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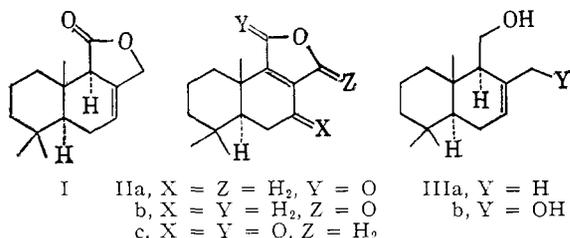
Synthesis of Some Drimanic Sesquiterpenes¹

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The synthesis of four drimanic sesquiterpenes from O-methylpodocarpane and dehydroabietane, by way of drimic acid, is reported. The chemistry of various decalin intermediates is discussed.

Despite the abundance of sesquiterpenes in nature and the great variety of their structural types no representative of the bicycloparnesol type has been isolated until quite recently. However, the last 10 years have witnessed the discovery of a small, but growing, group of substances of this terpene family, among which may be found the constituents of the stem barks of the South American *Drimys* species.² The latter, *e.g.* drimenin (I), isodrimenin (IIa), confertifolin (IIb), and drimenol (IIIa), are of special interest since their structural relationship with the steroids and triterpenes, as evidenced by their gross structure as well as absolute configuration, suggests a close biosynthetic kinship with the higher terpenes.³ The structural similarity of the drimanic sesquiterpenes with the diterpenic resin acids, *e.g.*, abietic and podocarpic acids, and the recent total synthesis of these acids⁴ made the conversion of the latter into the sesquiterpenes an inviting problem of organochemical synthesis. The present communication portrays the synthesis of the natural substances depicted in formulas I, IIa, IIb, and IIIa.



Drimic Acid.—The starting material for our syntheses was to be the anhydride IVa of drimic acid (Va), a well-known product of degradation of various terpenes.^{1a,b,5,6} It was prepared from derivatives (VI) of abietic and podocarpic acids in the following manner. Dehydroabietane (VIa)⁷ was oxidized with chromic acid and the resultant 7-keto derivative (VIb) was converted to the lactone VII on treatment with trifluoroacetic acid. Basic hydrolysis of the lactone yielded the hydroxyacid Vb, whose ozonolysis led to drimic acid (Va). The latter was transformed to its anhydride IVa by refluxing in acetic anhydride.

(1) The authors are indebted to the National Science Foundation for financial support of this work. It was presented for the first time in the course of a series of lectures at the Institut de Chimie des Substances Naturelles (C.N.R.S.), Gif-sur-Yvette, France, in April–May, 1963.

(2) (a) H. H. Appel, C. J. W. Brooks, and K. H. Overton, *J. Chem. Soc.*, 3322 (1959); (b) H. H. Appel, J. D. Connolly, K. H. Overton, and R. P. M. Bond, *ibid.*, 4685 (1960); (c) K. H. Overton, H. H. Appel, and R. P. M. Bond, *Tetrahedron*, **19**, 635 (1963).

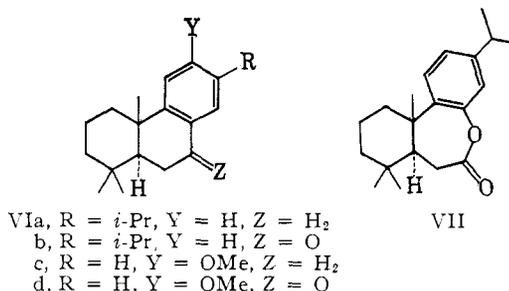
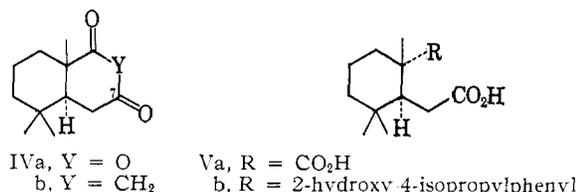
(3) A. Eschenmoser, D. Felix, M. Gut, J. Meier, and P. Stadler in G. E. W. Wolstenholme and M. O'Connor, "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols," Little, Brown and Co., Boston, Mass., 1959, p. 217.

(4) E. Wenkert, A. Afonso, J. B.-son Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964).

(5) K. Schaffner, R. Viterbo, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **39**, 174 (1956).

(6) Y. Chow and H. Erdtman, *Acta Chem. Scand.*, **16**, 1305 (1962).

(7) E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963).



A podocarpic acid derivative was converted into drimic anhydride (IVa) in similar fashion. O-Methylpodocarpane (VIc)⁸ was oxidized with chromic acid, and the 7-keto product VIId⁹ transformed to the anhydride IVa by trifluoroacetic acid oxidation, alkaline hydrolysis, ozonolysis, and acetic anhydride-induced cyclization without characterization of intermediates. The anhydrides obtained from the degradations of the two resin acid derivatives proved to be identical and their hydrolysis product Va showed physical properties in accord with those reported for the terpene degradation product^{1a,b,5,6}

7-Ketoisodrimenin.—When drimic anhydride was treated with dimethylcadmium,¹⁰ the crude acidic product esterified with diazomethane, and the resultant ketoesters treated with potassium *t*-butoxide, the decalindione IVb was obtained. The use of excess organocadmium reagent led to a lactone to which structure VIII (in preference of IX) could be assigned on the basis of an assumed preferential alkylation of C-7 of drimic anhydride (IVa) and the absence of 2–3 p.p.m. signals in the proton magnetic resonance spectrum of the lactone expected for the C-6 methylene hydrogens of a substance of structure IX.¹¹ Etherification of the diketone IVb with acetic methanol¹² afforded the enol ethers Xa and XIa, in 84 and 13% yields, respectively.

Lithium aluminum hydride reduction of Xa and XIa, followed by acid treatment, yielded the unsaturated ketones Xb and XIb, respectively. The optical rotatory dispersion curve¹³ of ketone XIb was strikingly similar to that of its benz-analog 7-ketodehydroabietane

(8) E. Wenkert, V. I. Stenberg, and P. Beak, *J. Am. Chem. Soc.*, **83**, 2320 (1961).

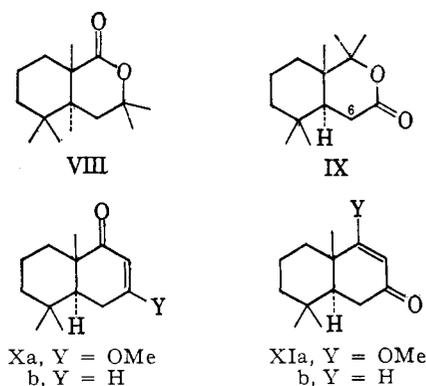
(9) J. Delobelle and M. Fétizon, *Bull. soc. chim. France*, 1894 (1961).

(10) Cf. J. Cason, *J. Org. Chem.*, **13**, 227 (1948).

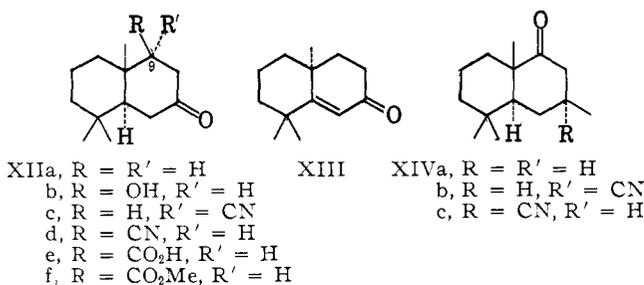
(11) (a) J. B.-son Bredenberg and J. N. Shoolery, *Acta Chem. Scand.*, **14**, 556 (1960); (b) E. Wenkert and R. W. J. Carney, unpublished data.

(12) Cf. (a) H. Conroy, *J. Am. Chem. Soc.*, **74**, 3046 (1952); (b) A. J. Speziale, J. A. Stephens, and Q. E. Thompson, *ibid.*, **76**, 5011 (1954).

(13) The authors are most grateful to Mr. M. M. Marsh, Eli Lilly and Co., for this measurement.



(VIb).^{11b} Catalytic hydrogenation of XIb yielded the saturated ketone XIIa. Comparison of the physical properties of the 2,4-dinitrophenylhydrazone of the latter with those of the derivative of the trimethyldecalone degradation product of widdrol¹⁴ showed the two substances to be optical antipodes.¹⁵ This finding confirms the absolute configuration of the sesquiterpenes widdrol and thujopsene¹⁶ as well as the difficultly predictable stereochemical course of the lithium-ammonia reduction of XIII, the last step of the degradation of widdrol to XIIa enantiomer. Catalytic hydrogenation of Xb yielded the saturated ketone XIVa whose infrared and p.m.r. spectra were identical with those of the known XIVa racemate.¹⁷



The second step of the two-reaction sequence in the reduction of β -alkoxy- α,β -unsaturated ketones to α,β -unsaturated ketones (e.g., Xa \rightarrow XIb) has been exposed recently to mechanistic reinterpretation. In an elegant study Stiles and Longrey¹⁸ have shown that the acid-catalyzed dealcoholation of the β -alkoxyallyl alcohol products of the lithium aluminum hydride reduction of some β -alkoxycyclohexenones proceeds by way of O-protonation and the hemiketal of the final product (path B below) rather than *via* C-protonation and a β -ketol (path A below) as heretofore assumed.¹⁹ When, as a consequence, an unpremeditatedly mild acid work-up of the lithium aluminum hydride reduction of Xa once led to an unexpected ketol, along with the desired unsaturated ketone XIb, the mechanism of the dealcoholation of our bicyclic system became of interest. Hence a qualitative study thereof was undertaken.

(14) C. Enzell, *Acta Chem. Scand.*, **16**, 1553 (1962).

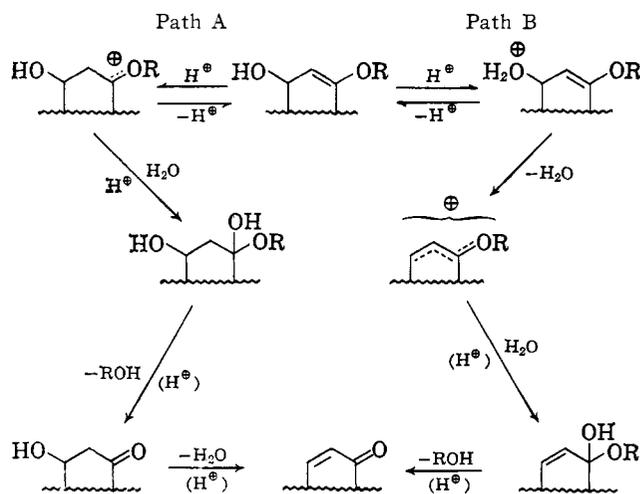
(15) The authors are most grateful to Dr. Enzell for a gift of a sample of his derivative. While this 2,4-dinitrophenylhydrazone was reported to melt at 169–184°, several crystallizations from 95% ethanol converted it to a substance with m.p. 164–166°.

(16) T. Norin, *Acta Chem. Scand.*, **17**, 738 (1963).

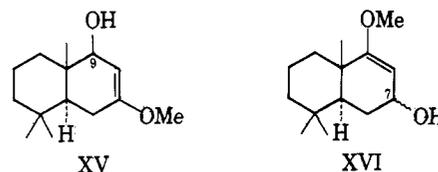
(17) (a) F. Sondheimer and D. Elad, *J. Am. Chem. Soc.*, **79**, 5542 (1957); (b) J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 3441 (1957); (c) the authors are most grateful to Professor Sondheimer for a gift of *d,l*-XIVa.

(18) M. Stiles and A. Longrey, *Tetrahedron Letters*, 337 (1961).

(19) *Inter alia* (a) ref. 11a; (b) C. Tamm, *Helv. Chim. Acta*, **43**, 1700 (1960).



Lithium aluminum hydride reduction of Xa, followed by nonacidic, aqueous work-up, yielded predominantly the enol ether alcohol XV, lesser amounts of the ketol XIIb, and a small quantity of the enone XIb. The C-9 stereochemistry of the primary product as well as the ketol was assigned on the basis of the p.m.r. spectrum of the latter. Its carbinol methine signal (one-proton signal at 3.25–3.58 p.p.m.) was characteristic of an axial hydrogen both in chemical shift and multiplicity. Lithium aluminum hydride reduction of XIa, followed by merely aqueous work-up, gave XVI, whose spectral properties showed it to be an enol ether alcohol although the product resisted purification and, hence, full characterization. It may have been a C₇-epimer mixture. On standing at room temperature for 12 hr. the crude solid became oily. An infrared spectrum of the resulting mixture revealed that XVI had been decomposing into the unsaturated ketone Xb.



Treatment of the enol ether XV with 0.01 *N* alcoholic sulfuric acid for 36 hr. at room temperature afforded a mixture of starting material, ketol XIIb, and unsaturated ketone XIb, as shown by thin-layer chromatography and thereafter by isolation. A similar treatment of XV with 1.0 *N* alcoholic sulfuric acid was complete in 5 min. and yielded ketol and enone in *ca.* 1:1 ratio. The ketol could be shown to be stable to acid under either of these conditions, although it was converted quantitatively to the octalone XIb on being refluxed in 2 *N* alcoholic acid solution for half an hour. In contrast to these observations on the chemistry of XV, the enol ether alcohol XVI proved to be most labile in acid solution. When (immediately after its isolation from a reduction of XIa) the alcohol XVI was exposed to 0.01 *N* alcoholic sulfuric acid, it was transformed quantitatively to the octalone Xb in 30 min. Thus it appears that the hydrolysis of XVI follows path B (*vide supra*) in analogy with the behavior of the simple alkoxy cyclohexenols,¹⁷ while the hydrolysis of XV follows both paths A and B (*vide supra*) and, furthermore, takes place more slowly.

Two reasons can be offered for the anomalous reactivity of XV. The ease of carbinol bond rupture leading

to the alkoxyallyl cation (path B) may be dependent on the conformation of the hydroxyl group. The quasi-equatorial nature of the hydroxyl function in XV is least favorable for optimum p-orbital overlap with the adjacent double bond in the transition state of the bond-breaking step. However, the orientation of the hydroxyl group of the 7 α -isomer of the XVI epimer pair is quasi-axial and, hence, of proper conformation with respect to the C–O bond-breaking step, while the quasi-equatorial hydroxyl function of the 7 β -epimer, although of unfavorable conformation and reminiscent of the situation in XV, is located on a carbon atom whose greater conformational flexibility than that of C-9 in XV (made more rigid by the proximity of a bridgehead of the *trans*-bicyclic system) may permit enough ring deformation for at least partial p-orbital overlap with the neighboring double bond. A second reason for the dissimilarity of the reactivity of XV and XVI toward acid might be found in the possible difference of ease of conversion of the tetrahedral carbinol carbons of the two systems to a trigonal state in the alkoxyallyl cations (path B). Since a double bond in a *trans*-octalin system is more stable at the 7,8- rather than 8,9-positions,²⁰ the extension of multiple-bond character from C₇–C₈ to C-9 in XV might be expected to be energetically less favorable than such extension from C₈–C₉ to C-7 in XVI.

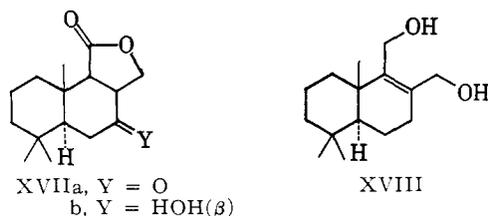
Hydrocyanation²¹ of the unsaturated ketone XIb gave the cyanoketone XIIc in high yield. Conversion of the latter to its C₉-epimer XIIId by ketalation with ethylene glycol and acid, potassium *t*-butoxide-induced isomerization of the intermediate ketal nitrile, and acid hydrolysis of the resultant epimeric ketal nitrile proved the axiality of the cyano group in the hydrocyanation product (XIIc). The complete stereoselectivity of the hydrocyanation was intriguing enough to make a second test of the steric course of this reaction worth undertaking. For this reason the unsaturated ketone Xb was exposed to the same chemical process. It also led to one product (XIVb) exclusively. The latter was shown to possess an axial cyano group by the conversion of XIVb to XIVc in a manner equivalent to the transformation of XIIc to XIIId. Thus the hydrocyanation of conformationally rigid cyclohexenones is a stereoselective process and proceeds by introduction of axial cyano groups. While this fact has been noted previously,^{21,22} the present cases are unique since they represent the first cyclohexenone examples whose carbon-carbon bond-forming site is solely in one ring.

It was noteworthy that the base-catalyzed equilibration of the axial cyano function in XIIc ethylene ketal resulted in complete conversion to XIIId ethylene ketal (and similarly XIVb ethylene ketal \rightarrow XIVc ethylene ketal) despite the fact that in the case of the simple 4-*t*-butylcyanocyclohexanes both axial and equatorial nitrile isomers are present at equilibrium.²³ Presumably the unfavorable steric and polar 1,3-interactions between the cyano group and the axial half of the ketal function greatly destabilize the axial nitrile with respect

to its equatorial epimer. These nonbonded interactions are detected readily in the proton magnetic resonance spectra of the ketals. While the four-proton signals of the ketal bridges in the equatorial ketal nitriles of XIIId and XIVc at *ca.* 4.0 p.p.m. were near-singlets, those of the axial ketal nitriles of XIIc and XIVb were broad multiplets.

Vigorous alkaline hydrolysis of XIIId ethylene ketal and acid-catalyzed deketalation led to ketoacid XIIe. Epimerization at C-9 must have preceded the nitrile hydrolysis, since the same hydrolysis treatment of XIIc ethylene ketal yielded the ketoacid XIIe also. The physical properties of the methyl ester XIIIf of the acid were identical with those recorded for a lanosterol degradation product of like structure.²⁴ Base-induced condensation of the ketoacid XIIe with ethyl formate and subsequent treatment of the formylated product with acetic anhydride and sodium acetate yielded 7-ketoisodrimenin (IIc). Its physical properties were in accord with those reported for the drimenin oxidation product.^{2b}

The Drimanic Sesquiterpenes.—Reduction of 7-ketoisodrimenin (IIc) by chemical means^{2b} or by catalytic hydrogenation afforded the dihydro derivative XVIIa whose sodium borohydride reduction led to the hydroxylactone XVIIb. If it be assumed that hydride attack on XVIIa occurs preferentially from the α -side of the molecular framework, the equatorial β -orientation can be assigned to the 7-hydroxy group of XVIIb. Tosylation of the alcohol and heating of the resultant sulfonic ester in dimethyl sulfoxide solution²⁵ gave drimenin (I),^{2b,26} some starting alcohol XVIIb, and some ketolactone XVIIa. In view of the previous isomerization of drimenin (I) into isodrimenin (IIa)^{2b} the total synthesis of the two sesquiterpenes is complete.



Manganese dioxide oxidation of the diol XVIII, the lithium aluminum hydride reduction product of isodrimenin (IIa),^{2b} yielded confertifolin (IIb)²⁶ and isodrimenin (IIa).²⁶ Acetylation of the diol IIIb, the lithium aluminum hydride reduction product of drimenin (I),^{2b} followed by lithium-ammonia reduction and alkaline hydrolysis, produced drimenol (IIIa).^{26,27} These transformations completed the total synthesis of the remaining two sesquiterpenes (IIb and IIIa).

Experimental

Lactone VII.—A stirring ice-cold mixture of 11.0 g. of 7-ketodehydroabietane (VIb), m.p. 92–93° (lit.⁵ m.p. 83–84°), and 11.0 g. of anhydrous disodium hydrogen phosphate in 300 ml. of

(24) E. Kyburg, B. Riniker, H. R. Schenk, H. Heusser, and O. Jeger, *Helv. Chim. Acta*, **36**, 1891 (1953).

(25) Cf. H. R. Nace, *Chem. Ind. (London)*, 1629 (1958).

(26) The authors are most grateful to Dr. Overton for a comparison sample.

(27) For previous syntheses of *d,l*-drimenol see (a) A. Caliezi and H. Schinz, *Helv. Chim. Acta*, **32**, 2556 (1949); **33**, 1129 (1950); **35**, 1637 (1952); P. A. Stadler, A. Eschenmoser, H. Schinz, and G. Stork, *ibid.*, **40**, 2191 (1957); and (b) E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Am. Chem. Soc.*, **85**, 3295 (1963).

(20) Cf. L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 276.

(21) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963), and previous papers.

(22) W. L. Meyer and N. G. Schnautz, *J. Org. Chem.*, **27**, 2011 (1962), and subsequent papers.

(23) (a) N. L. Allinger and W. Szkrybalo, *ibid.*, **27**, 4601 (1962); (b) B. Rickborn and F. R. Jensen, *ibid.*, **27**, 4606 (1962).

methylene chloride was treated with a cold solution of 18.5 ml. of trifluoroacetic anhydride and 2.2 ml. of 90% hydrogen peroxide in 100 ml. of methylene chloride. After warming to room temperature the mixture was refluxed for 2 hr., washed with 5% sodium hydroxide, and dried over magnesium sulfate. Evaporation of the solvent yielded 10.6 g. of a red oil whose chromatography on silica and elution with benzene produced 7.7 g. of a yellow solid. Two crystallizations from hexane gave 5.9 g. of colorless crystalline lactone VII, m.p. 86.5–87.5°, $[\alpha]_D^{25} -234^\circ$ (c 1.86, CHCl_3); spectra: infrared (CHCl_3), $\text{C}=\text{O}$ 5.74 (s), $\text{C}=\text{C}$ 6.20 (m) μ ; proton magnetic resonance (deuteriochloroform with TMS as internal standard), 3-proton singlets 0.89, 1.12, 1.49 p.p.m. (C—Me); 6-proton doublet 1.23 p.p.m. (J 7 c.p.s.) (i -Pr methyls); 1-proton septet 2.5–3.2 p.p.m. (i -Pr methine); 2-proton multiplet 2.52, 2.57, 2.63, 2.64 p.p.m. (C_6 -methylene).

Anal. Calcd. for $\text{C}_{20}\text{H}_{28}\text{O}_2$: C, 79.95; H, 9.39. Found: C, 80.27; H, 9.45.

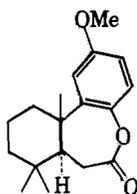
Acid Vb.—A solution of 5.85 g. of lactone VII and 100 ml. of 10% potassium hydroxide in 200 ml. of isopropyl alcohol was refluxed for 1 hr., whereupon it was concentrated under vacuum to ca. a third of its volume, washed with ether, acidified with hydrochloric acid, and extracted with ether. The extract was dried over anhydrous magnesium sulfate, evaporated, and the semisolid residue, 6.2 g., chromatographed on silica. Elution with 9:1 benzene–ether led to 5.91 g. of solid whose crystallization from aqueous methanol gave the hydroxyacid Vb, m.p. 147–149°, $[\alpha]_D^{25} 28.8^\circ$ (c 1.38, CHCl_3); infrared spectrum (CHCl_3), $\text{C}=\text{O}$ 5.90 (s), $\text{C}=\text{C}$ 6.20 (w) μ .

Anal. Calcd. for $\text{C}_{20}\text{H}_{30}\text{O}_3$: C, 75.43; H, 9.50. Found: C, 75.34; H, 9.37.

Drimic Anhydride (IVa). (a).—A solution of 1.84 g. of the acid Vb in 100 ml. of methylene chloride was ozonized exhaustively for 4 hr. at room temperature. The solution was added slowly to a mixture of 100 ml. of 10% sodium hydroxide and 50 ml. of 30% hydrogen peroxide. After stirring for 12 hr. at room temperature, during which time much of the methylene chloride had evaporated, the solution was washed with ether, acidified with hydrochloric acid, and extracted with ether. The extract was washed with water, dried over magnesium sulfate, and evaporated. Chromatography of the residual oil, 1.3 g., on silica and elution with 4:1 benzene–ether yielded 0.60 g. of crude drimic acid Va. A solution of the acid in 15 ml. of acetic anhydride was refluxed for 1.5 hr. and then evaporated. Treatment of the solid residue with Norit in hexane and crystallization from hexane yielded 0.37 g. of drimic anhydride IVa, m.p. 113–114° (crystal change at 66–66.5°), $[\alpha]_D^{25} -42.8^\circ$ (c 8.58, CHCl_3); spectra: infrared (KBr), $\text{C}=\text{O}$ 5.57 (s) and 5.68 (s) μ ; p.m.r., 3-proton singlets 0.96, 0.96, 1.28 p.p.m. (C—Me); 7-proton multiplet 1.3–2.2 p.p.m.; 2-proton multiplet 2.69, 2.78, 2.86, 2.89 (C_6 -methylene).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_3$: C, 68.54; H, 8.63. Found: C, 68.54; H, 8.49.

(b).—An ice-cold mixture of 0.33 ml. of trifluoroacetic anhydride and 0.83 ml. of 90% hydrogen peroxide in 20 ml. of methylene chloride was added to a solution of 0.29 g. of freshly prepared 7-keto-O-methylpodocarpane (VII)⁹ in 25 ml. of methylene chloride and the mixture allowed to stand for 70 hr. at room temperature. Upon evaporation of the solvent the crude product was mixed with 10 ml. of 10% sodium hydroxide and 25 ml. of isopropyl alcohol and refluxed for 0.5 hr. The hydrolysis was worked up as in the preparation of Vb (*vide supra*) and the resulting oily acid, 0.30 g., chromatographed on silica. Elution with 4:1 benzene–ether yielded an oily solid which was dehydrated pyrolytically and sublimed (175°, 2 mm.). Silica chromatography of the product and elution with 19:1 benzene–ether, followed by crystallization from hexane and sublimation (140°, 1 mm.), gave crystalline lactone XIX, m.p. 114–115°, $[\alpha]_D^{25} -254^\circ$ (c



XIX

2.59, CHCl_3); spectra: infrared (CHCl_3), $\text{C}=\text{O}$ 5.72 (s), $\text{C}=\text{C}$ 6.20 (m), 6.61 (s) μ ; p.m.r., 3-proton multiplet 6.6–7.2 p.p.m. (aromatic); 3-proton singlets 3.81 p.p.m. (O—Me); 0.90, 1.13,

1.50 p.p.m. (C—Me); 2-proton multiplet 2.52, 2.55, 2.62, 2.63 p.p.m. (C_6 -methylene).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_3$: C, 74.97; H, 8.39. Found: C, 75.30; H, 8.18.

Exhaustive ozonolysis of 1.70 g. of the crude acid, whose pyrolysis had led to XIX, and work-up as above, followed by acetic anhydride-induced dehydration (*vide supra*), yielded 0.28 g. of drimic anhydride (IVa), m.p. 112–113°, m.m.p. 111–113°; infrared spectrum identical with that of a sample prepared from dehydroabietane (VIa).

A solution of 182 mg. of drimic anhydride (IVa) and 20 ml. of 10% sodium hydroxide in 20 ml. of 95% ethanol was refluxed for 0.5 hr. The solvent was removed by distillation and the solution acidified with hydrochloric acid and extracted with ether. The extract was washed with water, dried (magnesium sulfate), and evaporated. Crystallization of the solid residue, 198 mg., from hexane gave drimic acid (Va), m.p. 166–168° (lit.^{2a} m.p. 167–168°), $[\alpha]_D^{25} -6.5^\circ$ (c 1.44, acetone) [lit.⁵ $[\alpha]_D -6^\circ$ (c 1.04, acetone)].

The Decalindione IVb.—Magnesium turnings, 1.49 g., were added to an ice-cold stirring solution of 55 ml. of methyl iodide in 150 ml. of ether under nitrogen. Upon the disappearance of the magnesium, 5.72 g. of anhydrous powdered cadmium chloride was added and the mixture refluxed under nitrogen for 0.5 hr. It then was concentrated to low volume, 300 ml. of sodium-dried benzene and 4.00 g. of drimic anhydride (IVa) added, and the mixture stirred and refluxed under nitrogen for 8 hr. It was cooled, treated with 200 ml. of 10% sulfuric acid, and stirred for 10 min. The aqueous layer was washed and the combined benzene solutions extracted with 5% sodium hydroxide. The aqueous extract was acidified with hydrochloric acid and extracted with ether. Drying (magnesium sulfate) and, thereafter, evaporation of the extract yielded 4.3 g. of crude ketoacids. An ether solution of the latter was treated with excess diazomethane and left standing at room temperature for 1 hr. The unreacted diazomethane was decomposed with acetic acid and the solution washed with sodium bicarbonate and dried over magnesium sulfate. Solvent evaporation left 4.3 g. of oily ketoesters, which were added to a previously prepared solution of 1.7 g. of potassium in 300 ml. of t -butyl alcohol and the mixture refluxed under nitrogen for 3 hr. The cooled solution was acidified with hydrochloric acid and the solvent evaporated under vacuum. A chloroform solution of the solid residue was washed with water and extracted with 5% sodium hydroxide. The extract was acidified with hydrochloric acid and extracted with chloroform. Drying (magnesium sulfate) and evaporation of the extract and crystallization of the solid residue, 3.67 g., from ethyl acetate–methanol yielded 2.64 g. of crystalline dione IVb, m.p. 194–201°, $[\alpha]_D^{25} -94.8^\circ$ (c 1.43, methanol); infrared spectrum (CHCl_3), $\text{C}=\text{O}$ 5.78 (s), 5.88 (s) μ .

Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{O}_2$: C, 74.96; H, 9.68. Found: C, 74.67; H, 9.52.

Lactone VIII.—Repetition of the above reaction of drimic anhydride with a threefold increase of dimethylcadmium led to a 3:1 mixture of a neutral substance and the ketoacids. Distillation of the former (bath temp. 155–160° (5 mm.)) yielded a clear liquid (solidification on standing; m.p. 40–48°, without crystallization), $[\alpha]_D^{25} 24.1^\circ$ (c 4.22, CHCl_3); spectra: infrared (CHCl_3), $\text{C}=\text{O}$ 5.85 (s) μ ; p.m.r., 3-proton singlets 0.90, 0.92, 1.25, 1.36, 1.47 p.p.m. (C—Me); no signal downfield of 2.2 p.p.m.; p.m.r. spectrum of 7-ketodehydroabietane (VIb): 3-proton singlets 0.93, 1.00, 1.22 p.p.m. (C—Me); 6-proton doublet 1.24 p.p.m. (J 7 c.p.s.) (i -Pr methyls); 1-proton septet 2.4–3.2 p.p.m. (i -Pr methine); 2-proton multiplet 2.59, 2.62, 2.75, 2.76 (C_6 -methylene).

Enol Ethers Xa and XIa.—A solution of 2.00 g. of the diketone IVb and 0.2 g. of p -toluenesulfonic acid in 100 ml. of methanol and 150 ml. of benzene was refluxed with distillation for 5.5 hr. The residual 25 ml. of solution was diluted with 100 ml. of ether, washed with 5% sodium hydroxide, dried (magnesium sulfate), and evaporated. Chromatography of the semisolid residue, 2.19 g., on alumina, elution with benzene, and crystallization of the eluted solid, 1.78 g., from hexane yielded the enol ether Xa, m.p. 55.5–57°, $[\alpha]_D -81.1^\circ$ (c 2.55, CHCl_3); spectra: infrared (CHCl_3), $\text{C}=\text{O}$ 6.09 (s), $\text{C}=\text{C}$ 6.18 (s) μ ; p.m.r., 3-proton singlets 0.93, 0.98, 1.08 p.p.m. (C—Me); 2-proton multiplet 2.3–2.5 p.p.m. (C_6 -methylene); 3-proton singlet 3.68 p.p.m. (O—Me); 1-proton singlet 5.20 p.p.m. [C_8 -H].

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_2$: C, 75.63; H, 9.97. Found: C, 75.59; H, 9.71.

Further elution, with 4:1 benzene-ether, led to 0.31 g. of an isomeric product whose distillation (bath temp. 130° (1 mm.)) and subsequent sublimation yielded crystalline enol ether XIa, m.p. 68–70°, $[\alpha]_D^{25}$ 78.8° (*c* 2.48, CHCl_3); spectra: infrared (CHCl_3), $\text{C}=\text{O}$ 6.10 (s) μ ; p.m.r., 3-proton singlets 0.92, 0.95, 1.23 p.p.m. (C—Me); 2-proton multiplet 2.30, 2.37, 2.48, 2.49 p.p.m. (C_6 -methylene); 3-proton singlet 3.68 p.p.m. (O—Me); 1-proton singlet 5.20 p.p.m. (C_8 -H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_2$: C, 75.63; H, 9.97. Found: C, 75.89; H, 9.78.

Lithium Aluminum Hydride Reductions of (a) Xa and (b) XIa.
(a).—A solution of 1.00 g. of the enol ether Xa in 100 ml. of ether was treated slowly with 0.25 g. of lithium aluminum hydride and the mixture stirred at room temperature for 1 hr. The excess hydride was decomposed by the cautious addition of moist sodium sulfate. The mixture was filtered and the filtrate evaporated. A solution of the residue and 4 ml. of concentrated hydrochloric acid in 100 ml. of 95% ethanol was left standing at room temperature for 10 min. The solvent was evaporated and an ether solution of the residue washed with 5% sodium hydroxide and dried (magnesium sulfate). Evaporation of the ether and distillation (bath temp. 90–95° (1.5 mm.)) of the residue gave 0.75 g. of liquid unsaturated ketone XIb, $[\alpha]_D^{25}$ 7.4° (*c* 2.81, CHCl_3); spectra: infrared (CHCl_3), $\text{C}=\text{O}$ 6.00 (s), $\text{C}=\text{C}$ 6.11 (w) μ ; p.m.r., 3-proton singlets 0.90, 0.92, 1.10 p.p.m. (C—Me); 2-proton multiplet 2.31, 2.38, 2.48 p.p.m. (C_6 -methylene); 1-proton doublets 5.67 p.p.m. (*J* 10 c.p.s.) (C_8 -H); 6.65 p.p.m. (*J* 10 c.p.s.) (C_9 -H); O.R.D. in dioxane (*c* 0.097): $[\alpha]_{450} + 67^\circ$, $[\alpha]_{400} + 235^\circ$, $[\alpha]_{370} + 490^\circ$, $[\alpha]_{372} + 470^\circ$, $[\alpha]_{365} + 480^\circ$, $[\alpha]_{350} - 140^\circ$, $[\alpha]_{323} - 770^\circ$, $[\alpha]_{317} - 750^\circ$, $[\alpha]_{312} - 770^\circ$, $[\alpha]_{300} - 690^\circ$; in methanol: $[\alpha]_{450} + 100^\circ$, $[\alpha]_{450} + 235^\circ$, $[\alpha]_{362} + 750^\circ$, $[\alpha]_{350} + 502^\circ$, $[\alpha]_{320} - 1010^\circ$.

Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: C, 81.20; H, 10.48. Found: C, 80.91; H, 10.31.

When the ethereal filtrate from the above work-up with moist sodium sulfate was dried (anhydrous sodium sulfate) and evaporated and the oily residue, 988 mg., tested by thin layer chromatography on silica, a three-component mixture was revealed. Chromatography of the mixture on alumina and elution with 19:1 benzene-ether gave 58 mg. of XIb; infrared spectrum identical with that of the above sample. Elution with 9:1 benzene-ether afforded 416 mg. of a solid whose crystallization from hexane gave the enol ether alcohol XV, m.p. 96–97°, $[\alpha]_D^{25}$ -53.3° (*c* 1.24, CHCl_3); spectra: infrared (CHCl_3), OH 2.80 (w), 2.92 (w, broad), $\text{C}=\text{O}$ 6.00 (s), 6.13 (w) μ ; p.m.r., 3-proton singlets 0.86, 0.89, 0.93 p.p.m. (C—Me); 3.52 p.p.m. (O—Me); 2-proton multiplet *ca.* 2.0 p.p.m. (C_6 -methylene); 1-proton singlets (broad) *ca.* 3.9 p.p.m. (C_8 -H); *ca.* 4.4 p.p.m. (C_9 -H). Further elution, with ether, led to 174 mg. of a solid whose crystallization from hexane yielded colorless needles of ketol XIIb, m.p. 111–112°, $[\alpha]_D^{25}$ -27.3° (*c* 2.43, CHCl_3); spectra: infrared (CHCl_3), OH 2.79 (w), 2.90 (w, broad), $\text{C}=\text{O}$ 5.84 (s) μ ; p.m.r., 3-proton singlets 0.87, 0.90, 1.06 p.p.m. (C—Me); 4-proton multiplet 2.3–2.6 p.p.m. (C_6 - and C_8 -methylenes); 1-proton multiplet 3.25–3.58 (C_9 -methine).

Anal. Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 74.24; H, 10.54. Found: C, 73.96; H, 10.47.

(b).—Lithium aluminum hydride, 30 mg., was added slowly to a solution of 70 mg. of enol ether XIa in 10 ml. of ether and the mixture stirred at room temperature for 1 hr. The excess hydride was decomposed with water and the ether solution filtered and dried (magnesium sulfate). Evaporation of the solvent led to 63 mg. of a solid, m.p. 80–94° after crystallization from hexane and vacuum drying. The substance (XVI), whose infrared spectrum revealed no carbonyl band but the presence of hydroxyl and enol ether groups, could not be purified further and became oily on standing at room temperature for 12 hr. The infrared spectrum of the oil showed the presence of the unsaturated ketone Xb. The combined fractions of the solid were dissolved in 10 ml. of ethanolic 0.01 *N* sulfuric acid and left standing at room temperature for 0.5 hr. The solution was neutralized with 5% sodium bicarbonate and evaporated under vacuum. An ether solution of the residue was washed with water, dried (magnesium sulfate), and evaporated. Distillation (bath temperature 95–100° (1 mm.)) of the residual oil, 60 mg., yielded liquid unsaturated ketone Xb, $[\alpha]_D^{25}$ -41° (*c* 1.38, CHCl_3); spectra: infrared (film), $\text{C}=\text{O}$ 5.99 (s), $\text{C}=\text{C}$ 6.01 (w) μ ; p.m.r., 3-proton singlets 0.94, 1.01, 1.09 p.p.m. (C—Me); 2-proton multiplet 2.2–2.5 p.p.m. (C_6 -methylene); 1-proton hexet 5.91 p.p.m. (*J* 2, 10

c.p.s.) (C_8 -H); 1-proton 12-line signal 6.95 p.p.m. (*J* 2, 10, <1 c.p.s.) (C_7 -H).

Anal. Calcd. $\text{C}_{13}\text{H}_{20}\text{O}_2$: C, 81.20; H, 10.48. Found: C, 80.91; H, 10.63.

Decalones XIII and XIVa.—A mixture of 100 mg. of ketone XIb and 40 mg. of 5% palladium-charcoal in 15 ml. of ethyl acetate was stirred under hydrogen at atmospheric pressure and room temperature for 4 hr. Filtration of the catalyst and evaporation of the filtrate led to 92 mg. of an oil whose distillation (bath temperature 80–90° (1 mm.)) afforded 72 mg. of liquid decalone XIIa, $[\alpha]_D^{25}$ -11.5° (*c* 3.99, CHCl_3); spectra: infrared (CHCl_3), $\text{C}=\text{O}$ 5.85 (s) μ ; p.m.r., 3-proton singlets 0.87, 0.87, 1.12 p.p.m. (C—Me); 4-proton multiplet 2.1–2.5 p.p.m. (C_6 - and C_8 -methylenes).

Anal. Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 80.35; H, 11.41. Found: C, 79.99; H, 11.28.

Its 2,4-dinitrophenylhydrazone was prepared by standard procedure and crystallized from 95% ethanol. Its m.p. 164–165° was the same as that of the Enzell derivative.^{14,15} Their infrared spectra (Nujol) were identical in all details.

A mixture of 107 mg. of Xb and 30 mg. of 10% palladium-charcoal in 15 ml. of ethyl acetate was stirred under hydrogen at atmospheric pressure and room temperature for 1 hr. Filtration of the catalyst and evaporation of the filtrate led to 105 mg. of oil whose distillation (bath temp. 80–85° (1 mm.)) gave liquid decalone XIVa, $[\alpha]_D^{25}$ -39.4° (*c* 2.14, CHCl_3); spectra: infrared (film), superposable on the spectrum of its racemate¹⁷; p.m.r., 3-proton singlets 0.90, 0.93, 1.14 p.p.m. (C—Me). Crystallization of its 2,4-dinitrophenylhydrazone from methanolic ethyl acetate gave a derivative, m.p. 165.5–167°.

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_2\text{N}_4$: C, 60.94; H, 7.00; N, 14.96. Found: C, 60.83; H, 7.24; N, 15.04.

Hydrolyses of XV and XIIb.—A solution of 135 mg. of hydroxy enol ether XV in 10 ml. of 0.01 *N* ethanolic sulfuric acid was left standing at room temperature for 36 hr. The solution was neutralized with 5% sodium bicarbonate and evaporated under vacuum. An ether solution of the residue was washed with water, dried (magnesium sulfate), and evaporated. Thin layer chromatography (t.l.c.) of the residual oil, 121 mg., showed it to be a mixture of starting material, XIIb, and XIb. Alumina chromatography of the mixture and elution with benzene gave 33 mg. of unsaturated ketone XIb. Elution with 19:1 benzene-ether afforded 19 mg. of unreacted starting compound and elution with ether yielded 62 mg. of ketol XIIb, m.p. 110.5–111.5°.

A solution of 339 mg. of XV in 25 ml. of 1.0 *N* ethanolic sulfuric acid was left standing at room temperature for 5 min. Work-up as above led to 268 mg. of oily solid which a t.l.c. (silica) analysis showed to be a mixture of XIb and XIIb. Alumina chromatography and benzene elution yielded 135 mg. of ketone XIb, while ether elution yielded 144 mg. of ketol XIIb.

A solution of 35 mg. of ketol XIIb in 5 ml. of 0.01 *N* ethanolic sulfuric acid was left standing at room temperature for 36 hr. Work-up as above led to 33 mg. of unreacted ketol. Similar treatment of 90 mg. of ketol with 10 ml. of 1.0 *N* ethanolic sulfuric acid for 5 min. gave 90 mg. of unreacted starting compound.

A solution of 75 mg. of ketol XIIb in 12 ml. of 2 *N* alcoholic sulfuric acid was refluxed for 0.5 hr. Usual work-up led to 67 mg. of unsaturated ketone XIb.

Ketones of Type XII.—A solution of 2.19 g. of XIb in 50 ml. of dimethylformamide was treated with a solution of 1.16 g. of potassium cyanide and 0.84 g. of ammonium chloride in 20 ml. of water and the mixture stirred at 100° for 3 hr. It then was cooled, added to 500 ml. of ether, washed with water, dried (magnesium sulfate), and evaporated. Alumina chromatography of the semisolid residue, 2.59 g., and elution with 19:1 benzene-ether afforded 2.19 g. of a solid whose crystallization from hexane gave 2.00 g. of cyanoketone XIIc, m.p. 102–103°, $[\alpha]_D^{25}$ -33.7° (*c* 1.91, CHCl_3); spectra: infrared (KBr), $\text{C}=\text{N}$ 4.50 (w), $\text{C}=\text{O}$ 5.83 (s) μ ; p.m.r., 3-proton singlets 0.89, 0.89, 1.21 p.p.m. (C—Me).

Anal. Calcd. for $\text{C}_{14}\text{H}_{21}\text{ON}$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.82; H, 9.45; N, 6.40.

A solution of 1.31 g. of the cyanoketone XIIc, 30 mg. of *p*-toluenesulfonic acid, and 25 ml. of ethylene glycol in 300 ml. of benzene was refluxed for 7 hr. in the presence of a Dean-Stark water separator. Much of the benzene was removed by distillation, 200 ml. of ether was added, and the solution washed with water and dried (magnesium sulfate). Evaporation of the solvent left 1.66 g. of colorless crystalline XIIc ketal; spectra: infrared (CHCl_3), carbonyl band absent; p.m.r., 3-proton singlets 0.81,

0.90, 1.04 p.p.m. (C—Me); 1-proton triplet 2.47 p.p.m. (*J* 4 c.p.s.) (probably C₆-H); 4-proton multiplet 3.90–4.05 p.p.m. (ketal methylenes). A solution of the ketal and 0.66 g. of potassium in 75 ml. of *t*-butyl alcohol was left standing at room temperature for 10 hr. The solution was diluted with 400 ml. of ether, washed with water, and dried (magnesium sulfate). Solvent evaporation yielded 1.63 g. of crystalline XIId ketal; p.m.r. spectrum, 3-proton singlets 0.82, 0.88, 1.11 p.p.m. (C—Me); 4-proton singlet (broad) 3.95 p.p.m. (ketal methylenes).

A solution of this ketal and 5 ml. of concentrated hydrochloric acid in 150 ml. of acetone was refluxed for 0.5 hr. The solution was evaporated and an ether solution of the residue washed with water, dried (magnesium sulfate), and evaporated. Decoloration of the residue, 1.28 g., with Norit in ether and crystallization from hexane yielded colorless crystals of XIId, m.p. 100–101°, [α]_D²⁵ -4.2° (*c* 1.50, CHCl₃); spectra: infrared (KBr), C≡N 4.48 (w), C=O 5.83 (s) μ ; p.m.r., 3-proton singlets 0.89, 0.89, 1.28 p.p.m. (C—Me); 5-proton multiplet 2.1–2.7 p.p.m. (C₆- and C₈-methylenes and C₉-H).

Anal. Calcd. for C₁₄H₂₁ON: C, 76.66; H, 9.65. Found: C, 77.00; H, 9.57.

A solution of 128 mg. of XIc ketal and 3.0 g. of potassium hydroxide in 15 ml. of diethylene glycol was stirred at 200° under nitrogen for 24 hr. The cooled solution was diluted with 50 ml. of water, washed with ether, acidified with hydrochloric acid, and extracted with ether. The extract was evaporated and a solution of the residue and 1 ml. of concentrated hydrochloric acid in 25 ml. of acetone refluxed for 0.5 hr. The solvent was evaporated and an ether solution of the residue washed with water, dried (magnesium sulfate), and evaporated. Treatment of the residue with Norit in methanol, followed by crystallization from aqueous methanol and sublimation (170° (1 mm.)), gave 73 mg. of the ketoacid XIIE, m.p. 210–212°, [α]_D²⁵ 37.2° (*c* 1.84, CHCl₃); infrared spectrum (CHCl₃), OH 2.88 (w) 3.2–3.3 (m, shoulder), C=O 5.85 (s) μ . Treatment of 52 mg. of XIId ketal with 2.0 g. of potassium hydroxide in 10 ml. of diethylene glycol under the aforementioned conditions led to the identical ketoacid XIIE (identical m.p. and infrared spectrum).

An ether solution of 95 mg. of ketoacid XIIE was treated with excess of diazomethane in ether and left standing at room temperature for 3 hr. Work-up in the usual manner and crystallization of the product from aqueous methanol and sublimation (80° (1 mm.)) gave 83 mg. of ketoester XIIIf, m.p. 67–68° (lit.²⁴ m.p. "under 50°"), [α]_D²⁵ 40° (*c* 1.75, CHCl₃) (lit.²⁴ [α]_D²⁵ 38°); spectra: infrared (CCl₄), C=O 5.76 (s), 5.82 (s) μ ; p.m.r., 3-proton singlets 0.88, 0.90, 1.18 p.p.m. (C—Me); 3.71 p.p.m. (O—Me); 5-proton multiplet 2.2–2.7 p.p.m. (C₆- and C₈-methylenes and C₉-H).

Anal. Calcd. for C₁₅H₂₄O₃: C, 71.39; H, 9.59. Found: C, 71.24; H, 9.53.

Crystallization of XIIIf 2,4-dinitrophenylhydrazone from methanolic methylene chloride yielded the derivative, m.p. 221–223° (lit.²⁴ m.p. 216–217°).

Ketones XIVb and c.—A solution of 78 mg. of ketone Xb in 10 ml. of dimethylformamide was treated with a solution of 53 mg. of potassium cyanide and 32 mg. of ammonium chloride in 4 ml. of water and the mixture stirred at 100° for 3 hr. It then was cooled, added to 100 ml. of ether, washed with water, dried (magnesium sulfate), and evaporated. Crystallization of the solid residue, 93 mg., from hexane and sublimation (110° (0.4 mm.)) yielded the cyanoketone XIVb, m.p. 102–103°, [α]_D²⁵ -43.6° (*c* 3.46, CHCl₃); spectra: infrared (CHCl₃), C≡N 4.48 (w), C=O 5.84 (s) μ ; p.m.r., 3-proton singlets 0.96, 0.96, 1.17 p.p.m. (C—Me); 1-proton multiplet 3.2–3.6 p.p.m. (C₇-H), 2-proton multiplet 2.5–3.0 p.p.m. (C₈-methylene).

Anal. Calcd. for C₁₄H₂₁ON: N, 6.39. Found: N, 6.29.

A solution of 190 mg. of the cyanoketone XIVb, a trace of *p*-toluenesulfonic acid, and 5 ml. of ethylene glycol in 30 ml. of benzene was refluxed for 7 hr. in the presence of a Dean-Stark water separator. The cooled solution was diluted with 50 ml. of ether, washed with water, and dried (magnesium sulfate). Evaporation of the solvent gave colorless crystalline XIVb ketal, 226 mg.; spectra: infrared (CHCl₃), C=O band missing; p.m.r., 3-proton singlets 0.82, 0.94, 1.04 p.p.m. (C—Me); 1-proton multiplet 2.95–3.22 p.p.m. (C₇-H); 4-proton multiplet 3.7–4.2 p.p.m. (ketal methylenes). A solution of the ketal and 100 mg. of potassium in 15 ml. of *t*-butyl alcohol was left standing at room temperature for 10 hr. The solution was added to 100 ml. of ether, washed with water, and dried (magnesium sulfate). Solvent evaporation yielded 205 mg. of liquid XIVc ketal; p.m.r.

spectrum, 3-proton singlets 0.85, 0.90, 1.07 p.p.m. (C—Me); 4-proton multiplet 3.8–4.0 p.p.m. (ketal methylenes).

A solution of this ketal and 1 ml. of concentrated hydrochloric acid in 50 ml. of acetone was refluxed for 15 min. The solution was evaporated and an ether solution of the residue washed with 5% sodium bicarbonate, dried (magnesium sulfate), and evaporated. Distillation (bath temp. 135–140° (1 mm.)) of the residue, 183 mg., yielded colorless liquid cyanoketone XIVc, which refused to solidify although being shown to be a single substance, different from XIVb, by t.l.c. on silica; [α]_D²⁵ -47.4° (*c* 2.39, CHCl₃); spectra: infrared (film), C≡N 4.45 (w), C=O 5.86 (s) μ ; p.m.r., 3-proton singlets 0.96, 0.96, 1.20 p.p.m. (C—Me); 5-proton multiplet 2.5–3.0 p.p.m. (C₈-methylene and C₇-H).

Anal. Calcd. for C₁₄H₂₁ON: N, 6.39. Found: N, 6.28.

7-Ketoisodrimenin (IIc).—A solution of 70 mg. of ketoacid XIIE, 2 ml. of ethyl formate, and 50 mg. of potassium in 2 ml. of *t*-butyl alcohol was stirred at room temperature for 12 hr. Upon evaporation of the solvent under vacuum 5% hydrochloric acid was added and the mixture extracted with ether. The extract was washed with water, dried (magnesium sulfate), and evaporated. A mixture of the residue and 30 mg. of fused sodium acetate in 3 ml. of acetic anhydride was heated on a steam bath for 0.5 hr. The reaction mixture was taken to dryness under vacuum and an ether solution of the residue washed with water, dried (magnesium sulfate), and evaporated. Chromatography of the residual oil, 80 mg., on alumina (Giulini, activity III), elution with 4:1 hexane–benzene, and sublimation (140° (1 mm.)) gave 35 mg. of a solid whose crystallization from hexane yielded crystalline plates of 7-ketoisodrimenin (IIc), m.p. 111–112° (lit.^{2b} m.p. 112–113°); infrared spectrum (CCl₄), C=O 5.63 (s), 5.91 (s) μ .

7-Ketodihydrodrimenin (XVIIa).—A mixture of 10 mg. of 7-ketoisodrimenin, 10 mg. of 10% palladium–charcoal, and 2 drops of sulfuric acid in 5 ml. of ethyl acetate was stirred under hydrogen at atmospheric pressure and room temperature for 12 hr. The catalyst was filtered and the filtrate diluted with ether, washed with 5% sodium bicarbonate, dried (magnesium sulfate), and evaporated. Distillation (bath temp. 140° (1 mm.)) of the residual oil, 10 mg., and crystallization of the distillate from hexane yielded XVIIa, m.p., m.m.p. 124–125° (lit.^{2b} m.p. 124–126°); infrared spectrum (CCl₄), C=O 5.64 (s), 5.85 (s) μ ; identical in all respects with a sample obtained by zinc–acetic acid reduction of IIc.^{2b}

7 β -Hydroxydihydrodrimenin (XVIIb).—A solution of 100 mg. of 7-ketodihydrodrimenin and 20 mg. of sodium borohydride in 25 ml. of 95% ethanol was stirred at room temperature for 2 hr. The solution was evaporated and an ether solution of the residue washed with water, dried (magnesium sulfate), and evaporated. Crystallization of the residual oil, 74 mg., from hexane–benzene and sublimation (135° (1 mm.)) yielded colorless needles of 7-hydroxydihydrodrimenin (XVIIb), m.p. 159–161°, [α]_D²⁵ -66.8° (*c* 2.39, CHCl₃); infrared spectrum (CHCl₃), OH 2.80 (m), 2.90 (w, broad), C=O 5.67 (s) μ .

Anal. Calcd. for C₁₅H₂₄O₂: C, 71.39; H, 9.59. Found: C, 71.69; H, 9.38.

Drimenin (I).—A solution of 46 mg. of 7-hydroxydihydrodrimenin and 100 mg. of *p*-toluenesulfonyl chloride in 10 ml. of pyridine was left standing at room temperature for 5 days. The solution was diluted with 50 ml. of water and extracted with ether. The extract was washed with 5% hydrochloric acid, 5% sodium bicarbonate, and water, dried (magnesium sulfate), and evaporated. A solution of the residual, pale yellow oil, 65 mg., in 15 ml. of dimethyl sulfoxide was stirred under nitrogen at 100° for 1.5 hr. The cooled solution was diluted with 70 ml. of water and extracted with ether. The extract was dried (magnesium sulfate) and evaporated. Chromatography of the residue, 47 mg., on silica and elution with benzene yielded 17 mg. of a solid whose crystallization from hexane and sublimation (120° (0.4 mm.)) led to drimenin (I), m.p., m.m.p. 132–133° (lit.^{2b} m.p. 133°); spectra: infrared[(KBr) C=O 5.70 (s) μ], identical with that of an authentic sample²⁶; p.m.r., 3-proton singlets 0.89–0.92 p.p.m. (3 C—Me); 2-proton multiplet 4.57–4.72 p.p.m. (lactone methylene); 1-proton multiplet 5.62–5.84 p.p.m. (C₇-H). Continued elution with 4:1 benzene–ether yielded 8 mg. of crude ketolactone XVIIa (identified by its infrared spectrum and t.l.c. behavior), while elution with 1:1 benzene–ether gave unreacted hydroxylactone XVIIb.

Confertifolin (IIb).—A mixture of 12 mg. of diol XVIII, prepared by the reduction of isodrimenin,^{2b} and 100 mg. of manganese dioxide in 3 ml. of ether was stirred at room temperature for 12 hr. The undissolved solid was filtered and washed with

methanol and the combined filtrates evaporated. Thin layer chromatography of the residue, 10 mg., revealed the presence of both isodrimenin and confertifolin. Crystallization of the solid mixture from hexane and sublimation (120° (1 mm.)) afforded needles of confertifolin, m.p. $152.5\text{--}153.5^{\circ}$ (lit.^{2b} m.p. 152°), m.m.p. $152\text{--}153^{\circ}$; infrared spectrum identical with that of an authentic sample.^{2b}

Drimenol (IIIa).—A solution of 21 mg. of the diol IIIb, prepared by the reduction of drimenin,^{2b} and 3 mg. of sodium acetate in 5 ml. of acetic anhydride was heated on the steam bath for 0.5 hr. The solution was evaporated under vacuum and a solution of the residue in 6 ml. of sodium-dried tetrahydrofuran and 15 ml. of liquid ammonia was treated with 18 mg. of lithium wire and stirred for 1.5 hr. The solvents were allowed to evaporate at room temperature, the residue dissolved in ether, and the resulting solution washed with water, dried (magnesium sulfate), and evaporated. A solution of the residual oil, 20 mg. in 7 ml. of 5% sodium hy-

droxide and 10 ml. of 95% ethanol, was refluxed for 1 hr. The mixture was concentrated and extracted with ether. The extract was dried (magnesium sulfate), evaporated, and the residual oil chromatographed on a 5-mm. thick silica plate. The chromatogram was developed with 19:1 benzene-ethyl acetate, the positions of the products determined by their fluorescence under ultraviolet light and the products isolated by the extraction of individual portions of the silica plate with the aforementioned solvent pair. Filtration and evaporation of one eluate and sublimation (70° (1 mm.)) of the resultant oil, 9 mg., gave 8 mg. of a solid whose crystallization from hexane afforded drimenol, m.p., m.m.p. $94\text{--}95^{\circ}$ (lit.^{2a} m.p. $97\text{--}98^{\circ}$) spectra: infrared [(KBr) OH 3.15 (m, broad), C=C 5.98 (w) μ] identical with that of an authentic sample^{2b}; p.m.r., 9-proton singlet 0.88 p.p.m. (3 C—Me); 3-proton multiplet 1.80 p.p.m. (C₈-Me); 2-proton multiplet 3.70–3.86 p.p.m. (hydroxymethyl); 1-proton multiplet 5.45–5.62 p.p.m. (C₇-H).

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Isothermal Unfolding of Globular Proteins in Aqueous Urea Solutions¹

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The theoretical equations for the unfolding of globular proteins, presented in an earlier paper, are applied to the unfolding produced by the action of urea. The course of unfolding is shown to depend primarily on interactions with the solvent, which can be determined from solubility studies on model compounds. Since appropriate solubility studies have been carried out in urea solutions, it is possible to make a quantitative comparison between theoretical and experimental unfolding curves in urea. The theoretical calculation depends on an estimate of the fraction of hydrophobic and peptide groups which are buried in the native structure and exposed during unfolding. With reasonable estimates of this fraction, it is found that, for most proteins, the observed course of unfolding in urea is incompatible with calculations based on an all-or-none reaction. Stable intermediate states must occur between the native and fully unfolded conformations. The number of such intermediate states is small for β -lactoglobulin: for this protein the possibility of an all-or-none process is not excluded entirely. In ribonuclease the data suggest the presence of about three regions able to unfold independently. In larger protein molecules the number of intermediate states may be even larger. The urea concentration at the midpoint of the experimental transition curve gives a value for the difference in free energy ($\Delta F_{u,H_2O}^{\circ}$) between native and unfolded proteins in water. This result does not depend on whether stable intermediate forms occur during unfolding. The value of $\Delta F_{u,H_2O}^{\circ}$ at 25° , for several proteins, is found to lie in the neighborhood of 100–200 cal./mole per amino acid residue.

It is the purpose of this paper to account quantitatively for the unfolding of globular proteins by aqueous urea solutions, using the general theoretical treatment of unfolding proposed in an earlier paper.² It will be seen that the calculations required can be made with considerably greater certainty than those presented in the earlier paper, because fewer assumptions are necessary. In the earlier paper the objective was to calculate the difference in free energy between a native globular protein conformation and an unfolded conformation of the same protein. It was necessary to make assumptions about the detailed structure within the globular form, and about the degree of flexibility in the unfolded form. For the present calculations, a much less detailed model is necessary; only the effect of solvent composition on the free energy of unfolding is required, and to make this calculation one only has to know which parts of the molecule are in contact with the solvent in both the globular and unfolded forms. The actual structure within the globular conformation does not enter into the calculation.

As was true of the earlier paper, the quantitative estimates of free energies of interaction with solvent are based on solubility studies of model compounds.

In this paper, the solubilities of amino acids and related compounds in aqueous urea solutions, determined in this laboratory,³ will be employed.

Theory

A schematic representation of the native, compactly folded conformation of a globular protein is shown in Fig. 1. It is a linear chain of $-\text{NH}-\text{CH}-\text{CO}-$ groups (rectangles) from which side chains (circles) project. Some of the peptide units and side chains, shown in black, are in contact with the solvent, but many more, shown in white, are assumed to be within the globular structure and to have no contact with solvent. It will be assumed that only a single conformation of this kind exists in the water-urea solvent system at a given temperature, and that practically all molecules possess this conformation when no urea is present.

A similar schematic representation of a highly unfolded protein molecule also is shown in Fig. 1. The polypeptide chain in this state of the molecule is assumed to be flexible, so that the relative positions of various parts of the chain do not remain fixed: the figure may be taken to represent a time average. From the point of view of the present paper, the important feature of the unfolded molecule, as contrasted with the native form, is that nearly all of its parts are in

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