Pyridylmethylindanol Derivatives. Reductive Cyclization to Octahydroindenoindolizine[1]

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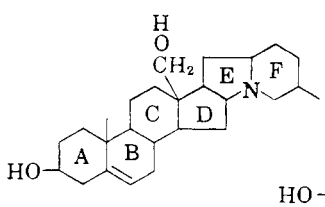
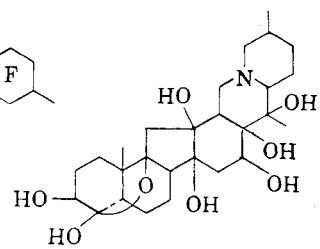
The ring opening reaction of picolyllithium with 1,2-epoxyindan to yield 1-(2-pyridylmethyl)-2-indanol (V) is described. The latter undergoes reductive cyclization to 5a,7,8,9,10,10a,11,11a-octahydroindeno[1,2-*b*]indolizine (XVIII).

A previous publication[3] describes the preparation of a number of substituted aminoalkoxyindanones bearing some structural similarity to the veratrum alkaloid, Jervine, and possessing hypotensive activity characteristic of the veratrum ester alkaloids. In a continuation of the study of structural relatives of the veratrum alkaloids[4] [isorubijervine (I) and veracevine (II)] we were interested in preparing some pyridylmethylindanol derivatives as well as compounds possessing the C, D, E, and F rings of I. In the course of these studies we also became interested in the ring opening reactions of 1, 2-epoxyindan (IV).



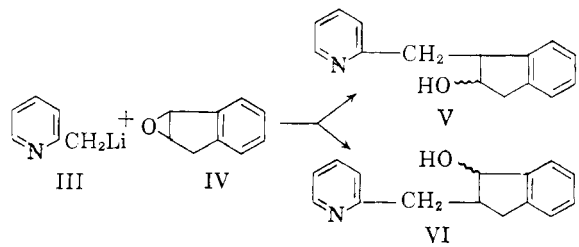
I



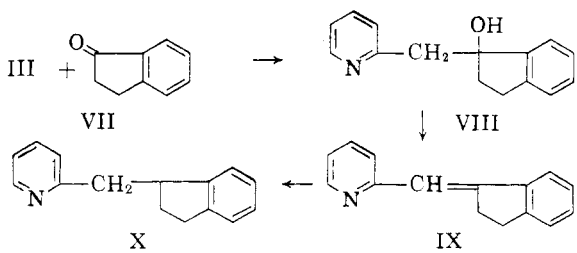
II

Although there are many publications on the reactions of epoxides, only a limited amount of information is available on the ring opening reactions of 1,2-epoxindan. Catalytic reduction yields 2-indanol.[5] The reaction of ammonia and amines with 2-bromo-1-indanol to give 1-amino-2-indanol derivatives was presumed to proceed through the oxide.[6] We provided further evidence that the oxide is an intermediate by the isolation of 1-benzylamino-2-indanol in our laboratories from the reaction of benzylamine with 1,2-epoxyindan.

It is apparent that the reaction of 1,2-epoxyindan (IV) with picolyllithium (III) can proceed in two directions to give either a 2-indanol (V) or 1-indanol (VI) derivative. However, if one considers the phenyl ring of 1,2-epoxyindan as an electron sink producing a partial positive charge on the carbon atom adjacent to the benzene ring, then a nucleophilic attack would predominate at this point to yield V. One may consider, also, that this reaction involves first an opening of the oxide ring to form a carbonium ion (the carbonium ion in the 1 position would be stabilized through resonance and would be preferred over the carbonium ion in the 2 position) followed by a nucleophilic attack to give V.



We assumed that the product was V and proceeded to substantiate this assumption via the attempted preparation of 1-(2-pyridylmethyl)indan (X) by dehydration of the indanol (V), followed by reduction. Comparison of this product therefore with 1-(2-pyridylmethyl)indan (X) obtained by the unequivocal synthesis from 1-indanone (VII) would identify the course of ring opening of 1,2-epoxyindan. The product from the reaction of picolyllithium and 1-indanone readily dehydrated to 2-(1-indanylidenemethyl)pyridine (IX) and reduction of the latter gave 1-(2-pyridylmethyl)indan (X).



Thus far, however, all attempts to dehydrate the indanol (V) have been unsuccessful. The use of phosphorus pentoxide, potassium acid sulfate, or sulfuric acid gave tars from which neither product nor starting material was isolated. Starting material was recovered when mixtures of acetic and hydrochloric acid were employed. The use of acetic

(1) Presented, in part, before the Division of Medicinal Chemistry, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960.

(2) University of Mississippi, University, Miss.

(3) J. Sam and J. N. Plampin, *J. Am. Chem. Soc.*, **82**, 5205 (1960).

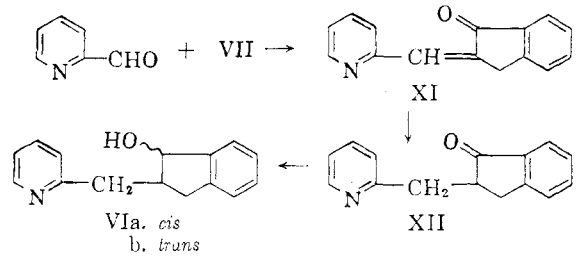
(4) O. Jeger and V. Prelog, "The Alkaloids," Vol. VII, R. R. Manske, ed., Academic Press, New York, N. Y., 1960, chap. 17.

(5) W. F. Whitmore and A. I. Gebhart, *J. Am. Chem. Soc.*, **64**, 912 (1942).

(6) N. Levin, B. E. Graham, and H. G. Kolloff, *J. Org. Chem.*, **9**, 380 (1944).

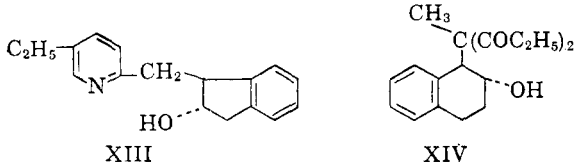
anhydride containing a trace of sulfuric acid yielded 1-(2-pyridylmethyl)-2-indanyl acetate. The acetate, also, was prepared readily from the indanol using sodium acetate and acetic anhydride. Decomposition of the methyl sulfite ester (not isolated) gave a black intractable residue. Attempts to oxidize V, either with chromic oxide or *via* the Oppenauer method to a 2-indanone derivative, also were unsuccessful. Conversion of the indanol (V) to the corresponding chloroderivative was accomplished and the latter was subjected to reduction and dehydrohalogenation conditions. Reduction to the corresponding indan failed to occur and dehydrohalogenation produced an intractable residue. The behavior of V in the above reactions is indicative of a *trans* configuration.

Although all attempts to obtain X from V by no means were exhausted we turned our attention to the facile preparation of VI shown below. The reaction of 2-pyridine aldehyde with 1-indanone readily gave 2-(2-picolylidene)-1-indanone (XI). Reduction with palladium–carbon catalyst to XII followed by sodium borohydride reduction yielded the *cis*-indanol (VIa).

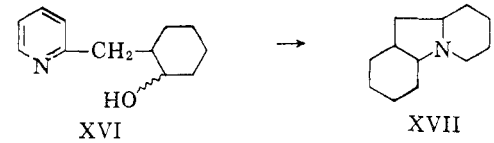


The reduction of either XI or XII with sodium amalgam produced a mixture (VI) of the *cis* and *trans* isomers. The *trans* isomer (VIb, higher melting form) was isolated after repeated recrystallization from an alcohol and *n*-hexane mixture. Similar reductions have been reported in the literature.[7]

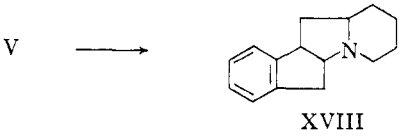
Inasmuch as the product from the reaction of 2-picolyllithium and 1,2-epoxyindan is different than either VIa or VIb, it is concluded that the ring opening reaction yielded 1-(2-pyridylmethyl)-2-indanol (V). Likewise, the reaction of 5-ethyl-2-picolyllithium with 1,2-epoxyindan gave 1-(5-ethyl-2-pyridylmethyl)-2-indanol (XIII). It is assumed that the ring opening of 1,2-epoxyindan in these reactions produced the *trans* configuration. A similar reaction, that of 1,2-epoxy-1,2,3,4-tetrahydronaphthalene and sodio diethyl methylmalonate, was reported[8] to give the *trans* derivative (XIV). The discussion in the latter paper is applicable to our work.



Prior to the conversion of 1-(2-pyridylmethyl)-2-indanol to octahydroindenoindolizine, some preliminary experimental work was carried out with 2-(2-pyridylmethyl)cyclohexanol (XVI). A four-step conversion of the latter to dodecahydro[*b*]-indolizine (XVII) has been described by Prelog and co-workers.[9] The preparation of XVII was accomplished in our laboratories in moderate yield (42%) by the reductive cyclization of XVI at 200° with Raney nickel.



Application of the same procedure to 1-(2-pyridylmethyl)-2-indanol (V) resulted in octahydroindenoindolizine (XVIII).



Preliminary pharmacological studies on the compound reported in this paper did not disclose any marked activity when screened in experimental animals.

Experimental[10]

1-(5-Ethyl-2-pyridylmethyl)-2-indanol (XIII).—To an ethereal solution of phenyllithium,[11] prepared from 6.1 g. (0.88 g.-atom) of lithium and 69 g. (0.44 mole) of bromobenzene, was added gradually with stirring 54 g. (0.44 mole) of 2-methyl-5-ethylpyridine and the resulting deep red mixture was stirred for an additional 2 hr. The mixture was cooled in an ice bath and 58 g. (0.44 mole) of 1,2-epoxyindan was added dropwise. The resulting light gray mixture was decomposed by the careful addition of 100 ml. of water and 100 ml. of concentrated hydrochloric acid, respectively. The aqueous phase was separated and carefully poured into a saturated solution of sodium carbonate. The oily layer was extracted with ether and dried over anhydrous sodium sulfate. Evaporation of the ether and distillation of the residual oil gave 45 g. (40%) of product, b.p. 194–200° (0.6 mm.).

The *hydrochloride* was recrystallized from a mixture of methyl ethyl ketone and methanol, m.p. 165–166.5°.

Anal. Calcd. for $C_{17}H_{20}ClNO$: C, 70.5; H, 7.0; N, 4.8. Found: C, 70.9; H, 6.9; N, 4.8.

1-(2-Pyridylmethyl)-2-indanol (V).—The procedure described above was followed using 68 g. (0.51 mole) of 1,2-epoxyindan, 6.9 g. (1 g.-atom) of lithium, 78.5 g. (0.50 mole) of bromobenzene, and 46.5 g. (0.50 mole) of 2-picoline. There was obtained 61 g. (50%) of product, b.p. 175–180°

(7) K. Hoffmann and H. Schellenberg, *Helv. Chim. Acta*, **27**, 1782 (1944); E. R. Alexander and A. Mudrak, *J. Am. Chem. Soc.*, **73**, 59 (1951).

(8) E. E. van Tamlen, G. Van Zyl, and G. D. Zuidema, *ibid.*, **72**, 488 (1950).

(9) V. Prelog, L. Frenkiel, and S. Szpilfogel, *Helv. Chim. Acta*, **29**, 484 (1946).

(10) Melting and boiling points are uncorrected.

(11) R. B. Woodward and E. C. Kornfeld, "Organic Synthesis," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p. 413.

(0.8 mm.), which was crystallized from methanol, m.p. 85–86°.

Anal. Calcd. for $C_{15}H_{15}NO$: N, 6.2. Found: N, 6.3.

The *hydrochloride* was recrystallized from a mixture of ether and methanol, m.p. 152–153°.

Anal. Calcd. for $C_{15}H_{16}ClNO$: C, 68.8; H, 6.2. Found: C, 69.0; H, 6.8.

2-(1-Indanylidenemethyl)pyridine (IX).—The reaction between 2-picoline and 1-indanone was carried out following the above procedure. From 60 g. (0.45 mole) of 1-indanone, 78.5 g. (0.50 mole) of bromobenzene, 6.9 g. of lithium, and 46.5 g. (1 mole) of 2-picoline was obtained 33 g. of product, b.p. 132–133.5° (0.3 mm.). A solution of 24 g. of the above distillate in 100 ml. of dry benzene was added gradually to a mixture of 25 g. of phosphorus pentoxide and 50 ml. of boiling benzene. Most of the benzene was distilled from the reaction mixture and the latter heated in an oil bath at 145° for 7 hr. The mixture was cooled, decomposed with 10% sodium hydroxide solution, and extracted with ether. Evaporation of the ether and distillation of the residual oil gave 15.3 g. of product, b.p. 150–155° (0.7 mm.).

The *hydrobromide* was recrystallized from methanol to yield straw colored crystals, m.p. 258.5–260°.

Anal. Calcd. for $C_{15}H_{14}BrN$: C, 62.5; H, 4.9; N, 4.9. Found: C, 62.6; H, 5.0; N, 4.8.

1-(2-Pyridylmethyl)indan (X).—A solution of 15 g. (0.07 mole) of 2-(1-indanylidenemethyl)pyridine in 120 ml. of methanol was hydrogenated with 10% palladium–carbon catalyst at 3 atm. Isolation of the product in the usual manner and distillation gave 11.2 g. (73.5%), b.p. 125–135° (0.3 mm.).

The *hydrochloride* was recrystallized from a mixture of ether and methanol, m.p. 179–180.5°.

Anal. Calcd. for: $C_{15}H_{16}ClN$: C, 73.3; H, 6.6; N, 5.7. Found: C, 73.6; H, 6.1; N, 5.8.

2-Chloro-1-(2-pyridylmethyl)indan Hydrochloride.—To a well stirred and ice-cooled solution of 24 g. (0.11 mole) of 1-(2-pyridylmethyl)-2-indanol in 200 ml. of ether was added dropwise 100 ml. of thionyl chloride. The resulting mixture was stirred at room temperatures for 2 hr. The product (10 g.) was removed by filtration and recrystallized from a mixture of methanol and ether, m.p. 184–185.5°.

Anal. Calcd. for $C_{15}H_{15}Cl_2N$: C, 64.3; H, 5.4; N, 5.0. Found: C, 64.6; H, 5.2; N, 5.1.

1-(2-Pyridylmethyl)-2-indanyl Acetate.—A mixture of 10 g. (0.45 mole) of 1-(2-pyridylmethyl)-2-indanol, 8 g. of sodium acetate, and 65 ml. of acetic anhydride was refluxed for 15 min., cooled, and poured into 800 ml. of water. The oily layer was extracted with ether and dried over anhydrous sodium sulfate. Evaporation of the ether and distillation of the residual oil gave 9 g. (68%) of product, b.p. 136–138° (0.2 mm.).

The *hydrochloride* was recrystallized from a mixture of methanol and ether, m.p. 181–182.5°.

Anal. Calcd. for $C_{17}H_{18}ClNO_2$: C, 67.2; H, 6.0; N, 4.6. Found: C, 67.0; H, 5.9; N, 4.8.

2-(2-Picolylidene)-1-indanone (XI).—To 2 g. of piperidine cooled in an ice bath was added 2 g. of glacial acetic acid, 10.7 g. (0.1 mole) of 2-pyridinealdehyde, and 13.2 g. (0.1 mole) of 1-indanone, respectively. The resulting mixture was heated on a steam bath for 20 min., solidification occurring within this period. The solid was dissolved in hot methanol, treated with charcoal, and filtered. After cooling, the product was removed by filtration and washed with cold methanol. Fourteen grams (63.5%) of product was obtained, m.p. 152–154°. Recrystallization several times from methanol raised the m.p. to 154–155°, λ_{max}^{KBr} 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.4; H, 5.0. Found: C, 81.5; H, 5.2.

2-(2-Pyridylmethyl)-1-indanone (XII).—A solution of 22 g. (0.1 mole) of 2-(2-picolylidene)-1-indanone in 200 ml. of absolute ethanol was hydrogenated at 50 lbs./in.^{2} at room temperature in the presence of 5% palladium–carbon catalyst. Hydrogenation was complete in 30 min. and no further drop in pressure occurred after shaking an additional hour. The catalyst was removed by filtration and after distillation of the solvent, the product (17.2 g., 74%) was distilled at 156–158° (0.3 mm.), $n^{26.5}D$ 1.5965, $\lambda_{max}^{CCl_4}$ 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.7; H, 5.9. Found: C, 80.6; H, 5.9.

2-(2-Picolylidene)-1-indanol.—To a well stirred solution of 10 g. (0.26 mole) of sodium borohydride in 100 ml. of methanol was added gradually a warm solution of 10 g. (0.045 mole) of 2-(2-picolylidene)-1-indanone in 500 ml. of methanol and the resulting solution refluxed for 2 hr. The solvent was distilled *in vacuo* and 200 ml. of water was added to the residual material. The non-aqueous phase was extracted with ether and dried over anhydrous sodium sulfate. The ether was evaporated and the residual solid was triturated with hot cyclohexane and removed by filtration. Five grams (49.5%) of product was obtained, m.p. 132–134°. Recrystallization from a small amount of acetone did not alter the m.p.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.7; H, 5.9. Found: C, 80.7; H, 6.0.

***cis*-2-(2-Pyridylmethyl)-1-indanol (VIa). Method A.**—To a well stirred solution of 10 g. (0.26 mole) of sodium borohydride in 200 ml. of methanol was added gradually a solution of 10 g. (0.045 mole) of 2-(2-pyridylmethyl)-1-indanone in 100 ml. of methanol. The resulting solution was heated to reflux and then removed from the heating bath. When the initial heat of reduction subsided, the mixture was heated under reflux for 2 hr. and allowed to stay overnight at room temperature. The solvent was distilled *in vacuo* and the residual solid treated with 300 ml. of water. The solid was removed by filtration and washed thoroughly with cyclohexane to give 8 g. (79%) of product, m.p. 140–145°. Recrystallization several times from cyclohexane gave product (VIa) m.p. 149–150°, λ_{max}^{KBr} 3200 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 80.0; H, 6.7. Found: C, 80.0; H, 6.6.

Method B.—A solution of 4 g. (0.02 mole) of 2-(2-picolylidene)-1-indanol in 200 ml. of absolute ethanol was hydrogenated at 50 lbs./in.^{2} in the presence of 5% palladium–carbon catalyst for 6 hr. The catalyst was removed by filtration and the solvent was distilled *in vacuo*. Recrystallization of the residual solid several times from cyclohexane gave product (VIa) m.p. 149–150°. A mixed m.p. with the sample obtained by Method A showed no depression.

Method C.—The Raney nickel reduction of 2-(2-picolylidene)-1-indanone in absolute ethanol at 3–4 atm. and 60° yielded product, m.p. 149–150° after recrystallization from benzene. A mixed m.p. with product from Method A showed no depression.

***trans*-2-(2-Pyridylmethyl)-1-indanol (VIb) (Method A.)**—A suspension of 11.0 g. (0.05 mole) of 2-(2-picolylidene)-1-indanone in 110 ml. of absolute ethanol was reduced in the usual manner[12] with sodium amalgam. After shaking for 1 hr., the mixture was poured into 500 ml. of water and the product (8.0 g. 73%) removed by filtration, m.p. 190–200°. Recrystallization of this material four times from an ethanol and *n*-heptane mixture gave product, m.p. 247–249, λ_{max}^{KBr} 3400 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 80.0; H, 6.7. Found: C, 80.2; H, 6.3.

Method B.—The above procedure was followed using 2-(2-pyridylmethyl)-1-indanone. Although most of the starting material was recovered, a low yield (20%) of *trans*-2-(2-pyridylmethyl)-1-indanol, m.p. 247–249°, was obtained. A mixed m.p. with the product obtained from Method A showed no depression; infrared spectra, also were identical.

Dodecahydro[*b*]indolizine (XVII).—A solution of 19 g. (0.1 mole) of 2-(2-pyridylmethyl)cyclohexanol in 200 ml. of methanol was reduced with 2 g. of Raney nickel at 1800 lbs./in.^{2} and 200° for 5 hr. The catalyst was removed by filtration and after distillation of the solvent, the residual oil

(12) A. F. Holleman, "Organic Synthesis," Coll. Vol. I, 1951, p. 554.

was distilled at 119–121° (15 mm.) to yield 7.5 g. (42%) of product, $n^{19.5}$D 1.4963.

The picrate was recrystallized from methanol, m.p. 205–207°.[1]

5a,7,8,9,10,10a,11,11a - Octahydroindeno[1,2-*b*]indolizine (XVIII).—A solution of 22.5 g. (0.1 mole) of 1-(2-pyridylmethyl)-2-indanol in 100 ml. of methanol was hydrogenated with 2 g. of Raney nickel at 2000 lbs./in.^{2} and 200° for 24 hr. The product (5 g., 23%) was isolated as described above, b.p. 107–112° (0.3 mm.).

The *hydrochloride* was recrystallized from a mixture of methyl ethyl ketone, ether, and methanol, m.p. 250–251°.

Anal. Calcd. for $C_{15}H_{20}ClN$: C, 72.1; H, 8.1; N, 5.6. Found: C, 72.1; H, 7.7; N, 5.5.

1-Benzylamino-2-indanol.—A solution of 13.2 g. (0.1 mole) of 1,2-epoxyindan and 11.4 ml. (0.1 mole) of benzylamine in 100 ml. of dry benzene was heated under reflux for 22 hr. The solvent was distilled *in vacuo* and the residual material was recrystallized from dilute methanol to give 10 g. (42%) of product, m.p. 100–102°.[6]

The Constituents of *Ecballium elaterium L.* XV.[1,2] The Structures of Elatericin A and Related Cucurbitacins

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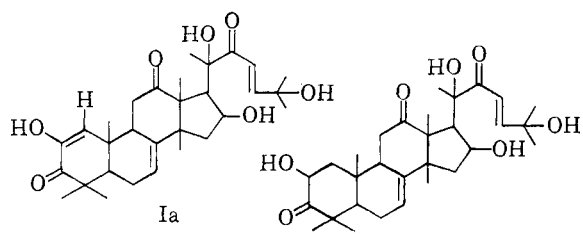
Elatericin A has been degraded to various compounds. The study of these degradation products labeled the final location of the inert double bond at Δ^5, the hindered carbonyl group at C-11, and a methyl group at C-9 leading to the elucidation of the structure of this substance. Three other cucurbitacins namely, elatericin B, cucurbitacin B, and elaterin, which have been correlated previously with elatericin A, are thereby identified.

In previous papers we[3] dealt with the functions of elatericin A (cucurbitacin D) and certain structures were proposed for this substance and related cucurbitacins; a sequence of experiments was described interrelating 4 of these substances.[4] On the basis of several selenium dehydrogenation experiments done by different investigators[5] as well as by ourselves,[3a,b] and in view of the nature of the side chain which was identified unequivocally during degradation, a "regular" tetracyclic triterpenoid carbon skeleton has been assigned to the cucurbitacins. Subsequently, however, it was found that the proposed structures were incompatible with certain physical and chemical properties. We wish now to describe the detailed sequence of experiments, which induced us to reallocate certain groupings of our previous formulas.

From various considerations, structures Ia and Ib had been proposed[3c] for elatericin B and elatericin A, respectively. The corresponding modified structures now presented[6] are shown in IIa and IIIa and are supported by the following observations.

The n.m.r. data for diosphenol systems[7] have



Ia

Ib

indicated that when a proton is present at the γ carbon atom (allylic position) of such α,β-unsaturated α-hydroxy ketone systems, the signal located at the region $\tau \sim 4$ is a spin–spin doublet ($J \sim 2$ c.p.s.). Alternatively, if a hydrogen is not present on the γ carbon atom, a singlet is present in that region. In both cases this signal is attributed to the vinylic hydrogen of the diosphenol system. Since a doublet, centered at $\tau = 4.03$ has been found[7] for a compound formed by the air oxidation of cucurbitacin B,[8] a hydrogen atom has to be present at the γ carbon atom (C-10) of the diosphenol system which was formed during this oxidation (ring A of II). We have confirmed these observations using diosphenol containing cucurbitacins, namely elaterin (IIb), elatericin B (IIa), their acetates, and their dihydro derivatives, for all of them a doublet at the $\tau \sim 4$ region ($J \sim 2$ c.p.s.) has been recorded. It is noteworthy that a model compound, the diosphenol form of 4,4-dimethylcholestane-2,3-dione[9] (no proton at C-10) exhibited a single sharp peak at $\tau = 3.65$, and that dihydroelatericin A[10] (dihydro IIIa) in which the

(1) This investigation was supported by a research grant CY-2810 (C3) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) A previous version of this paper was accepted for publication, June, 1960. It was withdrawn in order to avoid unnecessary misinterpretations in the literature. Meanwhile, various communications have been published; however, for the sake of continuity we have kept the numbering of the original version; Part XIV, O. R. Gottlieb and D. Lavie, *Anais assoc. brasil quim.*, **19**, 185 (1960).

(3) (a) D. Lavie and Y. Shvo, *J. Am. Chem. Soc.*, **82**, 966 (1960); (b) D. Lavie and D. Willner, *ibid.*, **82**, 1668 (1960); (c) D. Lavie and Y. Shvo, *Chem. Ind.* (London), 403 (1960).

(4) D. Lavie, Y. Shvo, and D. Willner; P. R. Enslin, J. M. Hugo, and K. B. Norton, *ibid.*, 951 (1959).

(5) P. R. Enslin and D. E. A. Rivett, *J. Chem. Soc.*, 3682 (1956).

(6) D. Lavie, Y. Shvo, O. R. Gottlieb, and E. Glotter, *Tetrahedron Letters*, 615 (1961).

(7) C. R. Noller, A. Melera, and M. Gut; J. N. Shoolery and L. F. Johnson, *ibid.*, No. **15**, 15 (1960).

(8) Cucurbitacin B is IIIb; we have previously reported that the base catalysed autoxidation of the α-hydroxy ketone grouping in ring A resulted in the formation of a diosphenol system, *cf.* ref. 9.

(9) G. R. Chaudry, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 2725 (1961).

(10) D. Lavie and Y. Shvo, *J. Am. Chem. Soc.*, **81**, 3058 (1959).