water and 10 ml. of 2 *N* hydrochloric acid. The solution was stirred in the cold for 30 min. and then 1.06 g. of benzaldehyde was added. After 10 min. stirring at room temperature, solid began to appear in the mixture. The beige-colored solid was separated after 2 hr. yielding 2.15 g. (47.3%) of product melting at 107–111° with considerable bubbling. The product was purified by dissolving in cold ethanol and precipitating by the addition of water to yield a straw-colored solid, m.p. 109–111° dec.

Anal. Calcd. for $C_{10}H_9N_7$: C, 52.85; H, 4.00; N, 43.16. Found: C, 52.80; H, 4.18; N, 43.10.

Decomposition of 3-Azido-4-benzylideneamino-5-methyl-*s*-triazole (V).—A solution of 2.27 g. of V in 250 ml. of chlorobenzene was decomposed by heating at 115–120°. A smooth liberation of gas was observed at this temperature, although some bubbling was initially observed at about 100°. A total of 217 ml. (theory 224 ml.) was collected during the first 2 hr.; however, heating was continued for 4 hr. Upon cooling to room temperature, a white solid separated from the bright yellow reaction mixture. This solid was collected by filtration and the filtrate was concentrated to yield additional solid. A total of 1.78 g. (89.6%) of the 1H-6-methyl-2-phenyl-*s*-triazolo[3,2-*c*]-*s*-triazole (VI) melting at 223–226° was obtained. Recrystallizations from benzene containing a small amount of alcohol yielded white needles, m.p. 226–228° (lit.[7] m.p. 228.5°).

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.29; H, 4.56; N, 35.16. Found: C, 60.57; H, 4.63; N, 35.29.

4-Acetamido-3-benzylidenehydrazino-5-methyl-*s*-triazole Hydrochloride (VII). A.—Benzaldehyde (1.1 g.) was added to a solution of 2.48 g. of the diacetyl derivative II in 30 ml. of water, 2 ml. of ethanol, and 1 drop of concentrated hydrochloric acid. The yellow solution was heated gently at 60–80° for 30 min. when a voluminous quantity of white precipitate separated. The mixture was cooled to room temperature and the solid was collected by filtration to yield 1.75 g. (59.3%) of product melting at 275–283° dec. This product was recrystallized from ethanol containing a few drops of 6 *N* hydrochloric acid to yield an analytical sample, m.p. 302–304° dec.

Anal. Calcd. for $C_{12}H_{15}ClN_6O$: C, 48.89; H, 5.13; Cl, 12.03; N, 28.52. Found: C, 48.98; H, 5.32; Cl, 12.01; N, 28.5.

B.—A solution of 2.53 g. of 3-benzylidenehydrazino-4-amino-5-methyl-*s*-triazole hydrochloride (VIII) and 1.10 g. of acetic anhydride in 60 ml. of acetic acid was heated for 15 min. The white solid which separated was collected by filtration yielding 1.60 g. (54.3%) of product melting at 270–280° dec. The product was recrystallized from ethanol, m.p. 302–304° dec. A mixture melting point with 4-acetamido-3-benzylidenehydrazino-5-methyl-*s*-triazole hydrochloride (VII) prepared earlier showed no depression. Furthermore, their infrared spectra were identical.

4-Amino-3-benzylidenehydrazino-5-methyl-*s*-triazole Hydrochloride (VIII).—This compound was prepared from III and benzaldehyde in 83% yield. An analytical sample, m.p. 250–251° dec., was obtained by recrystallizations from ethanol.

Anal. Calcd. for $C_{10}H_{13}ClN_6$: C, 47.52; H, 5.19; N, 33.26. Found: C, 47.4; H, 5.12; N, 33.4.

4-Benzylideneamino-3-benzylidenehydrazino-5-methyl-*s*-triazole (IX).—This compound was prepared in 75.6% yield by the reaction of III with excess benzaldehyde and triethylamine. A bright yellow analytical sample, m.p. 187.5–189°, was obtained by recrystallizations from benzene.

Anal. Calcd. for $C_{17}H_{16}N_6$: C, 67.09; H, 5.30; N, 27.62. Found: C, 66.99; H, 5.21; N, 27.5.

1-(4-Amino-5-methyl-*s*-triazol-3-yl)-3,5-dimethylpyrazole Hydrochloride (X).—A solution of 1.65 g. of III and 1.00 g. of 2,4-pentanedione in 75 ml. of ethanol was refluxed for 1 hr. The solvent was removed leaving a pale yellow residue (2.14 g., 93.5%) melting at 183–192°. A white solid melting at 192–195° was obtained by recrystallizations from isopropyl alcohol containing a few drops of 6 *N* hydrochloric acid.

Anal. Calcd. for $C_8H_{13}ClN_6$: C, 42.02; H, 5.73; N, 36.75. Found: C, 42.17; H, 5.81; N, 36.9.

The treatment of X with benzaldehyde produced a 99% yield of 1-(4-benzylideneamine-5-methyl-*s*-triazol-3-yl)-3,5-dimethylpyrazole. An analytical sample was obtained by recrystallization from an ethanol–water mixture.

Anal. Calcd. for $C_{15}H_{16}N_6$: C, 64.26; H, 5.75; N, 29.98. Found: C, 64.2; H, 5.64; N, 29.7.

1-[5-Methyl-*s*-triazol-3-yl)-3,5-dimethylpyrazole (XI).—A solution of 0.78 g. of sodium nitrite in 5 ml. of water was added dropwise to a cold solution (ice–salt bath) of 2.29 g. of X in 10 ml. of water and 5 ml. of 2 *N* hydrochloric acid. The addition caused the mixture to froth vigorously and a precipitate separated. The mixture was stirred in the cold for 1 hr. and then filtered to yield 1.24 g. (70%) of a white solid melting at 150–154°. An analytical sample, m.p. 155–156°, was obtained by recrystallization from acetonitrile.

Anal. Calcd. for $C_8H_{11}N_5$: C, 54.22; H, 6.25; N, 39.53. Found: C, 54.2; H, 6.20; N, 39.6.

Acknowledgment.—The authors are indebted to Dr. L. Schieler for his helpful interest and to Dr. L. Krbechek for many helpful discussions of this work.

The Proton Magnetic Resonance Spectral Characteristics of Tricyclic Diterpenic Substances

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The proton magnetic resonance spectra of derivatives of dehydroabietic and podocarpic acids, of their 5-epimers, and of pimaric, sandaracopimaric, and isopimaric acids are discussed. A correlation of the chemical shifts of methyl groups and other side chains is presented. The stereochemistry of the conformationally flexible A/B *cis* compounds is analyzed.

In recent years we have become increasingly dependent on proton magnetic resonance (p.m.r.) spectra for rapid aid in the solution of structure problems in the chemistry of diterpenic substances. The spectral characteristics of the commonly encountered vinyl,[4] hydroxymethyl or acetoxymethyl,[5] and methyl[6] groups have been described and the chemical shifts and mul-

(1) Public Health Service Predoctoral Research Fellow, 1960–1961.

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(3) National Science Foundation Cooperative Fellow, 1962–1964.

(4) (a) E. Wenkert and P. Beak, *J. Am. Chem. Soc.*, **83**, 998 (1961). Our first-order analysis of the vinyl ABC patterns for rimuene, methyl pimarate, methyl sandaracopimarate, and methyl isopimarate has been shown by complete computational analysis [C. L. Leicht, unpublished data; R. M. Carman, *Australian J. Chem.*, **16**, 1104 (1963)] to yield incorrect coupling constants. (b) E. Wenkert, P. Beak, and P. K. Grant, *Chem. Ind.* (London), 1574 (1961). The coupling constants of the vinyl multiplets of manoyl and epimanoyl oxides, listed herein, are also suspect. The exact line positions and intensities of the reported systems are available from our laboratory on request.

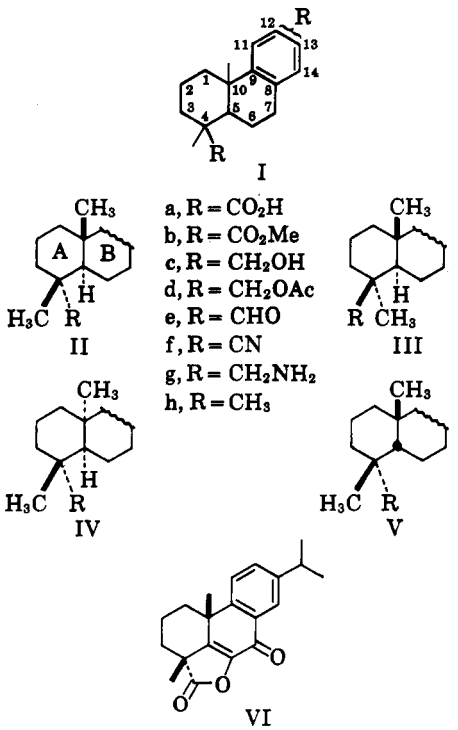
(5) (a) E. Wenkert and P. Beak, *Tetrahedron Letters*, 358 (1961); (b) A. Gaudemer, J. Polonsky, and E. Wenkert, *Bull. chim. soc. France*, 407 (1964).

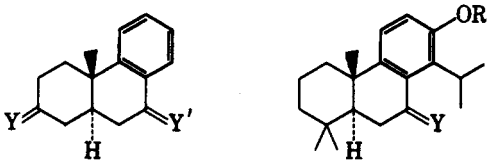
(6) (a) C. H. Brieskorn, A. Fuchs, J. B-s. Bredenberg, J. D. McChesney, and E. Wenkert, *J. Org. Chem.*, **29**, 2293 (1964); (b) E. Wenkert, P. W. Jeffs, and J. R. Mahajan, *J. Am. Chem. Soc.*, **86**, 2218 (1964); (c) J. C. W. Chien, *ibid.*, **83**, 4762 (1960).

tiplicities of some ring hydrogens[6] have been portrayed. However a body of p.m.r. data based on the vast array of diterpenic compounds which have accumulated through our structure and synthesis studies has only been alluded to[7] and not yet discussed. It is the purpose of the present communication to present these data and to illustrate their important potential as diagnostic criteria of stereochemistry.

Ring C Aromatic Tricyclic Compounds.—Absolute configuration aside, the three asymmetric centers, C-4, C-5, and C-10, of generalized formula I yield four classes of compounds. Three classes are represented by the well-known derivatives of (a) dehydroabietic and deisopropyldehydroabietic acids (IIa), (b) podocarpic and desoxypodocarpic acids (IIIa), and (c) 5-isodesoxypodocarpic acid enantiomer (IVa),[8] while the fourth class, typified by the derivatives of 5-isodehydroabietic acid (Va), became available upon discovery of Va as the product of hydrogenation of the enol lactone VI.[9,10] The last class was enlarged by the ready conversion of the acid Va into its derivatives (Vb, c, and d) (see Experimental). The availability of many derivatives (II–V) of the four types of acids permitted a correlation of their structures with their p.m.r. spectral characteristics.

The A,B *trans* configuration, ring A chair conformation, and unrestricted C-4 equatorial substituents of compounds of the dehydroabietic (II) type make this group a good reference series. The chemical shift of the 10-methyl function in this series is 1.18–1.22 p.p.m.[11a] and that of its 7-keto derivatives 1.22–1.26 p.p.m.[11b,12] These resonances are surprisingly downfield of those of perhaps the best models, the synthetic hydrocarbon VIIa (1.07 p.p.m.) and its 7-keto derivative VIIb (1.18 p.p.m.).[13] On the assumption that the 4,4-unsubstituted compounds VII possess ring A chair and ring B half-chair conformations the chemical shift discrepancy can be accommodated by assigning a ring B half-boat conformation to the 4,4-disubstituted compounds. While the ring B half-chair conformation places the angular methyl group as far above the plane of the aromatic ring C as possible within the constraints of the tricyclic system, the angle subtended by the ring C plane and that defined by C-9, C-10, and the 10-methyl carbon is decreased in the half-boat conformation and the resultant tilt of the angular methyl–C-9 axis places the methyl group into the stronger deshielding zone of the aromatic ring. This can account for the 0.13 p.p.m. difference of the $\delta_{10\text{-Me}}$-values of VIIa





(7) *Cf.* footnote 18 in ref. 6b.

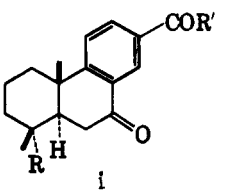
(8) *Cf.* E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963), and references therein.

(9) This hydrogenation has been reported previously [E. Wenkert, R. W. J. Carney, and C. Kaneko, *J. Am. Chem. Soc.*, **83**, 4440 (1961)] to yield dehydroabietic acid (IIa). However repeated hydrogenations of VI have led now exclusively to the 5-iso compound, in consonance with reported findings in a related case [S. N. Mahapatra and R. M. Dodson, *Chem. Ind.* (London), 253 (1963)]. Reduction of the enol lactone VI by sodium borohydride has been stated to yield a 7-hydroxy-6-lactone of assumed A/B *trans* stereochemistry. However it now has been shown that this reduction product belongs to the 5-iso series (R. W. J. Carney, unpublished observation). Furthermore, the borohydride reduction is most sensitive to changes to reaction conditions and capable of forming a variety of products (B. L. Mylari, unpublished observation).

(10) The Mahapatra and Dodson case[9] and ours represent only the first two examples of hydrogenation of 5,6-dehydro ring C aromatic diterpenic derivatives leading to A/B *cis* systems. Previous arguments notwithstanding [G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **84**, 284 (1962); G. Stork, A. Meisels, and J. E. Davies, *ibid.*, **85**, 3419 (1963)], the stereochemistry of hydrogenation of the conformationally flexible Δ^5-compounds cannot be predicted with certainty. One possible reason for the heretofore invariant formation of A/B *trans* products may be the result of preference of olefin adsorption on the catalyst from the olefin's α molecular face so as to yield optimum π-orbital (of both the Δ^5-linkage and the aromatic ring C) "immersion" into the catalyst surface in the substrate–catalyst complex. Inspection of models of compounds of type VI reveal that the strain introduced into such substances by the C-4–C-6 bridging lactone unit opens up the β-side of the molecular framework for catalyst approach by greatly increasing the nonbonded distance between the C-4 and C-10 methyl groups, while preventing simultaneous complexing of the Δ^5-linkage and the aromatic ring with the catalyst by distorting the α-side into concave shape.

(11) Based on analysis of the p.m.r. spectra of (a) fourteen, (b) six, (c) seventeen, (d) three, (e) eight, (f) three, and (g) four substances.

(12) Polar substituents of the aromatic ring at a position *para* to the carbon bearing the angular methyl group would be expected to affect the chemical shift of the 10-methyl function. Thus it is not surprising that the methyl signals of the above dehydroabietic compounds are slightly downfield of those (1.14–1.20 p.p.m.) cited for a similar group of substances containing, however, several totarol (VIIIa) derivatives.[6a] Moreover, 13-acyl-7-keto compounds reveal their 10-methyl signal downfield of their 7-ketodehydroabietic relatives, *e.g.*, i (R = Me, R′ = OMe), 1.27 p.p.m.,[8] and



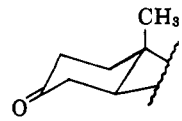
i

(R = CO_2Me, R′ = Me), 1.29 p.p.m. [first reference in footnote 9; P. F. Ritchie, T. F. Sanderson, and L. F. McBurney, *J. Am. Chem. Soc.*, **76**, 723 (1954)].

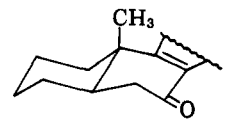
(13) E. Wenkert and J. W. Chamberlin, *J. Org. Chem.*, **25**, 2027 (1960).

and II.[14,15] Since the introduction of 4α- and 4β-substituents into the hydrophenanthrene ring system injects energetically unfavorable nonbonded interactions not only into ring A but also into ring B, a 1,3-diaxial interaction of the 4β-substituent and 6β-H and the *peri* interaction of the 4α-substituent and 6α-H, the deformation of ring B in the dehydroabietic (II) series is perhaps not too surprising.[16] The presence of the neighboring aromatic ring C decreases the otherwise unfavorable 1,2-eclipsing and stem-to-stern nonbonded interactions expected in a boat conformation.

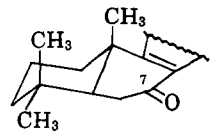
The difference of chemical shift of the methyl groups of the hydrocarbon VIIa and its 7-keto derivative VIIb, 0.11 p.p.m., is characteristic of the deshielding effect exerted by a carbonyl group in a chair form cyclohexane ring upon a "*para*" methyl group. The lower magnitude of the $\Delta\delta$-value, compared with *ca.* 0.2 p.p.m. for 7-ketoisopimaric,[6b] steroid derivatives,[17] and VIIc (δ_{Me} = 1.29 p.p.m.), may be ascribed to displacement of the methyl group from the strongest deshielding zone of the carbonyl group by the flattening of ring B through its fusion to an aromatic ring and, conceivably, to a change of the anisotropy of the carbonyl group through its conjugation with aromatic ring C. Further lowering of the size of the chemical shift difference, *e.g.*, $\Delta\delta_{10\text{-}Me}$ = 0.04 p.p.m. for II and 7-keto-II, reflects a change of conformation of ring B to one of half-boat, wherein the angular methyl group finds itself close to the boundary of carbonyl deshielding and the beginning of the shielding cone of the carbonyl function. This boundary is actually passed in the totarol series VIII. 7-Ketototarol acetate (VIIIb) has a more shielded angular methyl group (1.12 p.p.m.) than totarol acetate (VIIIc) (1.20 p.p.m.).[6a] Presumably, the strong buttressing by the C-13 and C-14 substituents in VIIIb compresses ring B into a nearly classical boat form and thus places the angular methyl group within the shielding cone of the 7-keto function. The ring B conformation differences of VIIb, 7-keto-II, and VIIIb are reflected also by the position and shape of the AB part of the ABC multiplets representing the C-5 and C-6 hydrogens of the three compounds.



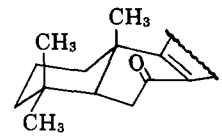
VIIc



VIIb



7-keto-II



VIIIb

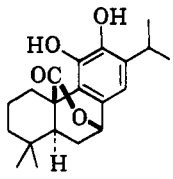
The C-4 methyl groups of the dehydroabietic series II are slightly deshielded by the aromatic ring C and hence show p.m.r. signals somewhat downfield (*e.g.*, IIh, $\delta_{4\text{-}Me}$ = 0.94 p.p.m.) of the 4-methyl signals of ring C hydroaromatic substances (*e.g.*, pimarane and isopimarane derivatives, $\delta_{4\text{-}Me} \sim 0.85$ p.p.m.).[6b] The axial 4-methyl groups of 7-ketodehydroabietic compounds are deshielded further by *ca.* 0.06 p.p.m., while the introduction of a 7-keto function into podocarpic compounds III[11d] leaves their equatorial 4-methyl groups unperturbed. This interaction of a C-4 axial substituent with the 7-keto group, a consequence of the proximity of the two groups in the ring B half-boat conformation, is reflected also in a paramagnetic shift of the signal (3.75 p.p.m.) of the carbomethoxy hydrogens of the 7-keto derivatives of podocarpic esters IIIb from its customary position (3.68 p.p.m.). The angular methyl signal (1.15 p.p.m.) of 7-keto-IIIb represents approximately the effect of the usual deshielding by the 7-keto group and shielding by the carbomethoxy function (*vide infra*).

The greatest influence on the chemical shift of the 4-methyl groups in the dehydroabietic series II is exerted by the other C-4 substituents. While hydroxymethyl (IIc) and aminomethyl (IIg) functions show some shielding (by 0.06 and 0.05 p.p.m., respectively) and the acetoxymethyl (IId) group exerts no effect, strong deshielding is shown by the carboxaldehyde (IIe), carboxy (IIa), carbomethoxy, and nitrile functions (by 0.23, 0.34, 0.34, and 0.46 p.p.m., respectively). This *gem* effect parallels the chemical shift differences we observed among neopentane derivatives.

The *gem* effect of the C-4 substituents is approximately the same in the podocarpic series III,[11c] with the exception of the effect of the hydroxymethyl (IIIc),

(14) (a) *Cf.* J. A. Steele, L. A. Cohen, and E. Mossettig, *J. Am. Chem. Soc.*, **85**, 1134 (1963). (b) Calculations based upon the results of C. E. Johnson and F. A. Bovey [*J. Chem. Phys.*, **29**, 1012 (1958)] predict that the resonance position of the C-10 methyl in the ring B half-boat conformation should appear at ~0.1 p.p.m. downfield of that of the ring B half-chair. This is in good agreement with our results. It is also noteworthy that *t*-butylbenzene, whose methyl groups have the same proximity relationship to the benzene ring as the angular methyl functions of VIIa and II but bear an approximately random steric relationship to the plane of the aromatic ring, shows a methyl signal at 1.31 p.p.m.

(15) Compounds of 7β-hydroxy-IIh and 7β-acetoxy-IIh structure, prepared by hydride reduction of 7-keto compounds (and, in the second case, by subsequent acetylation) and shown to possess the 7β-configuration by the identity of their $\delta_{7\text{-}H}$-value (4.80 and 6.09 p.p.m., respectively) with that of similar substances derived from carnosol (ii),[6a] have angular methyl



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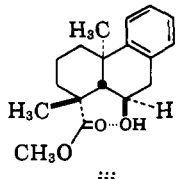
signals at 1.26 and 1.28 p.p.m., respectively. Thus, even these compounds appear to be in ring B half-boat conformation despite the fact that 7β-substituents are quasi-equatorial in the half-chair conformation. The 7β-substituents would be expected to contribute to the deshielding of the angular methyl function because of their proximity to the latter in the ring B half-boat conformation. This accounts for the difference of their chemical shift from that of IIh (= IIIh) (1.18 p.p.m.). Finally, a ring B half-boat conformation helps explain the extraordinary ease of lactonization in the carnosol (ii) series[6a] [C. H. Brieskorn and A. Fuchs, *Chem. Ber.*, **95**, 3034 (1962); J. D. McChesney, unpublished observations], involving the formation of a highly strained δ-lactone.

(16) In favorable cases ring A deformation can be expected also. While 3-keto-Δ^5-4,4-disubstituted compounds represent such cases [E. Wenkert, A. Afonso, J. B-s. Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964)], a striking example is iii, whose intramolecular hydro-



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gen bond (private communication from Dr. Akira Tahara) must be the consequence of a ring A twist conformation.

(17) *Cf.*, *inter alia*, D. H. Williams, N. S. Bhacca, and C. Djerassi, *ibid.*, **85**, 2810 (1963).

acetoxymethyl (IIId), and aminomethyl (IIIg) functions on the 4-methyl group. These substituents deshield the 4-methyl group by 0.12, 0.12, and 0.06 p.p.m., respectively, presumably because their bulk and 1,3-diaxial interaction with the angular methyl group leads to population predominance of the rotamer whose 4-methylene hetero atom resides in close proximity of the 4-methyl group. A further consequence of the equilibrium predominance of such rotamers is the complete lack of influence of the axial C-4 substituents on the angular methyl group (δ = 1.20 p.p.m.), in sharp contrast with the shielding by carbonyl groups (IIIa, b, and e, by 0.07, 0.15, and 0.13 p.p.m., respectively) and the strong deshielding by the cyano function (IIIf by *ca.* 0.20 p.p.m.).[18]

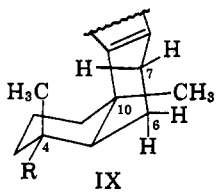
Analysis of the p.m.r. spectra of the A/B *cis* analogs of the dehydroabietic and podocarpic series on the basis of the above data for the parent compounds yields interesting insight into the structures of these conformationally complex substances. The flexibility of the ring system of the 5-isopodocarpic enantiomer series IV leads to an array of conformer possibilities, *e.g.*, the chain forms IX and X and ring A twist and ring B half-boat variants thereof, whose lowest energy form would be expected to be greatly dependent on the nature of the C-4 substituent. As Table I of chemical

TABLE I
CHEMICAL SHIFTS

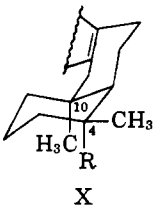
Compd.	$\delta_{4\text{-Me}}$[a]	$\delta_{10\text{-Me}}$[a]	7-Keto $\delta_{4\text{-Me}}$[a]	7-Keto $\delta_{10\text{-Me}}$[a]
IVa	1.12	1.30		
IVb	1.09	1.22	0.69	1.33
IVc	0.32	1.17		
IVd	0.41	1.20	0.32	1.33
IVe	0.85	1.22		
IVf	1.59	1.27	0.80	1.39
IVg	0.33	1.18		
IVh	0.32, 0.90	1.15		
Va	1.50	1.50		
Vb	1.36	1.36		
Vc	1.01	1.19		
Vd	1.00	1.19		

[a] Expressed in parts per million.

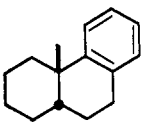
shifts of methyl groups (*vide infra*)[11e] indicates, the saturated substituents of IVc, d, g, and h limit these substances to varying degrees of the ring B half-boat form of IX. Such conformations satisfy the need of the bulky C-4 substituents to be equatorially oriented, while diminishing the unfavorable interactions of IX between the 6α-, 6β-, and 7β-hydrogens and the 10-methyl group, the C-4 substituent and the 4-methyl function, respectively. As a consequence, the 4-methyl group is located above the aromatic ring C and strongly shielded, while the angular methyl group is approximately within the same ring C environment it occupies in the dehydroabietic (II) and podocarpic (III) series. The equatorial nature of the C-4 substituents in compounds IVc and d is further confirmed by the presence of an AB pair of doublets [$(\delta_A + \delta_B)/2$ = 3.34 and 3.90 p.p.m., respectively; J = 11.3 c.p.s.] characteristic of equatorial hydroxy- and acetoxymethyl groups, respectively.[5,19] Lack of sufficient data precludes a definitive assignment of the conformation of the ring system of the synthetic A/B *cis* hydrocarbon XI.[13] Its methyl signal at 1.23 p.p.m. suggests a conformation intermediate between IX and X or its equilibrium mixture equivalent.



IX



X



XI

The methyl chemical shift data of the remaining members of the 5-isopodocarpic enantiomer series (IV) and of three 7-keto-IV cases indicate these substances to be further examples of conformational complexity. The ester IVb, aldehyde IVe, and nitrile IVf appear to be ring B half-boat, ring A twist variants of the conformation IX. Such states would be favored over the aforementioned conformation of the compounds IV with tetrahedral C-4 side chains, since the smaller C-4 substituents have less need for equatorial status and their reorientation gives strain relief by allowing the bulky 4-methyl group to assume a more equatorial orientation. The resultant intermediary conformational state of the C-4 side chain is verified at least in one case by the aldehyde hydrogen signal of IVe (9.58 p.p.m.) whose position is between that characteristic of axial and that of equatorial carboxaldehyde units (*vide infra*). Despite the distortion of ring A from a chair conformation the 4-methyl group remains within the sphere of magnetic influence of aromatic ring C. In the ester IVb and aldehyde IVe the methyl group is shielded by *ca.* 0.2–0.3 p.p.m., while in the nitrile it is outside the shielding cone of the benzene ring and is deshielded by *ca.* 0.2 p.p.m.

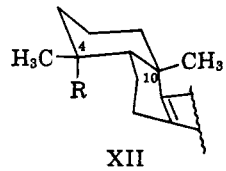
Introduction of a 7-keto group into the 5-isopodocarpic enantiomer IV[11f] skeleton would be expected to lead to conformational changes because of the removal of the unfavorable nonbonded interaction of the 7β-hydrogen in IX and the diminishing interactions of the C-6 hydrogens. The strong deshielding of the angular methyl group of the three cases studied, 7-keto-IVb, d, and f, suggests a general bond reorientation of 7-keto-IX in the direction of 7-keto-X. While placing the 10-methyl group into a strong deshielding zone of the 7-keto group, the reorientation is mild enough to keep the 4-methyl function within the shielding cone of the carbonyl group.[20]

(18) Since our initial observation on the 1,3-diaxial effect of a cyano group on the chemical shift of a methyl function, this topic has been discussed by A. D. Cross and I. T. Harrison [*ibid.*, **85**, 3223 (1963), and references contained therein].

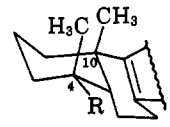
(19) (a) $(\delta_A + \delta_B)/2$ is cited in these cases since this is characteristic of the axial or equatorial orientation of the group in question. δ_A's and δ_B's are available on request. (b) The 0.09-p.p.m. difference of the chemical shift of the 4-methyl group of IVd from that of IVc or IVh may be due to slight deshielding by the acetate's carbonyl group.

(20) It is noteworthy that the resultant over-all conformation of 5-iso-7-ketopodocarpic enantiomer compounds, whose first approximation is 7-keto-IX, is the one put forward for these compounds in an attempt to justify the difference of rate of oxidation of A/B *trans* and *cis*, tricarbocyclic, ring C aromatic diterpenic substances, the basis of a diagnostic test of stereochemistry [E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80**, 211 (1958)].

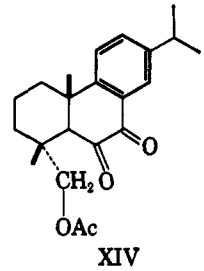
As Table I indicates, the 5-isodehydroabietic series V[11g] is reminiscent of the 5-isopodocarpic enantiomer series IV in its conformational complexity. However, it is evident from even cursory inspection of the p.m.r. data that XIII, one of the two all-chair conformations of V and 5-isodehydroabietic analog of X, can be excluded from further consideration.[21] While the 10-methyl chemical shift data also rule out the other all-chair conformation XII, the methyl signals of Vc and d and their comparison with those of the hydrocarbon IVh suggest a ring B half-boat form of XII or, more likely, a generally bond-redistributed form of XII (in the direction of XIII) for these 5-isodehydroabietic compounds. The ester Vb appears to be a more drastically reoriented form of XII. Despite these bond reorientations the C-4 substituents remain within the shielding cone of the aromatic ring C, as illustrated by the anomalous upfield positions of the signals of the carbomethoxy hydrogens (3.40 p.p.m.) of Vb and the oxymethylene hydrogens of Vc and d [$(\delta_A + \delta_B)/2$ = 2.96 and 3.38 p.p.m., respectively; J = 11 c.p.s.[5]]. The ready chromic acid oxidation of Vd to the diketone XIV is in agreement with its conformational analysis.[20]



XII

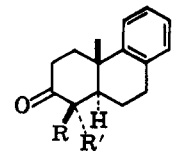


XIII



XIV

In connection with our syntheses in the resin acid field[22] we have encountered several 3-keto A/B *trans* compounds XV whose methyl chemical shifts are listed in Table II. With the exception of the aforementioned all-chair conformation of ketone VIIc, all 3-keto compounds appear to exist in ring A chair, ring B half-boat conformation. Calculations, based on this conformation and taking into account all previously discussed functional group effects, including the deshielding of a 4α-methyl group by a 3-keto function by *ca.* 0.2 p.p.m., are in accord with the data. The carbomethoxy hydrogens of the esters XVa and c have normal δ-values, while the aldehyde hydrogen of XVb shows a signal of chemical shift (9.77 p.p.m.) similar to that of axial aldehydes (IIIe, 9.93 p.p.m.) and greatly different from that of equatorial aldehydes (IIe, 9.29 p.p.m.).[23] The aldehyde XVb does not exhibit the long-range spin–spin coupling ($J \sim 1$ c.p.s.), characteristic of the aldehydes IIIe and IVe.[24]



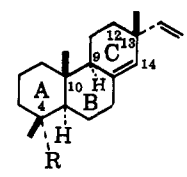
XVa, R = CO_2Me; R' = Me
b, R = CHO; R' = Me
c, R = Me; R' = CO_2Me

TABLE II
CHEMICAL SHIFTS

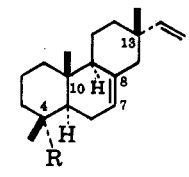
Compd.	$\delta_{4\text{-Me}}$[a]	$\delta_{10\text{-Me}}$[a]
VIIc		1.29
XVa	1.46	1.31
XVb	1.36	1.33
XVc	1.30	1.42

[a] Expressed in parts per million.

Pimaradienic Compounds.—In connection with our study of the structure of rimuene[4a] and the synthesis of hibaenic diterpenes[6b] an analysis of the p.m.r. spectra of derivatives of sandaracopimaric (XVI), pimaric (13-iso-XVI), and isopimaric (XVII) acids was undertaken.[6c] Table III lists the methyl chemical shifts of compounds of the three series with varying C-4 substituents.[25] The difference of location of the nuclear double bond in the isopimaric (XVII) compounds[26] makes this series distinct from the other two. While the isopimaric 13-methyl signal is upfield of that of the other series, its 4β-methyl, 10-methyl, and nuclear olefinic hydrogen (5.35 p.p.m.) signals are located downfield of those of the other two groups of pimaradienic substances. More strikingly, interesting differences can be discerned between the two 13-epimer series. The 10-methyl, 13-methyl, and nuclear olefinic (XVI, 5.23 p.p.m.; 13-iso-XVI, 5.15 p.p.m.) hydrogen signals are downfield in the p.m.r. spectra of the sandaracopimaric (XVI) series compared with those of the pimaric (13-iso-XVI) series, while the 4α-substituent [XVIc, 9.19 p.p.m.; XVId, $(\delta_A + \delta_B)/2$ = 3.24 p.p.m. (J = 10.6 c.p.s.)[5b]; 13-iso-XVIc, 9.25 p.p.m.; 13-iso-XVId; $(\delta_A + \delta_B)/2$ = 3.32 p.p.m. (J = 10.6 c.p.s.)[5b]] hydrogen resonances appear at higher field in



XVI



XVII

a, R = CO_2H
b, R = CO_2Me
c, R = CHO
d, R = CH_2OH
e, R = CH_2OAc
f, R = Me

(21) This ignores the acid Va whose anomalous δ_{Me}-values preclude complete conformational analysis. The methyl chemical shifts of the acids IIIa and IVa suffer from similar anomalies. Since these compounds may exist in varying degrees as dimers in deuteriochloroform solution, the apparent anisotropy and size of the carboxyl group is unpredictable in the absence of more data.

(22) Reference in footnote 16.

(23) *Cf.* T. J. King and J. P. Yardley, *J. Chem. Soc.*, 4308 (1961); R. A. Laidlaw and J. W. Morgan, *ibid.*, 644 (1963); W. R. Chan, C. Willis, M. P. Cava, and R. P. Stein, *Chem. Ind.* (London), 495 (1963).

(24) This coupling was first observed in the laboratory of Professor W. L. Meyer on O-methylpodocarpal (IIIe). Other examples of long-range coupling of aldehyde hydrogen are presented by D. R. Davis, R. P. Lutz and J. D. Roberts [*J. Am. Chem. Soc.*, **83**, 246 (1961)]; P. Schudel, H. Mayer, J. Metzger, R. Rüegg, and O. Isler [*Helv. Chim. Acta*, **46**, 636 (1963)]; H. Mayer, P. Schudel, R. Rüegg, and O. Isler [*ibid.*, **46**, 650 (1963)]; and W. T. de Kock, P. R. Enslin, K. B. Norton,, D. H. R. Barton B. Sklarz, and A. A. Bothner-By [*J. Chem. Soc.*, 3828 (1963)].

(25) In the case of close δ-values the chemical shift assignment is arbitrary and may be inverted. However this has no effect on the ensuing discussion.

(26) W. Antkowiak, J. W. ApSimon, and O. E. Edwards, *J. Org. Chem.*, **28**, 1930 (1962), and references contained therein. The conversion of isopimaradiene (XVIIf) to isohibaene[6b] also serves as proof of the 7,8-location of the nuclear double bond of the isopimaric series.

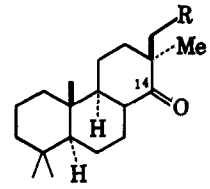
TABLE III
CHEMICAL SHIFTS

Compd.	$\delta_{4\text{-Me}}$[a] XVI	$\delta_{4\text{-Me}}$[a] 13-iso-XVI	$\delta_{4\text{-Me}}$[a] XVII	$\delta_{10\text{-Me}}$[a] XVI	$\delta_{10\text{-Me}}$[a] 13-iso-XVI	$\delta_{10\text{-Me}}$[a] XVII	$\delta_{13\text{-Me}}$[a] XVI	$\delta_{13\text{-Me}}$[a] 13-iso-XVI	$\delta_{13\text{-Me}}$[a] XVII
a	1.20	1.21	1.27	0.84	0.79	0.87	1.03	1.00	0.92
b	1.18	1.20	1.26	0.83	0.79	0.87	1.03	1.00	0.92
c	1.08	1.09	1.16	0.86	0.80	0.87	1.03	1.00	0.93
d	0.80	0.82	0.88	0.84	0.80	0.87	1.03	1.01	0.92
e		0.87	0.96		0.78	0.87		0.99	0.92
f	0.78, 0.87	0.85, 0.88	0.87, 0.87	0.85	0.74	0.87	1.02	0.99	0.92

[a] Expressed in parts per million.

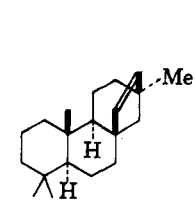
the sandaracopimaric (XVI) series. While changes of the chemical shifts of the 13-methyl group and 14-hydrogen on inversion of the C-13 asymmetry could be anticipated on the basis of steric and proximity considerations, the remaining changes are more subtle. The difference of steric requirements of methyl and vinyl groups would seem to be responsible for slight alteration of the conformation of ring C in the two 13-epimeric series sufficient to modify the shielding of the 10-methyl group and 4α-substituents by the nuclear double bond.

Introduction of a 12-keto function into XVIb, by Sarett oxidation of methyl hydroxysandaracopimarate,[27] changes, as expected, the chemical shifts of the 13-methyl group (1.13 p.p.m.) and the C-14 (5.18 p.p.m.) and vinyl hydrogens. A further change involves stronger shielding of the 10-methyl group (0.71 p.p.m.) probably because of ring C conformational modification. Saturation of the two double bonds of the three pimaradienic groups of compounds leads to 10- and 13-methyl chemical shifts of 0.8–0.9 p.p.m. While introduction of a 7-keto function into such saturated skeletons causes a paramagnetic shift of the 10-methyl group (1.08 p.p.m.), the insertion of a 14-keto group into the saturated pimaric (13-iso-XVI) skeleton has a similar effect on both the 10- (*ca.* 0.96 p.p.m.) and 13-methyl (1.0 p.p.m.) groups.

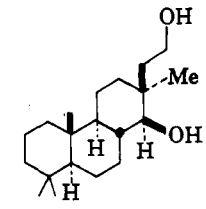


XVIIIa, R = CHO
b, R = CO_2H
c, R = CO_2ME
d, R = CH_2OH

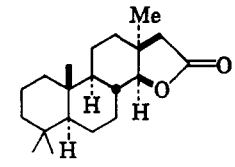
The new 14-keto compounds XVIII were prepared in connection with an as yet unsuccessful attempt of conversion of pimaradiene (13-iso-XVIf) into hibaene (XIX). For this purpose the ketoaldehyde XVIIIa was needed, since its intramolecular aldolization was envisaged to lead to the crucial fourth ring of the tetracyclic hydrocarbon XIX in analogy with a recent cyclization in the isopimaric (XVII) field.[6b] Hydroboration of pimaradiene (13-iso-XVIf), followed by alkaline hydrogen peroxide oxidation, yielded the alcohol XX.[28] Its chromic acid oxidation under a variety of conditions gave mixtures of lactone XXI and keto acid XVIIIb. Sodium methoxide induced equilibration of the keto ester XVIIIc, prepared by diazomethane treatment of the acid XVIIIb, left the C-8 asymmetry unchanged. Sodium borohydride reduction of the ester yielded the lactone XXI, while lithium aluminum hydride reduction of the latter produced the alcohol XX. These facts led to the stereochemical assignments already depicted in formulas XVIII, XX, and XXI.



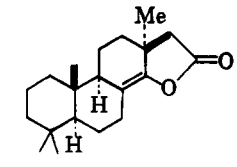
XIX



XX



XXI



XXII

In view of the overoxidation of the diol XX it was of interest to study the possible conversion of the ketol XVIIId to the desired keto aldehyde XVIIIa. Monobenzoylation of the diol, followed by chromic acid oxidation and alkaline hydrolysis, yielded the ketol XVIIId. However, its oxidation by various procedures merely led to the keto acid XVIIIb. Finally, attempted cyclization of the keto acid to a diketone of the hibaene XIX skeletal type by acetic anhydride–boron trifluoride treatment[29] merely produced the enol lactone XXII. The latter was also the product of acetyl chloride treatment of the keto acid.

Rimuene.—Upon removal of the various 9,13-epimers of XVI from consideration for the structure of rimuene, a presumed pimaradienic diterpene of unknown constitution,[30] it has been suggested to be possibly the 9-[31] or 13-epimer[32] of isopimaradiene (XVII). The methyl chemical shifts (0.67, 0.95, 1.00, and 1.05 p.p.m.)[31] of rimuene[33] appear to be inconsistent with these suggestions. The presence of a high-field signal (0.67 p.p.m.) indicates the interaction of a methyl group with the strong shielding zone of a double bond,[6b] a steric requirement unfulfilled by the structures 9-iso-XVIIf or 13-iso-XVIIf. Comparison of the remaining δ_{Me}-values

(27) J. W. ApSimon and O. E. Edwards, *Can. J. Chem.*, **39**, 2543 (1961). The authors are grateful to Drs. Edwards and ApSimon for their generous gift of samples of sandaracopimaric and hydroxysandaracopimaric acids.

(28) Its stereospecific formation speaks for the intervention of a cyclic borane intermediate.

(29) *Cf.* Y. Kos and H. J. E. Loewenthal, *J. Chem. Soc.*, 605 (1963).

(30) R. F. Church and R. E. Ireland, *J. Org. Chem.*, **28**, 17 (1963).

(31) R. M. Carman, *Australian J. Chem.*, **16**, 1104 (1963).

(32) A. I. Scott, F. McCapra, F. Comer, S. A. Sutherland, D. W. Young, G. A. Sim, and G. Ferguson, *Tetrahedron*, **20**, 1339 (1964).

(33) The authors are most grateful to Dr. P. K. Grant for a gift of a rimune sample.

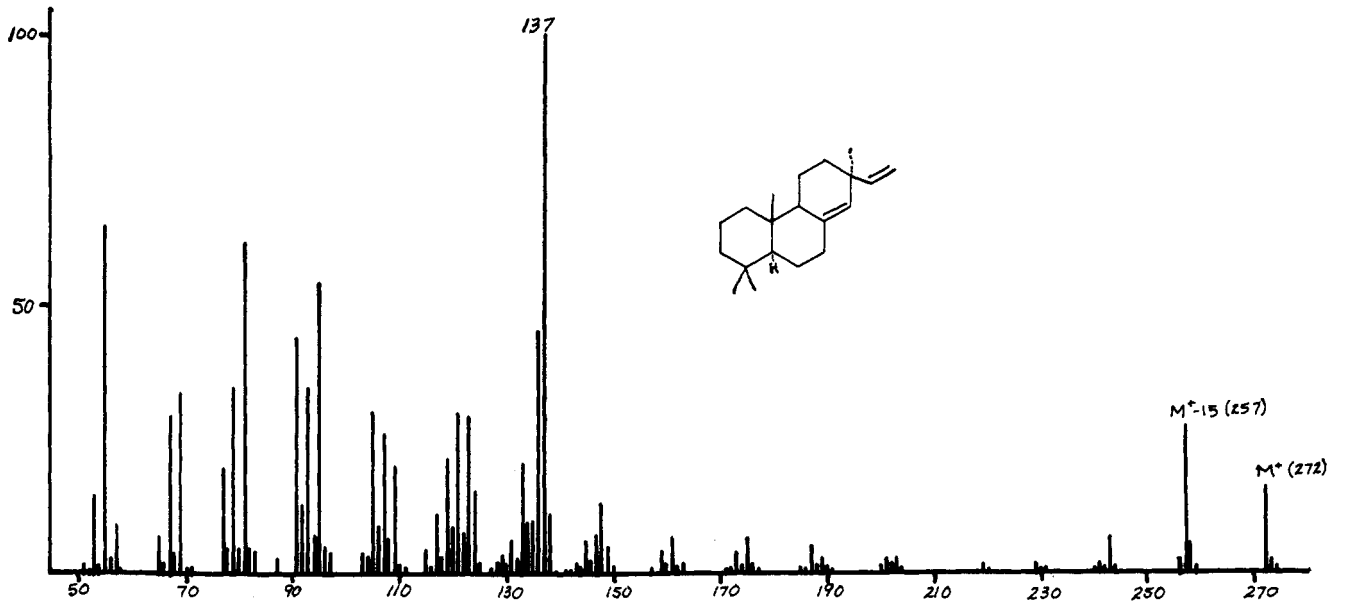


Figure 1.—Mass spectrum of pimaradiene (13-iso-XVIf).

with those of isopimaradiene (XVIIf) militates the 13-iso-XVIIf proposal. While previous dehydrogenation experiments[34] seem to have supported a ring B double bond, its proposed 7,8-site, at least in 13-iso-XVIIf, is in disagreement with decoupling results. Whereas the olefinic hydrogen of the nuclear double bond of isopimaric acid (XVIIa) (δ = 5.35 p.p.m.) couples with an allyl hydrogen multiplet at 1.95 p.p.m., that (δ = 5.50 p.p.m.) of rimuene couples with a 1.82-p.p.m. multiplet.

The mass spectra of pimaradiene (13-iso-XVIf), isopimaradiene (XVIIf), and rimuene (*vide infra*) show contrasting fragmentation patterns (see Figures 1–3). While a complete analysis of the rimuene spectrum is premature, its uniquely strong M − 15 peak characteristic of the loss of a methyl group suggests the presence of more than one methyl function on allylic carbon atoms. In view of recent discoveries of naturally occurring pimaradienic diterpenes with rearranged skeletons[35] rimuene may belong to this new group of compounds.[36]

Experimental[37]

5-Isodehydroabietic Acid (Va).—A mixture of 260 mg. of 5(6)-dehydro-6-hydroxy-7-ketodehydroabietic lactone,[9] 400 mg. of 10% palladium on charcoal, and 20 ml. of ethyl acetate containing 5 drops of concentrated sulfuric acid was stirred under hydrogen at atmospheric pressure and 20°. After the uptake of 4 moles of hydrogen the reaction ceased. The catalyst was filtered off, the solvent was removed *in vacuo*, and the residue was treated with water and extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, afforded on crystallization from aqueous methanol 5-isodehydroabietic acid: m.p. 121–124°; $[\alpha]^{23}D$ −106° (*c* 0.57, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.01; H, 9.18.

A solution of 120 mg. of the acid Va in ether on treatment with diazomethane in the usual way gave methyl 5-isodehydroabietate (Vb). Sublimation yielded the pure ester Vb: m.p. 98–100°; $[\alpha]^{23}D$ −5.85° (*c* 1.25, $CHCl_3$); infrared (Nujol), 5.76 (s) (C=O, ester) and 6.18 (w) μ (aromatic ring); and p.m.r., 3-proton singlet at 3.40 p.p.m. (carbomethoxy hydrogens).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.99; H, 9.48.

5-Isodehydroabietol (Vc).—To a solution of 100 mg. of methyl 5-isodehydroabietate (Vb) in 25 ml. of tetrahydrofuran was added 200 mg. of lithium aluminum hydride and the mixture was refluxed overnight. The excess hydride was decomposed with hydrated sodium sulfate, the solution was filtered, and the solvent was removed under reduced pressure leaving an oil. Distillation of the oil at ~110° (0.25 mm.) afforded the pure alcohol Vc: m.p. 61–62°; $[\alpha]^{23}D$ −9.7° (*c* 0.94, $CHCl_3$); infrared (film), 3.00 (s) (OH) and 6.20 (w) μ (aromatic ring).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.92; H, 10.59.

Acetylation of 25 mg. of the alcohol Vc in the usual way with acetic anhydride–sodium acetate gave 34 mg. of 5-isodehydroabietol acetate (Vd): b.p. ~90° (0.25 mm.); $[\alpha]^{23}D$ +3.3° (*c* 0.96, $CHCl_3$); infrared (film), 5.75 (s) (C=O) and 8.10 (s) μ (C–O acetate); and p.m.r., 3-proton singlet at 1.91 p.p.m. ($COCH_3$).

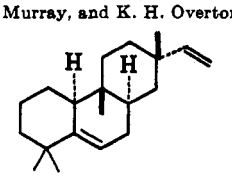
Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.87. Found: C, 80.44; H, 10.01.

5-Iso-6,7-diketodehydroabietol Acetate (XIV).—To a solution of 200 mg. of 5-isodehydroabietol acetate in 2.5 ml. acetic acid, was added 250 mg. of chromium trioxide dissolved in 1 ml. water and 4 ml. acetic acid. The mixture was stirred 16 hr. at room temperature, then diluted fivefold with saturated aqueous sodium chloride, and extracted with ether. The ether layer was washed with 5% sodium hydroxide solution followed by water and dried, and the solvent was removed *in vacuo*. Crystallization of the residue from hexane gave yellow crystals of 5-iso-6,7-diketodehydroabietol acetate (XIV): m.p. 102–108°; $[\alpha]^{22}D$ +115.4° (*c* 0.91, $CHCl_3$); infrared (Nujol), 5.75 (s), 5.81 (s), 5.93 (s) (C=O) and 6.23 (s) μ (C=C); and p.m.r., 3-proton singlet at 1.83 p.p.m. ($COCH_3$).

(34) R. M. Carman, *Australian J. Chem.*, **16**, 225 (1963).

(35) R. Soman and S. Dev, *Tetrahedron Letters*, 1181 (1964); Y. Kitahara and A. Yoshikoshi, *ibid.*, 1755 (1964); Y. Kitahara, A. Yoshikoshi, and S. Oida, *ibid.*, 1763 (1964); J. D. Connolly, R. McCrindle, R. D. H. Murray, and K. H. Overton, *ibid.*, 1859 (1964).

(36) Since the preparation of this manuscript the structure of rimuene (iv) has been independently elucidated in two laboratories: R. E. Corbett and S. G. Wyllie, *Tetrahedron Letters*, **29**, 1903 (1964), and J. D. Connally, R. McCrindle, R. D. H. Murray, and K. H. Overton, *ibid.*, **29**, 1983 (1964).



iv

(37) Proton magnetic resonance spectra were taken in dilute deuteriochloroform solutions containing tetramethylsilane as an internal standard on Varian A60, DP60, and HR60 spectrometers operating at 60 Mc. Infrared spectra were obtained on Perkin-Elmer spectrophotometers, Model 21 or 137B; ultraviolet spectra are of 95% ethanol solutions and were taken on a Cary Model 14 spectrophotometer. Optical rotations were recorded on a Rudolph and Sons polarimeter, Model 70. All melting points are uncorrected.

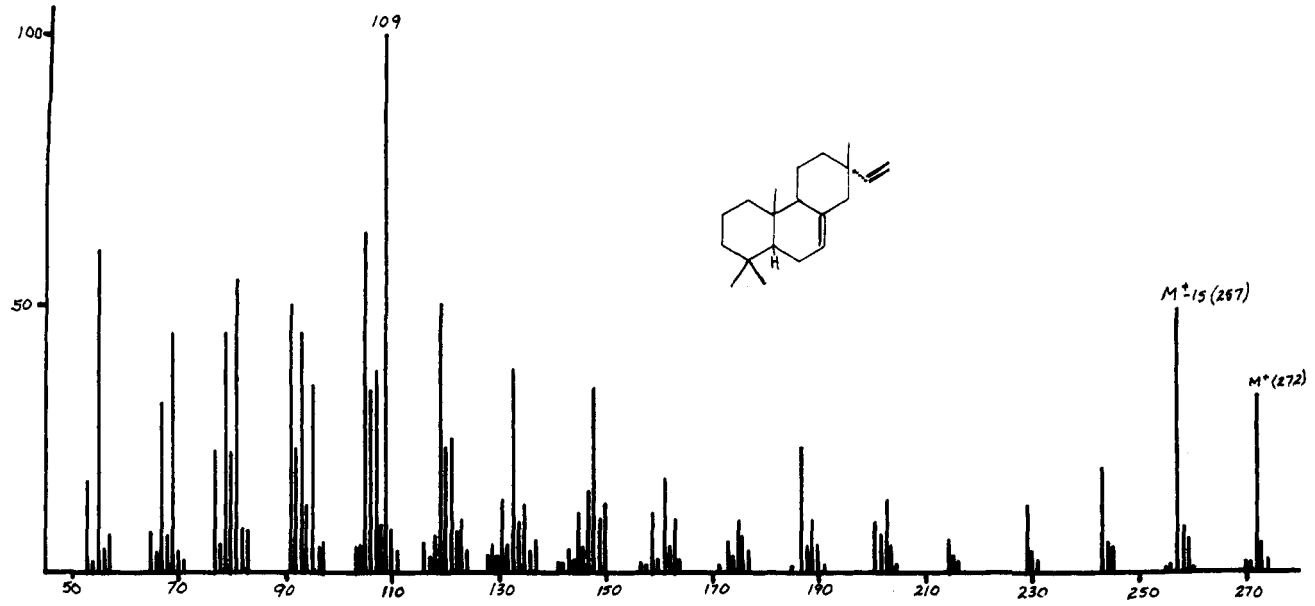


Figure 2.—Mass spectrum of isopimaradiene (XVIIf).

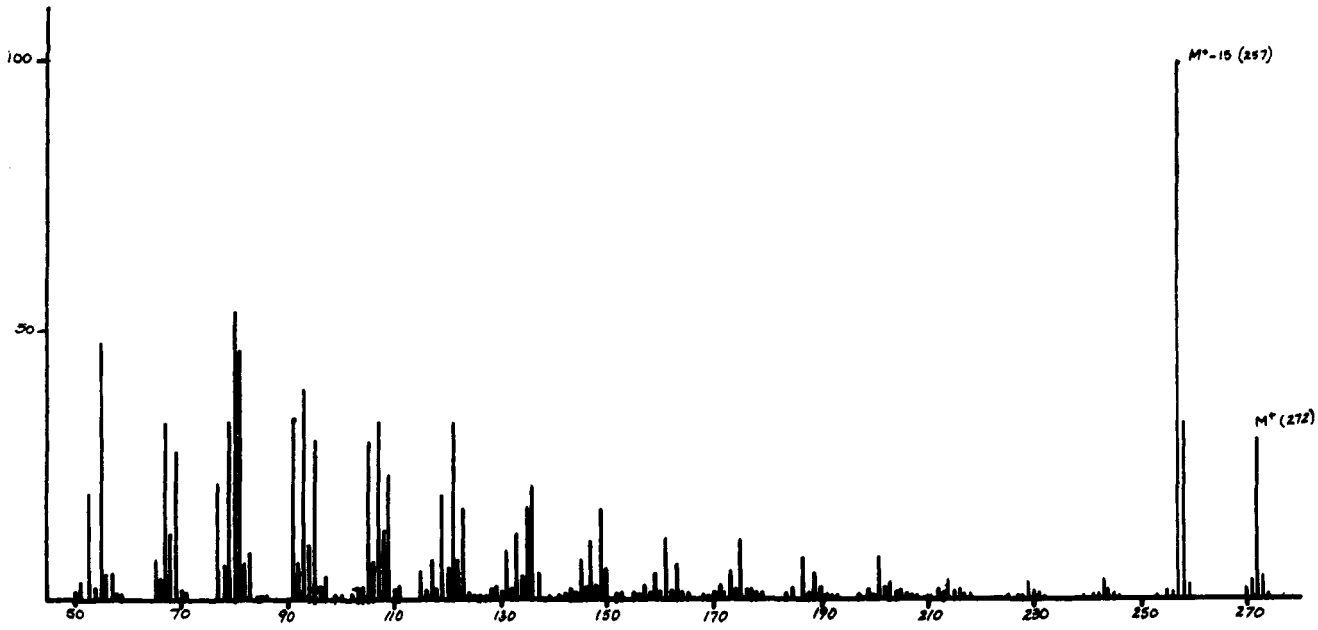


Figure 3.—Mass spectrum of rimuene.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.93; H, 8.03.

3-Ketodesoxypodocarpal (XVb).—To a cold suspension of 100 mg. of lithium aluminum hydride in 2.5 ml. of tetrahydrofuran was added a solution of 70 mg. of the methyl ester XVa[16] in 5 ml. of tetrahydrofuran. After the mixture was stirred for 24 hr. at room temperature, hydrated sodium sulfate was added, and the solution was filtered. The residue was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and combined with the above filtrate. Removal of the solvents left a gum which showed the absence of carbonyl absorption in its infrared spectrum. A solution of 60 mg. of this material in 0.6 ml. of pyridine was added to 2 ml. of pyridine containing 200 mg. of chromium trioxide. The mixture was stirred for 1 hr. at 0° and allowed to come to room temperature during stirring for a further 3 hr. Work-up in the usual manner afforded 40 mg. of material which was chromatographed over 2 g. of activity II alumina. Elution with hexane–benzene (1:1) gave 20 mg. of solid which crystallized from hexane to give pure keto aldehyde XVb: m.p. 89–91°; p.m.r. spectrum, 1-proton singlet at 9.77 p.p.m. (aldehyde).

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.76; H, 7.83.

Methyl 12-Ketosandaracopimarate (12-Keto-XVIb).—To a solution of 12-β-hydroxysandaracopimaric acid[27] in methanol an excess of ethereal diazomethane was added. Removal of the solvent and crystallization of the residue from hexane gave methyl 12-β-hydroxysandaracopimarate, m.p. 89–94°. A solution of 25 mg. of the ester (12-β-hydroxy-XVIb) in 0.25 ml. of pyridine was added to a slurry of the complex obtained from 25 mg. of chromic acid in 0.25 ml. of pyridine. The suspension was stirred for 14 hr. and then diluted with ether and filtered. After washing the filtrate with dilute hydrochloric acid followed by water, the ether was dried and removed *in vacuo*. The residue crystallized from hexane to yield pure methyl 12-ketosandaracopimarate: m.p. 105–106°; $[\alpha]^{23}D$ −284° (*c* 0.76, EtOH); infrared (KBr), 5.85 (s) (C=O) and 6.14 (w) μ (double bond); and p.m.r., 3-proton singlet at 3.62 p.p.m. (carbomethoxy).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 76.32; H, 9.15. Found: C, 76.38; H, 9.28.

Conversion of Methyl 12-Ketosandaracopimarate to 12-β-Hydroxysandaracopimaric Acid.—To a solution of 10 mg. of the 12-keto ester (12-keto-XVIb) in 1 ml. of 80% aqueous methanol was

added with stirring 10 mg. of sodium borohydride. After 2 hr. the reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. Removal of the ether afforded a gum which solidified on trituration with hexane. Thin layer chromatography showed the presence of impurities which could not be removed by crystallization. A preparative-scale thin layer separation using silica gel G and ethyl acetate–chloroform (5:95) as an eluent afforded methyl 12β-hydroxysandaracopimarate, m.p. 93–94°. A solution of 15 mg. of the 12-hydroxy ester and 70 mg. of anhydrous lithium iodide in 2 ml. of dry collidine, was refluxed under nitrogen for 8 hr. Ether extraction afforded a solid which on crystallization from acetone afforded 8 mg. of 12-β-hydroxysandaracopimaric acid, m.p. 268–269° (identical in all respects with an authentic sample).

Hydroboration–Oxidation of Pimaradiene (13-Iso-XVIf).[38]—To a stirring suspension of 300 mg. of sodium borohydride and 1.2 g. of pimaradiene in 25 ml. of tetrahydrofuran at 0° under nitrogen was added 700 mg. of boron trifluoride etherate. Stirring was continued at 0° for 3 hr. and then for a further 17 hr. at room temperature. Sodium hydroxide (30 ml. of 5 *N* solution) was added and the temperature was raised to 50°. This was followed by the addition of three 6-ml. portions of 30% hydrogen peroxide during the course of 3 hr. and a further 10 ml. of 30% hydrogen peroxide over a period of 6 hr. The solution was saturated with sodium chloride and extracted with ether. The ether extract was dried and the solvent was removed to afford 1.29 g. of gummy solid which crystallized from ether to yield pure diol XX: m.p. 187.5–188°; infrared, 3.00 (s) μ (OH).

Anal. Calcd. for $C_{20}H_{36}O_2$: C, 77.86; H, 11.76. Found: C, 78.02; H, 11.67.

The mother liquors from the crystallizations were combined with mother liquors from a subsequent experiment to give 3.3 g. which on chromatography in hexane over 100 g. of alumina (neutral, activity II) yielded a further 787 mg. of diol XX with benzene–ether (5:1 → 1:1).

Oxidation of Diol XX.—To a solution of 210 mg. of the diol XX in 2 ml. of acetic acid was added a solution of 140 mg. of chromium trioxide in 1 ml. of water and 2 ml. of acetic acid. The solution was heated at 60° for 5 min. before pouring into 25 ml. of water which was subsequently extracted with ether. The ether extract was fractionated into acidic and neutral fractions by extraction with base which afforded 90 mg. of the keto acid XVIIIb and 94 mg. of the lactone XXI, respectively. Several crystallizations of the acid from ethyl acetate afforded pure keto acid XVIIIb, m.p. 224–225°.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.69; H, 9.80.

Methylation with diazomethane gave the keto ester XVIIIc: m.p. 124–125°; infrared (Nujol), 5.78 (s) (ester C=O) and 5.86 (s) μ (ketone C=O); and p.m.r., 3-proton singlet at 3.62 p.p.m. (carbomethoxy).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.18; H, 10.13.

The lactone XXI crystallized from ether–ethyl acetate as large prisms: m.p. 133–135°; infrared (Nujol), 5.60 (s) μ (C=O, 5-ring lactone). A sample was sublimed at 110° (0.01 mm.) for analysis.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 79.01; H, 10.50.

The relative proportions of keto acid to lactone were found to be somewhat sensitive to experimental conditions. Oxidation of the diol XX with chromic acid–sulfuric acid in acetone[39] gave predominently keto acid XVIIIb.

Equilibration of the Keto Ester XVIIIc.—Addition of 10 mg. of the keto ester XVIIIc to *ca.* 2 ml. of methanol, to which 25 mg. of sodium had been added previously, was followed by heating on a steam bath for 1 hr. The solution was concentrated to *ca.* 1 ml., water was added, and then the solution was extracted with ether. The ether extract was washed with sodium bicarbonate solution. Acidification of the bicarbonate washings with dilute hydrochloric acid and extraction with ether gave 10 mg. of the keto acid XVIIIb, m.p. 223–225°, after five crystallizations from ethyl acetate. The total acid fraction (10 mg.) was methylated in ether with diazomethane. After removal of the solvent and crystallization of the residue from methanol, 9 mg. of pure methyl ester XVIIIc, m.p. 124–125°, was obtained.

(38) Prepared from pimaric acid according to the method described by R. E. Ireland and P. W. Scheirs [*J. Org. Chem.*, **28**, 6 (1963)].

(39) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1952).

Conversion of the Keto Ester XVIIIc to the Lactone XXI.—To an ice-cold solution of 29 mg. of the keto ester XVIIIc and 10 mg. of disodium hydrogen phosphate in 2 ml. of 30% aqueous methanol was added 25 mg. of sodium borohydride. The solution was stirred for 1 hr. at 0° and for 1 hr. further at 25°. Most of the methanol was removed *in vacuo* and the residual solution was diluted with *ca.* 15 ml. of water. Acidification with dilute hydrochloric acid followed by extraction with three 10-ml. portions of ether afforded 28 mg. of solid which was crystallized from hexane to give 15 mg. of the lactone XXI, m.p. 133–135° (mixture melting point undepressed and infrared spectrum identical with that of the lactone XXI obtained from oxidation of the diol XX).

Reduction of the Lactone XXI.—An excess (*ca.* 25 mg.) of lithium aluminum hydride was added to a solution of 12 mg. of the lactone XXI in 5 ml. of ether and the solution was refluxed gently for 3 hr. After the excess hydride was destroyed with hydrated sodium sulfate and the inorganic salts were filted off, the filtrate was diluted with ether and dried over anhydrous sodium sulfate. Removal of the ether left a gummy residue which after three recrystallizations from hexane–ethyl acetate gave 7 mg. of diol XX, m.p. 186–187° (identified by infrared spectral comparison and mixture melting point determination).

Keto Alcohol XVIIId.—A solution of 187 mg. of the diol XX in 2 ml. of pyridine was added dropwise to an ice-cold solution of 200 mg. of benzoyl chloride in 3 ml. of pyridine and the mixture was heated under gentle reflux for 15 min. The pyridine solution was cooled and poured into water; the aqueous solution was extracted with ether. After the extract was washed with sodium carbonate and water, it was dried over anhydrous sodium sulfate. The product, m.p. 130–134°, was recovered in the usual way and shown to be the diol XX-monobenzoate from its p.m.r. spectrum: 3-proton singlets at 0.81, 0.82, 0.85, and 1.06 (C-Me); 1-proton doublet at 2.86 (J = 9 c.p.s.) (C-14-methine); and 2-proton triplet at 4.38 p.p.m. (J = 7.5 c.p.s.) ($-CH_2OCO$-Ph). A solution of 166 mg. of the monobenzoate in 10 ml. of acetone was cooled in an ice bath and 0.1 ml. of chromic acid–sulfuric acid was added dropwise.[39] The mixture was allowed to stand for 30 min. before adding methanol. The solvents were removed in a stream of nitrogen and the residue was extracted repeatedly with ether. Isolation of the product in the usual way gave 170 mg. of a gum whose p.m.r. spectrum [3-proton singlets 0.81, 0.82, 0.93, and 1.06 p.p.m. (C-Me); 2-proton A_2 part of A_2B_2 pattern at 4.20 p.p.m. (CH_2OCOPh)] was in agreement with its formulation as a 14-keto benzoate. Treatment of 155 mg. of the keto benzoate in 5 ml. of methanol with 30 mg. of potassium hydroxide in 0.3 ml. of water for 17 hr. gave a solid on removal of the solvents *in vacuo*. The solid, on washing with water, left 100 mg. of crude keto alcohol XVIIId. Crystallization of this material from hexane afforded 72 mg. of the keto alcohol XVIIId: m.p. 106–107°; infrared (Nujol), 3.05 (m) (OH) and 5.90 (s) μ (C=O); and p.m.r., 2-proton A_2 part of A_2B_2 pattern at 3.58 p.p.m. (hydroxymethyl).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.17; H, 10.95.

Oxidations of Keto Alcohol XVIIId. A.—A solution of 100 mg. of the keto alcohol in 2 ml. of pyridine was added to an ice-cold slurry of the complex obtained from 200 mg. of chromium trioxide in 2 ml. of pyridine, and the mixture was stirred for 1 hr. The mixture was poured into 100 ml. of ether and the ether layer was separated, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent gave 73 mg. of gum showing broad carbonyl and hydroxyl absorption in its infrared spectrum. The gum was redissolved in ether and the ether was washed with three 10-ml. portions of 10% sodium carbonate solution. Acidification of the sodium carbonate extract and recovery of the product into ether gave 38 mg. of crude keto acid XVIIIb. The remaining neutral fraction was chromatographed over alumina (activity II) in hexane solution. Hexane–ether (95:5) eluted 16 mg. of solid which crystallized from hexane, m.p. 104–106°, and was shown to be identical with the starting keto alcohol by the usual criteria.

B.—An ice-cold solution of 50 mg. of the keto alcohol XVIIId was treated with 0.08 ml. of chromic acid[39] and immediately quenched with 2 ml. of methanol. Work-up gave 39 mg. of a product whose p.m.r. spectrum showed it to be largely keto alcohol containing a small amount of aldehydic material. The mixture was refluxed for 30 min. with acetic anhydride–sodium acetate and the product, isolated in the usual manner, was chromatographed over alumina (activity III) in hexane. The only

identifiable material obtained was 26 mg. of the acetate of the keto alcohol XVIIId, an oil: infrared (film), 5.72 (s), 5.85 (s) μ (C=O); p.m.r., 3-proton singlet at 1.96 p.p.m. (CH_3COO) and 2-proton A_2 part of A_2B_2 multiplet at 4.0 p.p.m. (CH_2OAc).

C.—To a solution containing 835 mg. of the keto alcohol XVIIId in 25 ml. of acetone was added 14 ml. of chromic acid[39] solution at 25°, to which, after standing for 30 min., water was added and the solution was extracted with ether. The ether extract was washed with three 25-ml. portions of 10% sodium carbonate solution which afforded 361 mg. of keto acid XVIIIb on appropriate work-up. The neutral faction consisted of 355 mg. of material showing two major spots on thin layer chromatography and as yet unidentified.

Enol Lactone XXII. A.—A solution of 300 mg. of the keto acid XVIIIb in 10 ml. of acetic acid–acetic anhydride (4:1) was cooled to 0° and 6 drops of boron trifluoride etherate was added. The solution was stirred for 1 hr. at 0° and 15 hr. at room temperature. The addition of water gave 240 mg. of a precipitate which was filtered off and washed well with water. Crystallization of the precipitate from hexane gave 210 mg. of the pure enol lactone XXII: m.p. 127–128°; infrared (CCl_4), 5.52 (s) (C=O) and 5.84 (s) μ (C=C); and p.m.r., 2-proton singlet at 2.05 p.p.m. ($-CH_2-OCO-$).

B.—A solution of 30 mg. of the keto acid XVIIIb in 5 ml. of acetyl chloride was refluxed for 48 hr. Removal of the acetyl chloride *in vacuo* left a white solid which crystallized from hexane to give 21 mg. of the enol lactone XXII, m.p. 124–126°, which was identical in all respects with that obtained by procedure A.

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An Approach to Ring E of Reserpinoid Substances

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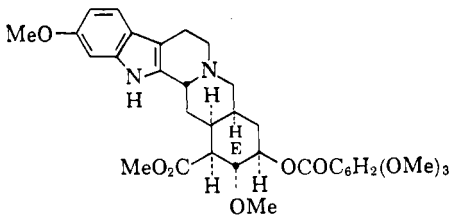
The preparation and reactions of a lactone acid containing many of the functional features of ring E of reserpine are described. The structure determination of this acid by the degradation of one of its derivatives to an aromatic compound and the latter's synthesis from hemimellitic acid are presented.

The elucidation of the stereochemistry of the medicinally important Rauwolfia alkaloid reserpine (I)[4] led us in 1955 to attempt its total synthesis.[5] A route fo synthesis leading first to the stereochemically crucial ring E of the alkaloid system was formulated and the aldehydo ester IV containing four of its five asymmetric centers in the required relative configuration was designated as the primary goal. The choice of IV was predicted on the assumption that the unnecessary ether linkage α to the aldehyde function would be cleaved by reduction and that only a few standard chemical processes would stand between the reduction product and the alkaloid. Furthermore, the ester IV appeared, at least in principle, to be derivable readily from furfural by Diels–Alder reaction with maleic acid or its derivatives, by halolactonization of the adduct II and reduction, and by Arndt–Eistert homologation of the resulting lactone III.

Past experience on the behavior of furans in the Diels–Alder reaction[6] placed severe limitations on the scope of the above scheme of synthesis. Whereas maleic anhydride was our preferred dienophile, we were restricted to the use of maleic acid, since on reaction with furan the anhydride has been reported to yield only *exo* product while the acid had afforded *endo* product,[7] a substance of the configuration needed for our compounds. Further, the recorded lack of reactivity of furfural in the Diels–Alder reaction[5] led us to the use of furfuryl alcohol and its relatives as dienes. While maleic acid interaction with furfuryl alcohol or its acetate resulted only in resinification of the furan derivatives, reaction of the acid with N-furfuryl acetamide, followed by exposure of the aqueous solution of the adduct to iodine and sodium bicarbonate,[8] led to a single iodo lactone in high yield.[9] It was hoped that its nitrogenous side chain would be amenable later to conversion to the desired carboxaldehyde unit (conceivably by deamination *via* an N-nitrosoamide intermediate and later oxidation).



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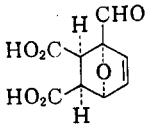

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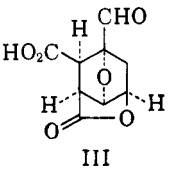

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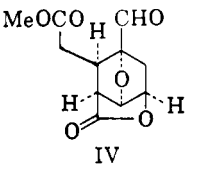

IV

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(4) C. F. Huebner and E. Wenkert, *J. Am. Chem. Soc.*, **77**, 4180 (1955); P. A. Diassi, F. L. Weisenborn, C. M. Dylion, and O. Wintersteiner, *ibid.*, **77**, 4687 (1955); E. E. van Tamelen and P. D. Hance, *ibid.*, **77**, 4692 (1955). For a full review *cf.* P. E. Aldrich, *et al.*, *ibid.*, **81**, 2481 (1959).

(5) *Cf.* R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *ibid.*, **78**, 2023, 2657 (1956); *Tetrahedron*, **2**, 1 (1958).

(6) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953.

(7) R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948), and references contained therein.

(8) *Cf.* C. D. Ver Nooy and C. S. Rondestvedt, Jr., *ibid.*, **77**, 3585 (1955).

(9) Maleic acid underwent no reaction with furfuryl amine or its N-benzoyl or N-benzenesulfonyl derivatives, although the failure of the amides to react may have been due mainly to their poor solubility in the aqueous reaction medium. On the other hand, a reaction between maleic acid and the N-carbobenzoxy derivative followed by iodolactonization yielded a mixture from which a crystalline iodo lactone (m.p. 106–108°; methyl ester, m.p. 103–104°) could be isolated. However, further study on this substance was abandoned in favor of an investigation of the product from N-furfurylacetamide.