpha]^{25}\mathrm{D}$ +11° (*c* 0.973); infrared bands at 1730 cm^{-1}; nmr signals at 2.95 t (J = 8, H-14), 1.18 (C-4 methyl), 0.88 (C-10 methyl), and 0.92 d and 0.78 d (J = 7, isopropyl).

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.74; H, 10.76.

Thin layer chromatography (silica gel G, benzene–acetone 4:1) of the mother liquors from the recrystallization of **12a** revealed the presence of small amounts of two other compounds which could not be obtained in a pure state.

Elution of the column with benzene–ether mixtures gave 0.10 g (3.5%) of a diol, mp 174–175°, which was undoubtedly diol **13a** reported by Burgstahler.[10]

In subsequent runs the hydroboration step was carried out for 1 hr, and the crude **12a** precipitated from the alkaline hydrogen peroxide mixture. From 4.38 g of crude **8b** there was obtained 3.43 g (74%) of pure **12a**.

Sodium–Alcohol Reduction of 10b.—To a solution of 0.086 g of **10b** (for preparation, *vide infra*) in 15 ml of 1-propanol was added 1.5 g of sodium over a 1-hr period. The reaction mixture was refluxed for 1 hr, poured into water, acidified, and extracted with methylene chloride. The organic layer was washed, concentrated to small volume, mixed with ethereal diazomethane (from 1.5 g of nitrosomethyl urea), and allowed to stand at room temperature for 3 hr. Evaporation of solvent furnished 0.06 g of oil which was recrystallized from hexane; yield of **12a** was 0.04 g (46%), mp 130–134°, mixture melting point undepressed. Tlc of the mother liquors (silica gel G, benzene–acetone 5:1) did not indicate the presence of any other compounds.

14β-Tosyloxy-8β,9α,13βH-abietanoate (12b).—A solution of 1.00 g of **12a** in 3 ml of pyridine was mixed with 0.74 g of tosyl chloride, stirred at room temperature overnight, and poured into water. Recrystallization from acetone gave 1.42 g (97%) of **12b**: mp 124–125°, $[\alpha]^{25}\mathrm{D}$ +8° (*c* 0.501).

Anal. Calcd for $C_{28}H_{42}OS_5$: C, 68.55; H, 8.63. Found: C, 68.73; H, 8.54.

8β,9α,13βH-Abietanoic Acid (5a). **A.**—To a solution of 0.69 g of **12b** in 30 ml of absolute ether was added 0.35 g of lithium aluminum hydride. The reaction mixture was refluxed for 18 hr, cooled, decomposed with water, and acidified with 10% hydrochloric acid. The ether layer was washed, dried, and evaporated and the residue (0.43 g) was taken up in hexane and passed through a column of 10 g of alumina. Evaporation of the hexane eluate furnished 0.34 g (84%) of **13b** which could not be induced to crystallize, but appeared to be homogeneous (tlc). A 0.25-g portion was dissolved in 10 ml of acetone, mixed with 1 ml of Jones reagent, stirred for 30 min, concentrated to small volume, and diluted with water. The precipitated solid was recrystallized from acetone, yield 0.24 g (88%) of solid, mp 177–179°, identified as acid D (**5a**) by direct comparison with an authentic sample[10] (nmr spectrum, infrared spectrum, tlc, mixture melting point). The diamylamine salt melted at 127–128° (lit.[10] mp 127–127.5°).

B.—A solution of 0.66 g of **8a** in 100 ml of acetic acid was hydrogenated with 0.1 g of platinum oxide at 50 psi and room temperature. The reaction mixture was filtered through Celite and the product was precipitated by addition of water. Recrystallization from acetone furnished 0.64 g of colorless crystals, mp 182–184°, identical in all respects with material prepared by method A.

C.—To a solution of 0.2 g of **14**[24,25] in 25 ml of diethylene glycol was added 0.2 g of solid potassium hydroxide and 2.0 ml of anhydrous hydrazine. The mixture was refluxed at 146° for 1.25 hr, the condenser was removed and the temperature was allowed to rise to 210°. After 2 hr of reflux at this temperature the solution was allowed to cool. Acidification yielded a white precipitate which was washed and recrystallized from methanol–water: yield 0.16 g, mp 174–178°. Two recrystallizations raised the melting point to 180–181°; $[\alpha]^{25}\mathrm{D}$ +10° (*c* 1.04); nmr signals at 1.18 (C-4 methyl), 0.86 (C-10 methyl) and 0.85 g (J = 6 cps, isopropyl). Direct comparison with material prepared by method A established identity.

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44. Found: C, 78.76; H, 11.06; O, 10.19.

D.—To a solution of 0.2 g of **14** in 1.0 ml of ethanedithiol was added 0.5 ml of boron trifluoride etherate. After 18 hr the reaction mixture was diluted with methanol. The thioketal which crystallized was recrystallized from methanol: yield 0.18 g (73%); mp 125.5–127°; infrared bands at 1725 and 1250 cm^{-1} (ester); nmr signals at 3.72 (methoxyl), 3.30 br (4 p, CH_2S), 1.20 (C-4 methyl), 0.98 d, 0.96 d (J = 6 cps, isopropyl), 0.88 (C-10 methyl). Raney nickel desulfurization of 0.1 g of this substance furnished **5b** as an oil: yield 75 mg (75%); infrared bands at 1725 and 1250 cm^{-1} (ester); nmr signals in methyl region superimposable on those of **5a**. The product was identical

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[34] Melting points are uncorrected. Infrared spectra were run as potassium bromide disks or liquid films unless indicated otherwise. Nmr spectra were run on Varian A-60 spectrometers in deuteriochloroform, using tetramethylsilane as internal standard. Signals are given in parts per million. Rotations were run in ethanol unless indicated otherwise.

[35] G. C. Harris and T. F. Sanderson, *Org. Syn.*, **32**, 1 (1952).

with an ester prepared by treatment of **5a** with ethereal diazomethane (infrared, nmr, tlc).

8α,9α,13αH-Abietanoic Acid (4a). A.—A mixture of 0.19 g of **16**, 25 ml of diethylene glycol, 0.19 g of solid potassium hydroxide, and 2.0 ml of anhydrous hydrazine was subjected to the Wolff–Kishner reduction as described in the previous section. The solid which precipitated on acidification appeared to be homogeneous (nmr, tlc) and was recrystallized from ethanol–water: yield 0.18 g (80%), mp 156–159°. Two recrystallizatinos from ethanol–water raised the melting point to 164°; $[\alpha]^{25}\text{D}$ +21° (*c* 0.795); nmr signals at 1.21 (C-4 methyl), 1.08 (C-10 methyl), and 0.88 d (J = 6 cps, isopropyl). Direct comparison with material prepared by hydrogenation of **19** (*vide infra*) and the acid, mp 163–164°, isolated by Sanderson[26] established identity.

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44. Found: C, 78.51; H, 10.92; O, 10.62.

B.—A solution of 0.42 g of **16** in 1.5 ml of ethanedithiol was mixed with 1.0 ml of boron trifluoride etherate and allowed to stand 24 hr. The thioketal crystallized on dilution with methanol: yield 0.35 g (70%), mp 146–152°, homogeneous by nmr and tlc criteria. Recrystallization from methanol raised the melting point to 158°; nmr signals at 3.70 (methoxyl), complex 4 p multiplet centered at 3.24 (CH_2S), 1.25 (C-4 methyl), 0.98 d and 0.95 d (J = 6.5 cps, isopropyl), 0.87 (C-10 methyl). As compared with the nmr spectrum of the thioketal of **14**, proximity of the C-10 methyl group imposed by the B/C-*cis* fusion causes the methylene groups of the thioketal function to be magnetically nonequivalent and produces a complex splitting pattern.

Raney nickel desulfurization of 0.3 g of the thioketal and concentration of the ethanol solution produced a colorless oil which crystallized at once, yield 0.18 g (70%). The product was homogeneous by tlc, but the nmr spectrum indicated the presence of a minor constituent (less than 20%) which could not be isolated. Two recrystallizations from methanol furnished analytically pure **4b**: mp 97–98°, $[\alpha]^{25}\text{D}$ +11° (*c* 0.84), nmr spectrum identical with that of **4a** in the methyl region.

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32; O, 9.92. Found: C, 78.27; H, 11.49; O, 10.37.

Hydrolysis of **4b** furnished an acid, mp 164°, identical with material prepared by route A.

C.—An ice-cold solution of **15a**[25] in 10 ml of pyridine was mixed with 1 ml of methanesulfonyl chloride, allowed to stand for 24 hr, poured on ice, and extracted with ether. The washed and dried ether extract was evaporated and the residual crystalline solid (0.28 g) was recrystallized from methanol: mp 101.5–102°; infrared bands at 1720 and 1250 (ester), 1340 and 1170 cm^{-1} (mesylate); nmr signals at 4.98 m, (H-12), 3.71 (methoxyl), 3.05 (mesylate), 1.21 (C-4 methyl), 1.08 (C-10 methyl), 0.93 d and, 0.85 d (J = 7 cps, isopropyl). Mesylate **15b** was somewhat unstable and eliminated the elements of toluenesulfonic acid on standing with production of a mixture of olefins (*vide infra*). It was therefore not analyzed, but reduced immediately by refluxing 0.2 g of **15b** with 0.4 g of lithium aluminum hydride in 45 ml of anhydrous ether. Excess hydride was destroyed by adding wet ether, water, and finally dilute hydrochloric acid until both layers were clear. The ether layer was washed, dried, and evaporated; yield of crude alcohol was 0.15 g. Treatment of the latter with excess Jones reagent at room temperature followed by the usual work-up and chromatography over silicic acid furnished **4a**, identified by melting point, mixture melting point, nmr, and infrared, as 55% of the eluted material. The remainder of the eluted material was a mixture of olefinic acids.

D.—Catalytic hydrogenation of **18** gave a quantitative yield of **4b**, mp and mmp 97° nmr and infrared spectra were superimposable.

Methyl 12β-Hydroxy-8α,9α,13αH-abietanoate (17).—A solution of 0.35 g of **16** in methanol was allowed to stand with an excess of sodium borohydride, poured into water, and extracted with ether. The washed and dried ether extract was evaporated and the residual oil was chromatographed over neutral alumina to yield 0.3 g of solid **17** (90%). The product was recrystallized from hexane: mp 110–111°; $[\alpha]^{25}\text{D}$ −31° (*c* 0.776); infrared bands at 3450, 1715, and 1250 cm^{-1}; nmr signals at 4.01 m ($w_{1/2}$ = 11 cps, equatorial H-12), 3.62 (methoxyl), 1.20 (C-4 methyl), 1.11 (C-10 methyl), 0.97 d and 0.95 d (J = 6 cps, isopropyl).

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78; O, 14.26. Found: C, 75.23; H, 10.61; O, 14.13.

Methyl Δ^{12}-8α,9αH-Abietenoate (18). A.—A solution of 0.1 g of **15b** in benzene was placed on a column of basic alumina. After 12 hr, the material was eluted. The ether eluates furnished 85 mg of a colorless oil which crystallized on standing. The nmr spectrum indicated the presence of a small amount of the Δ^{11} isomer. Recrystallization from methanol raised the melting point to 110–111°; $[\alpha]^{25}\text{D}$ −43° (*c* 0.802); infrared bands at 1715 and 1225 cm^{-1} (ester); nmr signals at 5.53 m (H-12), 3.68 (methoxyl), 1.17 (C-4 methyl), 0.98 d (J = 7 cps, isopropyl), and 0.91 (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05. Found: C, 79.39; H, 10.55; 0, 10.32.

B.—A solution of 80 mg of **17** in 15 ml of pyridine was chilled to ice bath temperature, mixed with 0.5 ml of methanesulfonyl chloride, allowed to stand at room temperature for 12 hr, poured onto ice, and extracted with ether. Evaporation of the washed and dried ether extract furnished 78 mg of crystalline **18** which was recrystallized from methanol and then melted at 110–111°, mixture melting point with material prepared by route A was undepressed; nmr and infrared spectra were superimposable.

Epoxidation of 8a.—The reaction was carried out following the method of Royals, Bailey, and Kennedy,[9] using *m*-chloroperbenzoic acid instead of monoperphthalic acid, to yield from 6.00 g of crude **8a** 6.00 g of colorless glass. Recrystallization from methyl ethyl ketone gave a mixture of two types of crytals which were separated mechanically. The principal product was **20a**: yield 4.10 g (65%); mp 170–171° (lit.[9] mp 167–168°); nmr signals at 2.50 (H-14), 1.25 (C-4 methyl), 1.00 and 0.94 (isopropyl doublet superimposed on C-10 methyl). The minor product **21a** was recrystallized from methyl ethyl ketone: yield 0.330 g; mp 154–155°; nmr signals at 2.98 (H-14), 1.21 (C-4 methyl), and 0.95 (isopropyl doublet superimposed on C-10 methyl).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.14; H, 10.08.

Esterification of **20a** and **21a** with ethereal diazomethane gave the oily esters **20b** and **21b**.

Methyl 14-Oxo-8α,9α,13βH-abietanoate (22).—To a solution of 0.70 g of **20b** in 10 ml of benzene was added 0.8 ml of freshly distilled boron trifluoride etherate. The reaction mixture was allowed to stand at room temperature for 3 min, then washed with 5% aqueous sodium bicarbonate solution and water and dried. Removal of solvent *in vacuo* yielded 0.73 g of an oil which on triturating with hexane furnished 0.24 g (33%) of **22**, mp 134–135°. The analytical sample was recrystallized from hexane: mp 134–135°; nmr signals at 1.15 (C-4 methyl), 0.89 d and 0.80 d (J = 7 cps, isopropyl), 0.72 (C-10 methyl); ORD curves, $[\alpha]_{600}$ +125°, $[\alpha]_{350}$ +855°, $[\alpha]_{316}$ +2710°, $[\alpha]_{275}$ −2480, $[\alpha]_{210}$ −428° (last reading).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.16; H, 10.09.

Thin layer chromatography of the mother liquors showed the presence of three compounds which could not be obtained in pure form.

When a sample of 0.1 g of **21b** was treated with boron trifluoride etherate in benzene and worked up in the same manner, 0.01 g (10%) of **22** was isolated in crystalline form.

14-Oxo-8β,9α,13βH-abietanoic Acid (10b).—To a solution of 4.27 g of a mixture of **20a** and **21a**, prepared by epoxidation of 5.00 g of crude **8a**, in 100 ml of benzene was added 5.6 g of boron trifluoride etherate. Isolation of the product in the manner described above furnished 3.64 g (85%) of glassy product. Recrystallization from ethanol gave pure **10b**: mp 256–257°; $[\alpha]^{25}\text{D}$ +21° (*c* 0.236) (lit.[10] mp 253–257°; $[\alpha]$ +12°); mmp 252–254°; infrared spectra superimposable; ORD curves (*c* 0.1), $[\alpha]_{600}$ +20.4°, $[\alpha]_{589}$ +20.4°, $[\alpha]_{309}$ −938, $[\alpha]_{264}$ +2535° (last reading).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.73; H, 10.22.

Treatment of 0.570 g of **10b** in 10 ml of tetrahydrofuran with ethereal diazomethane furnished 0.50 g (83%) of **10a**, mp 74–76°, identical (nmr, infrared, tlc) with material, mp 78–80°, supplied by Professor Burgstahler; nmr signals at 1.17 (C-4 methyl), 0.96 (C-10 methyl), 0.89 d (J = 7), and 0.82 d (J = 7 cps, isopropyl). The same substance was also prepared by oxidation of 0.20 g of **12b** in 7 ml of benzene with a solution of 0.25 g of sodium dichromate and 0.25 g of chromic acid in 0.4 ml of acetic acid and 2 ml of water at ice-bath temperature (3 hr) and at room temperature (14 hr). The organic layer was washed, dried, and concentrated. The residue (0.13 g, 65%) melted at 74–76°; the mixture melting point was undepressed.

Thioketals from 10a.—A mixture of 0.30 g of **10a**, 0.9 ml of ethanedithiol, and 0.6 ml of boron trifluoride etherate was stirred at room temperature for 16 hr and diluted with methanol. The solid was washed with methanol, weighed 0.33 g, and was a mixture of two very similar substances (tlc). Recrystallization from methanol–chloroform gave the major component **24**: mp 202–203° (lit.[10] mp 205–206°); nmr signals at 3.62 (methoxyl), 3.14 s (4 p, CH_2S), 1.17 (C-4 methyl), 0.98 d and 0.90 d (J = 7 cps, isopropyl), 0.84 (C-10 methyl). Concentration of the mother liquors gave a small quantity of **25**: mp 192–193°; $[\alpha]^{25}_{D}$ −41° (c 0.776, $CHCl_3$); nmr signals at 3.62 (methoxyl), 3.13 s (4 p, CH_2S), 1.17 (C-4 methyl), 1.07 d and 1.05 d (J = 6 cps, isopropyl), 0.86 (C-10 methyl).

Anal. Calcd for $C_{23}H_{38}O_2S_2$: C, 67.29; H, 9.33. Found: C, 67.03; H, 9.10.

Desulfurization of 0.20 g of **24** in 60 ml of ethanol by refluxing with Raney nickel for 50 hr, filtering, and evaporating *in vacuo* gave 0.14 g, of a colorless oil. Although this material was homogeneous on tlc, it could not be induced to crystallize. Glpc (230°, 6-ft column of silicone rubber on Diatoport S, carrier gas helium, flow rate 70 ml/min) indicated that the product was mainly **5b** contaminated with a trace of **3b** and 13% of a third ester, presumably **6b**, since the retention time of the third compound indicated that it was not **4b**. The infrared spectrum of the ester mixture was identical with that of **5b**.

Thioketals from 22.—When 0.50 g of **22** was mixed with 0.6 ml of ethanedithiol in 2 ml of acetic acid containing 0.6 ml of boron trifluoride etherate and the product was worked up as described in the preceding paragraph, there was obtained 0.38 g of **25**. Thin layer chromatography of the material from the mother liquors (0.22 g) indicated the presence of equal parts of **24** and **25**. When the reaction was carried out in the absence of acetic acid, the only isolable product was **24**.

8β,9α,13αH-Abietanoic Acid (3a). A.—To a solution of 3.52 g of **10b** in 100 ml of diethylene glycol was added 8.4 g of 85% hydrazine hydrate. The reaction mixture was heated at 110° for 2 hr, 6.12 g of potassium hydroxide was added, and the temperature was raised to 200° for 2 hr at which time an additional 6.12 g of potassium hydroxide was added. After 2 more hr at reflux, the solution was poured into ice water, acidified, and extracted with chloroform. The organic layer was washed, dried, and evaporated; the weight of the residue was 2.54 g (76%), mp 197–199°. Recrystallization from acetone gave the analytical sample: mp 201–201.5°, $[\alpha]^{25}_{D}$ +8° (c 0.67) (lit.[8] mp 202°, $[\alpha]$ +7°); nmr signals at 1.18 (C-4 methyl), 0.86 d (J = 6 cps, isopropyl), and 0.85 (C-10 methyl). The substance was identical with material prepared by hydrogenation of **19**.

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.12; H, 11.23.

B.—Desulfurization of 0.25 g of **25** in 60 ml of ethanol with Raney nickel by heating at reflux for 50 hr, filtering, and concentrating *in vacuo* furnished 0.18 g of the methyl ester **3b** as a clear oil which was homogeneous by tlc and glc criteria. It crystallized after lengthy standing and was recrystallized from aqueous methanol: mp 75–77° (lit.[8] mp 77°); nmr signals at 3.71 (methoxyl), 1.19 (C-4 methyl), 0.88 (C-10 methyl), and 0.87 d (J = 7 cps, isopropyl). A solution of this material in 2.6 ml of collidine was refluxed with 1.5 g of lithium iodide for 16 hr, poured into excess 10% hydrochloric acid, and extracted with ether. The washed and dried ether layer was evaporated; the residue melted at 200–201° and was identical with **3a**.

Catalytic Reduction of 19.[8]—A solution of 1.0 g of **19** in 50 ml of acetic acid was hydrogenated with 0.2 g of prereduced platinum oxide at 3 psi for 24 hr, filtered, and diluted with water. The solid was washed and dried (1.0 g); its nmr spectrum showed it to be a mixture of **3a** (60%) and **4a** (40%). No starting material was present. A preliminary separation was effected by preparation and recrystallization of the n-amylamine salts, the salt of **4a** being less soluble. By regenerating the acid with dilute hydrochloric acid and recrystallizing several times, pure **4a** was obtained, mp 162–164°; mixture melting point with **4a** (*vide supra*) was 162–164°; infrared and nmr spectra were superimposable. Regeneration of the acids from the mother liquors of the salts gave a mixture which was considerably enriched in **3a**. Several recrystallizations from ethanol furnished pure **3a**; mixture melting point with **3a** (*vide supra*) was undepressed; nmr and infrared spectra were superimposable.

Oxidation of the Thioketals 24 and 25.—To a solution of 0.20 g of **24** in 25 ml of methylene chloride was added, with cooling, 0.40 g of m-chloroperbenzoic acid. The mixture was allowed to stand at room temperature for 15 hr, heated at reflux for 5 hr, cooled, washed with 5% sodium bisulfite and 5% sodium bicarbonate solution, and evaporated. Recrystallization of the residual white solid (0.20 g, 80%) from acetone furnished the disulfone which melted above 250°: infrared bands at 1715 (ester) and 1123 cm^{-1} (sulfone); nmr signals at 3.70 (methoxyl and $CH_2S\rightarrow O$), 1.19 (C-4 methyl), 1.01 d (J = 7 cps, isopropyl), and 0.92 g (C-10 methyl).

Anal. Calcd for $C_{23}H_{38}O_6S_2$: C, 58.21; H, 8.08. Found: C, 58.05; H, 8.05.

Oxidation of 0.08 g of **25** in the same fashion furnished 0.70 g (70%) of the corresponding disulfone, mp 211–212° after recrystallization from methanol: infrared bands at 1706 (ester) and 1120 cm^{-1} (sulfone); nmr signals at 3.73 ($CH_2S\rightarrow O$), 3.67 (methoxyl), 1.17 (C-4 methyl), 1.13 d (J = 7 cps, isopropyl), and 0.93 (C-10 methyl).

Anal. Calcd for $C_{23}H_{38}O_6S_2$: C, 58.21; H, 8.08. Found: C, 57.94; H, 8.08.

Derivatives of 2-Hydroxyalkylmalonic Acids. Participation by γ-Hydroxy Groups in Reactions of Nucleophiles with the Carboxylic Centers

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Hydrogenation of 4,5-dimethyl-2-oxo-2,5-dihydro-3-furonitrile leads to a mixture of 4,5-dimethyl-2-oxotetrahydro-3-furonitriles in which the isomer with *cis* methyl groups predominates over that with *trans* by a ratio of five to one. Both isomers have been prepared independently and each rearranges on treatment with ammonia or primary amines to give the corresponding 2-amino-2,3-dihydro-3-furamide. From the ultraviolet spectra it appears that the enamino tautomer (with endocyclic double bond) is favored in the case of the simple amino furamides, but the imino tautomer (exocyclic double bond) in the case of the homologs with both nitrogens monomethylated. As do simple lactones, these compounds undergo hydrolysis, ammonolysis, and aminolysis with relative ease. Much of the chemistry can be explained in terms of the establishment of equilibria among open-chain species (which can be considered derivatives of 2-hydroxyethylmalonic acid) and a collection of cyclic species wherein the hydroxy group, γ with respect to each carboxyl function, engages one or the other of them.

That the α-cyano-γ-butyrolactone system will readily (and reversibly) rearrange in the presence of strong base to give a molecule containing an enamine grouping was first reported by Glickman and Cope.[2] More recently, Korte and co-workers have, as part of a much broader study of related isomerizations,[3] confirmed the nature of the reactions: that in the presence of 0.1 molar equiv of sodium ethoxide in ethanol, various 3-cyano-2-oxotetrahydrofurans are transformed into

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(1) To whom inquiries concerning this paper should be sent.

(2) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1012 (1945).

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