[JOINT CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF WAYNE STATE UNIVERSITY
AND FLORIDA STATE UNIVERSITY]

Optical Rotatory Dispersion Studies. XIII.[1] Assignment of Absolute Configuration to Certain Members of the Guaianolide Series of Sesquiterpenes*[2]

CARL DJERASSI,[3a] JEANNE OSIECKI,[3a] AND WERNER HERZ[3b]

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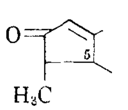
The rotatory dispersion curves of tenulin, helenalin, geigerin, and of many of their derivatives have been measured. These results demonstrate that (*a*) tenulin and helenalin contain the same substitution pattern in the cyclopentenone ring and (*b*) that they belong to the same stereochemical series insofar as the ring juncture is concerned. A tentative assignment of absolute configuration at C-1 and C-5 is made by comparison of their rotatory dispersion curves with those of steroid reference compounds.

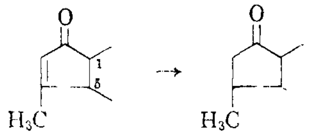
The guaianolide series of sesquiterpenes encompasses a group of lactones which is based on the skeleton I and which yields guaiazulene and/or chamazulene upon dehydrogenation. The most extensively studied members are tenulin (IIa)[4,5] and helenalin (VI),[6–9] but a considerable number of additional representatives are being uncovered[10–12] and a striking connection with the large group of eudalenoid sesquiterpenes has been presented.[13] In view of the key role which the guaianolides play in the biogenetic scheme of the sesquiterpenes, it appeared of interest to apply rotatory dispersion measurements[14] to certain outstanding structural and stereochemical problems in this field.

Structure IIa for tenulin, as proposed first by Barton and de Mayo[4] was in substantial agreement with the independent degradation experiments of the Florida group[5] except for certain ambiguities relating to the cyclopentenone ring for which a second alternative (IIb) was suggested.[5,15] This point of difference has now been settled in favor of IIa on the basis of two independent lines of evidence:

(*a*) In the nuclear magnetic resonance spectra of tenulin (IIa) and dihydrotenulin (III), or isotenulin (IV) and dihydroisotenulin (Va), the peak corresponding to the hydrogen atoms in $-\overset{|}{\underset{|}{C}}-CH_3$ remained constant. This is only consistent with partial structure A (=IIa) since hydrogenation of the double bond in the alternative B (=IIb) would lead to C, which possesses three more hydro-



A



B C

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Paper XII, C. Djerassi and D. Marshall, *Tetrahedron*, 1, 238 (1957).

(2) The work at Wayne State University was supported by a research grant (No. CY-2919) from the National Cancer Institute, National Institutes of Health. The work at Florida State University was supported by a grant from the Research Corp.

(3a) Wayne State University, Detroit, Mich.; (b) Florida State University, Tallahassee, Fla.

(4) D. H. R. Barton and P. De Mayo, *J. Chem. Soc.*, 1956, 142.

(5) B. H. Braun, W. Herz, and K. Rabindran, *J. Am. Chem. Soc.*, **78**, 4423 (1956).

(6) E. P. Clark, *J. Am. Chem. Soc.*, **62**, 597 (1940) and earlier papers.

(7) R. Adams and W. Herz, *J. Am. Chem. Soc.*, **71**, 2546, 2551, 2554 (1949).

(8) G. Büchi and D. Rosenthal, *J. Am. Chem. Soc.*, **78**, 3860 (1956).

(9) V. Herout, M. Romanuk, and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **21**, 1359 (1956).

(10a) Z. Cekan, V. Herout, and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **19**, 798 (1954); Z. Cekan, V. Herout, and F. Sorm, *Chemistry & Industry*, 604 (1954), 1234 (1956); V. Herout and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **18**, 854 (1953), **19**, 792 (1954); F. Sorm, L. Novotny and V. Herout, *Chemistry & Industry*, 569 (1955); V. Herout, L. Novotny and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **21**, 1484 (1956); V. Herout, L. Dolejs and F. Sorm, *Chemistry & Industry*, 1236 (1956).

(10b) A. Meisels and A. Weizmann, *J. Am. Chem. Soc.*, **75**, 3865 (1953); Y. Mazur and A. Meisels, *Chemistry & Industry*, 492 (1956).

(10c) Y. Naves, *Helv. Chim. Acta*, **31**, 1172 (1948); L. Crabalona, *Bull. soc. chim. France*, **15**, 357 (1948); M. Romanuk, V. Herout, and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **21**, 894 (1956).

(10d) T. Kariyone, S. Naito, and J. Chatani, *Pharm. Bull.*, **2**, 339 (1954); T. Kariyone and S. Naito, *J. Pharm. Soc. Japan*, **75**, 39 (1955); S. Naito, *J. Pharm. Soc. Japan*, **75**, 93, 325 (1955).

(11) G. W. Perold, *J. Chem. Soc.*, 47 (1957). The position of the hydroxyl group in geigerin was established by D. H. R. Barton and collaborators (to be published).

(12) W. Herz, unpublished observation.

(13) D. H. R. Barton, P. De Mayo, and M. Shafiq, *J. Chem. Soc.*, 929 (1957).

(14) For general survey see C. Djerassi, *Bull. soc. chim. France*, 741 (1957).

(15) Formula IIb was originally favored by one of us (W.H.) because of a remarkable base-catalyzed cleavage reaction which dehydrodesacetyldihydroisotenulin undergoes.[5] Barton, quoted by P. de Mayo, *Perfumery Essent. Oil Record*, **48**, 68 (1957), has recently suggested a rationalization for this transformation based on IIa. Work to establish more definitely the orientation of the lactone ring of tenulin is still in progress.

gen atoms contributing to the NMR peak under discussion.[16]

(*b*) As pointed out in earlier papers,[14] the characteristic shapes of rotatory dispersion curves of cycloalkanones and cycloalkenones should be governed chiefly by the carbonyl chromophore rather than by additional substituents (*e.g.*, esters, hydroxyl groups, lactones[17]) unless certain conformational factors interfere.[18] Since the structure of helenalin (VI) appears to be settled (cyclopentenone ring as in A),[8] it could serve as an adequate rotatory dispersion standard for differentiating between expressions IIa and IIb for tenulin, provided that the absence of major conformational distortion in the cycloheptane ring due to the different attachment of the butenolide ring could be demonstrated. This assumption was found to be valid as shown in the sequel.

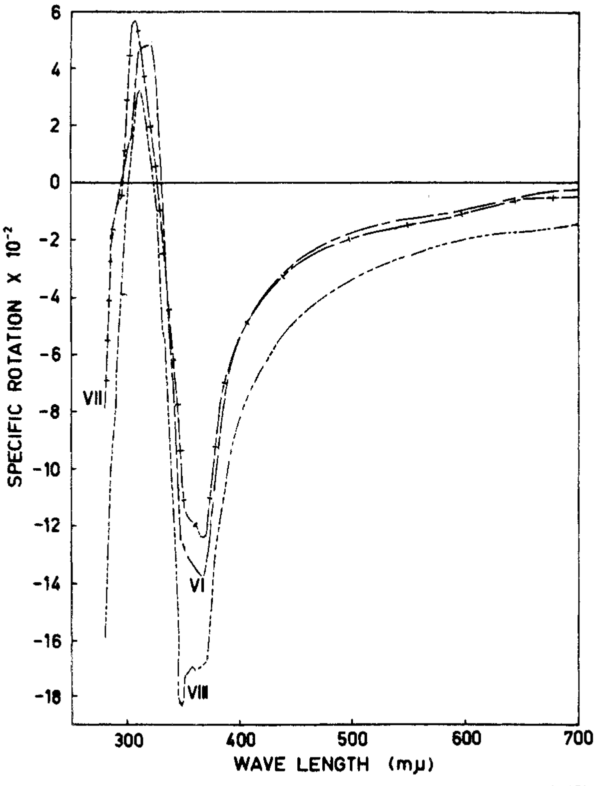

FIG. 1. ROTATORY DISPERSION CURVES OF HELENALIN (VI), DIHYDROHELENALIN (VII), AND ISOHELENALIN (VIII).

In Fig. 1 are reproduced the rotatory dispersion curves of helenalin (VI), dihydrohelenalin (VII), and isohelenalin (VIII). These three substances differ only in the lactone ring and it is evident that alterations in that portion of the molecule play only a negligible role, since except for some amplitude[19] changes, the rotatory dispersion curves are very similar and are characterized by a negative Cotton-effect curve[19] with some fine structure in the 350–375 mμ region.

The rotatory dispersion curves of tenulin (IIa) and isotenulin (IV) are given in Fig. 2 and the close correspondence of these two curves—except for some amplitude differences below 325 mμ—demonstrates that the additional ring involving the hemiketal system of tenulin (IIa) as compared to an ordinary acetoxyl substituent in isotenulin (IV) does not affect the rotatory dispersion picture.

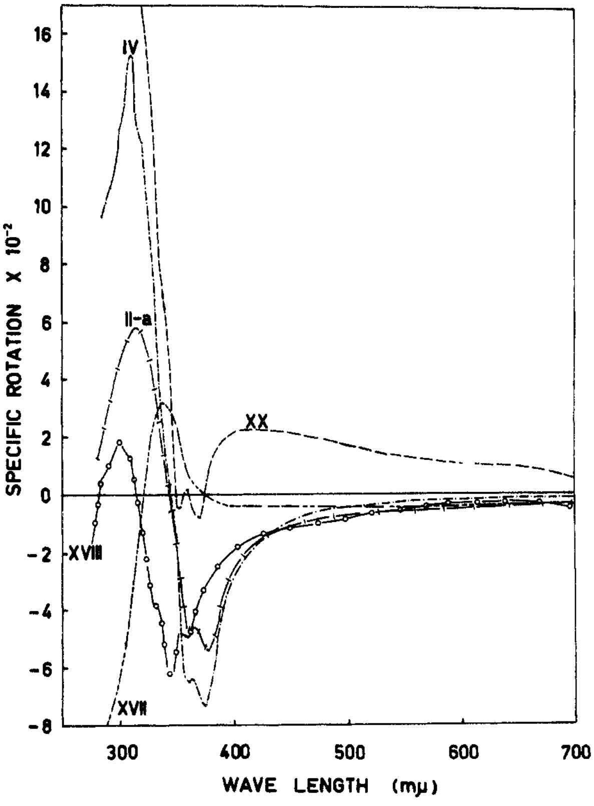

FIG. 2. ROTATORY DISPERSION CURVES OF TENULIN (IIa), ISOTENULIN (IV), DESACETYLNEOTENULIN (XVII), GEIGERIN (XVIII), AND ISOPHOTOSANTONIC LACTONE (XX).

With the above demonstration that alterations in the cycloheptane ring affect the amplitude but not the shape of the dispersion curve, a comparison of the pertinent curves in Figs. 1 and 2 (*e.g.* helenalin (VI) *vs.* tenulin (IIa) appears valid and the striking coincidence of their respective dispersion curves leaves little doubt that both sesquiterpenes must possess the same cyclopentenone chromophore (type A). This in turn implies that the angular hydrogen atom in both tenulin and helenalin must have the same orientation, since otherwise

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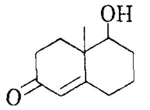
(16) We are indebted to Dr. R. E. Glick, now at Pennsylvania State University, who determined the NMR spectra of these compounds in the chemical laboratories of Harvard University.

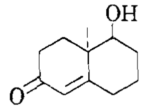
(17) The negligible effect of butenolide systems has been demonstrated in a detailed study of the rotatory dispersion of steroidal cardiac aglycones (to be published).

(18) A case in point is the marked difference in the rotatory dispersion curves of α- and β-vetivone (C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78,** 6377 (1956).

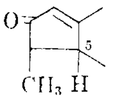
(19) For nomenclature and method of recording rotatory dispersion data in the experimental section, see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

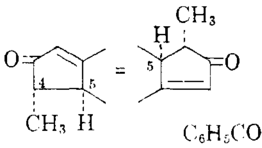
the curves in Fig. 1 and in Fig. 2 would have been of mirror image types in spite of the fact that helenalin and tenulin are not antipodes. This statement is best supported by a concrete example illustrated in Fig. 3 with the rotatory dispersion curves of (8S, 9S)-(+)-(XII) and (8S, 9R)-(−)-(XIII) Δ^4-9-methyl-8-hydroxy-3-octalones [prepared by Prelog and Acklin.[20] While these two substances are not antipodes, their dispersion curves are nevertheless of mirror image type since the angular substituents are of opposite orientation[21] and the hydroxyl group plays no role in this instance. The rotatory dispersion curve of XII is essentially identical with that of typical Δ^4-3-keto steroids (ref. 18), thus providing definitive proof for the assignments of absolute configurations made by Prelog and Acklin[18] by the less secure method of molecular rotation differences.

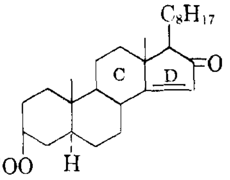

XII


XIII

The above rotatory dispersion evidence indicates that tenulin (IIa) and helenalin (VI) possess the same cyclopentenone chromophore and identical stereochemistry at C-5 and it appeared of interest to determine whether this type of approach could be extended to assign actual absolute configurations to these two sesquiterpenes, *i.e.* whether they should be represented by partial formulas D or E (the methyl group at C-4 being assumed to be equatorially oriented).


D


E


XIV

In an earlier paper,[22] it was shown that substitution of an angular methyl group by a hydrogen atom did not affect the rotatory dispersion curve. Similarly, introduction of equatorial alkyl groups α to the carbonyl system had no important effect,[22,23] and consequently, if one assumed that substitution of a cyclohexane for a cycloheptane ring would not result in drastic alteration of the dispersion picture, then it should be possible to utilize an appropriate steroid ketone as a reference substance of known absolute configuration. The steroid chosen by us for this purpose was Δ^{14}-cholesten-3β-ol-16-one benzoate (XIV)[24,25] and its rotatory dispersion curve (Fig. 3) is characterized by a strongly positive Cotton-effect curve[19] in contrast to the negative Cotton effect exhibited by helenalin (Fig. 1) and tenulin (Fig. 2). With the reservations outlined above, rings C and D of the steroid XIV can be used as a reference system of established absolute configuration, from which it follows that tenulin (IIa) and helenalin (VI) should be assigned the absolute configuration expressed by partial formula E (C-5 hydrogen atom α oriented).

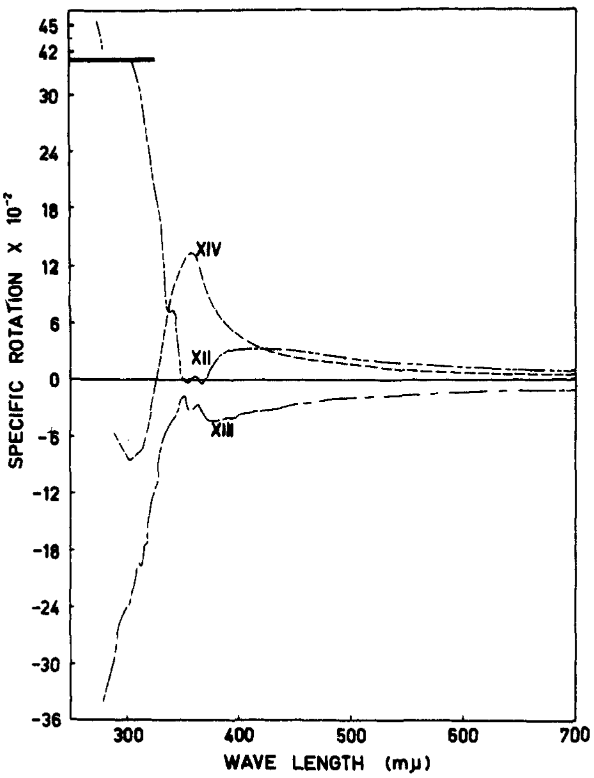


FIG. 3. ROTATORY DISPERSION CURVES OF (8S, 9S)-(+)-Δ^4-9-METHYL-8-HYDROXY-3-OCTALONE (XII), (8S, 9R)-(−)-Δ^4-9-METHYL-8-HYDROXY-3-OCTALONE (XIII) AND Δ^{14}-CHOLESTEN-3β-OL-16-ONE BENZOATE (XIV).

This same approach can also be extended to the reduction products of tenulin and helenalin with a saturated cyclopentanone ring. In Fig. 4 are collected the rotatory dispersion curves of dihydrotenulin (III), dihydroisotenulin (Va), its desacetyl derivative (Vb), and desacetyldihydroalloisotenulin (XI). All of these compounds are identical insofar as the bicyclic ring juncture is concerned and differ only in the nature of the attachment or substitution of the lactone ring. Since the cyclopentanone moiety and its immediate stereochemical environment should govern the shape of the rotatory dispersion curve, it is not surprising that, ex-

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(20) V. Prelog and W. Acklin, *Helv. Chim. Acta*, **39**, 748 (1956).

(21) The reason, of course, is that the governing chromophores—in this instance the octalone systems of XII and XIII—are enantiomeric.

(22) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(23) Unpublished observation.

(24) K. Tsuda and R. Hayatsu, *J. Am. Chem. Soc.*, **78**, 4107 (1956).

(25) Esters, such as acetates or benzoates, do not contribute to the shape of the rotatory dispersion curve.

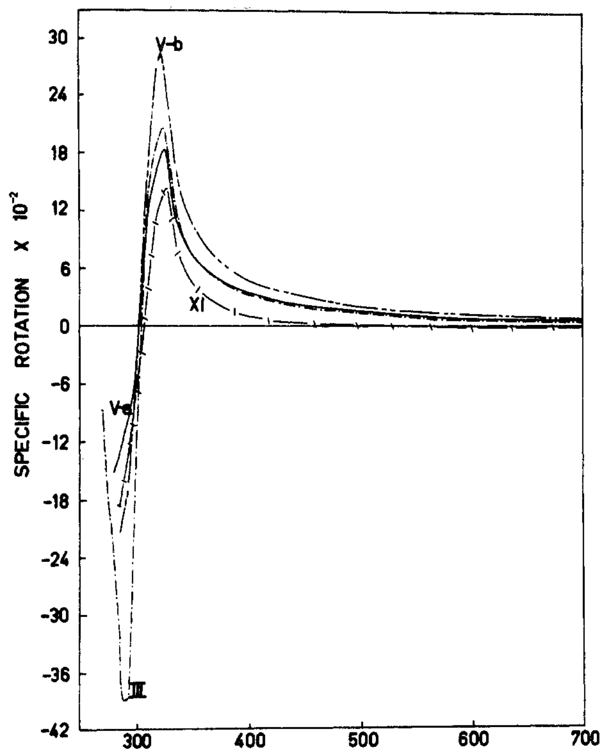


FIG. 4. ROTATORY DISPERSION CURVES OF DIHYDROTENULIN (III), DIHYDROISOTENULIN (Va), DESACETYLDIHYDROISOTENULIN (Vb), AND DESACETYLDIHYDROALLOISOTENULIN (XI).

cept for amplitude differences, all of the curves are similar and characterized by a single, positive Cotton-effect curve.[19] Virtually identical results are noted in Fig. 5 with the appropriate saturated helenalin derivatives, dihydroisohelenalin (IX) and tetrahydrohelenalin (X).[26]

The conclusion can be reached from Figs. 4 and 5 that the ring juncture (C-1 and C-5) in the saturated tenulin and helenalin derivatives is the same and it now remains to be determined whether absolute configurations F or G apply to these hydrogenation products, since either one could be derived from the cyclopentenone precursor E. In the absence of any knowledge of the stereochemistry of the substituents in the cycloheptane ring which could strongly affect the mode of hydrogen addition, no prediction could be made. However, if one again equates a cyclohexane with a cycloheptane ring, then rings A and B of the A-nor steroids XV and XVI could be selected as reference standards. The rotatory dispersion curve[22] of the *trans*-hydrindanone derivative XV is characterized by a powerful, positive, single Cotton effect[27] while the *cis*-ketone XVI exhibits a negative one. On that basis, the rotatory dispersion curves of the sesquiterpene reduction products discussed above are of the same type as that of the steroid XV and we assign tentatively the absolute configuration implicit in partial structure G to them.

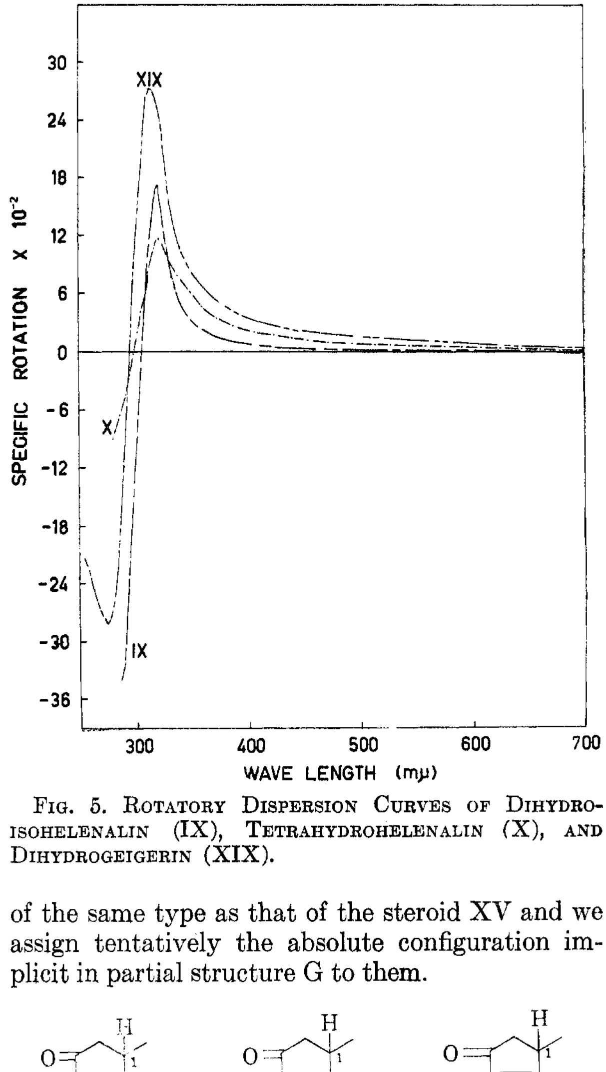
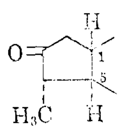
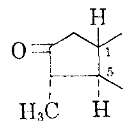


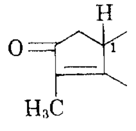
FIG. 5. ROTATORY DISPERSION CURVES OF DIHYDROISOHELENALIN (IX), TETRAHYDROHELENALIN (X), AND DIHYDROGEIGERIN (XIX).



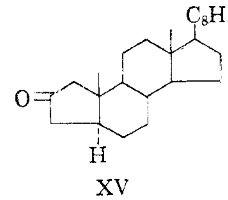
F



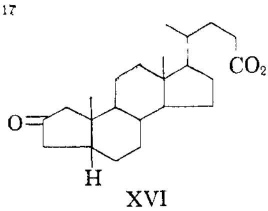
G



H



XV



XVI

An interesting case is represented by desacetylneotenulin (XVII),[4] geigerin (XVIII),[11] and isophotosantonic lactone (XX)[13] in which the double bond in the cyclopentenone ring occupies the alternate position as compared to tenulin (IIa) and helenalin (VI). The mode of substitution in that ring has been established by ultraviolet spectral measurements as well as by ozonolysis and isolation of acetic acid. The rotatory dispersion curves

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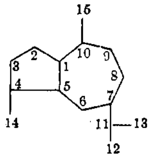
(26) Tetrahydrohelenalin (X) and desacetyldihydroalloisotenulin (XI) are not identical and must differ in the orientation of one or more asymmetric centers in the cycloheptane ring (*excluding* the ring juncture).

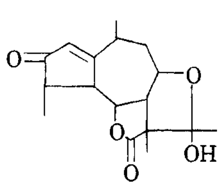
(27) This is to be expected since it should be the mirror image of a 16-ketosteroid which is known [C. Djerassi, W. Closson, and A. E. Lippman, *J. Am. Chem. Soc.*, **78**, 3163 (1956)] to show a strong negative Cotton effect.

of geigerin (XVIII) (Fig. 2) and of dihydrogeigerin (XIX) (Fig. 5) are so similar in shape to those of tenulin and dihydrotenulin, that we conclude that geigerin (XVIII) is represented by the partial, absolute structure H and dihydrogeigerin (XIX) by G. Desacetylneotenulin (XVII) on the other hand exhibits a completely different type of dispersion curve (Fig. 2) and while it is not the mirror image of that of geigerin (XVIII), the Cotton effect is nevertheless of opposite sign and barring some unknown conformational effect produced by substituents in the cycloheptane ring, desacetylneotenulin should be represented as the antipode of H (C-1 hydrogen atom α).

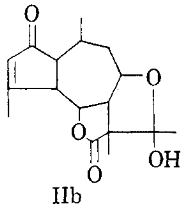
Isophotosantonic lactone (XX) exhibits a dispersion curve (Fig. 2) of the tenulin (IIa) type except that the entire curve is moved towards positive rotation and no peak is noticeable in the 300 mμ region. In fact, its curve is strikingly similar to that of Δ^4-3-keto steroids,[22,28] which again suggests that XX should be assigned the absolute configuration H with the C-1 hydrogen atom β-oriented.[29]



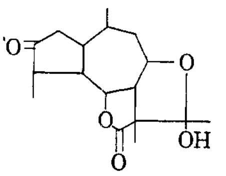
I



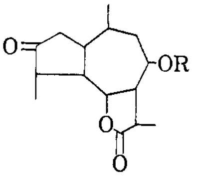
IIa



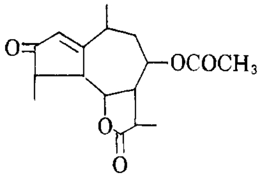
IIb



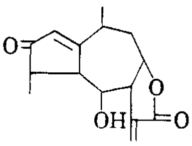
III



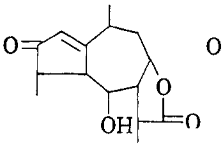
Va R=CH$_3$CO
b R=H



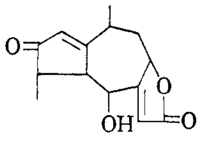
IV



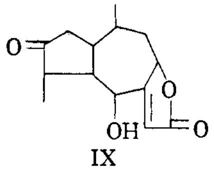
VI



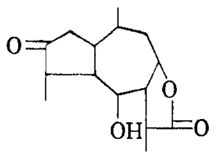
VII



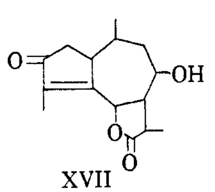
VIII



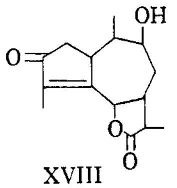
IX



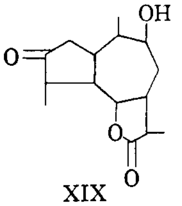
X (helenalin series)
XI (tenulin series)



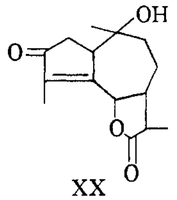
XVII



XVIII



XIX



XX

EXPERIMENTAL[30]

Tenulin (IIa). R. D. (Fig. 2) in dioxane (c 0.056), 25°: $[\alpha]_{700}$ −39°, $[\alpha]_{589}$ −50°, $[\alpha]_{375}$ −537°, $[\alpha]_{365-367.5}$ −461°, $[\alpha]_{360}$ −472°, $[\alpha]_{312.5}$ +577°, $[\alpha]_{280}$ +123°.

Dihydrotenulin (III). R. D. (Fig. 4) in dioxane (c 0.106), 25°: $[\alpha]_{700}$ +60°, $[\alpha]_{589}$ +106°, $[\alpha]_{325}$ +2050°, $[\alpha]_{290}$ −3890°, $[\alpha]_{270}$ −901°.

Isotenulin (IV). R. D. (Fig. 2) in dioxane (c 0.10), 26°: $[\alpha]_{700}$ −16°, $[\alpha]_{589}$ −20°, $[\alpha]_{372.5}$ −727°, $[\alpha]_{362.5}$ −638°, $[\alpha]_{360}$ −650°, $[\alpha]_{315}$ +1270° (infl.), $[\alpha]_{310}$ +1520°, $[\alpha]_{285}$ +960°.

Dihydroisotenulin (Va). R. D. (Fig. 4) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ +77°, $[\alpha]_{589}$ +99°, $[\alpha]_{325}$ +1837°, $[\alpha]_{280}$ −1500°.

Desacetyldihydroisotenulin (Vb). R. D. (Fig. 4) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ +80°, $[\alpha]_{589}$ +137°, $[\alpha]_{322.5}$ +2848°, $[\alpha]_{285}$ −2125°.

Helenalin (VI) (G. Büchi). R. D. (Fig. 1) in dioxane (c 0.10), 25°: $[\alpha]_{700}$ −25°, $[\alpha]_{589}$ −102°, $[\alpha]_{365}$ −1369°, $[\alpha]_{350}$ −1274° (infl.), $[\alpha]_{320}$ +485°, $[\alpha]_{300}$ +140° (infl.), $[\alpha]_{285}$ −190°.

Dihydrohelenalin (VII) (G. Büchi). R. D. (Fig. 1) in dioxane (c 0.087), 25°: $[\alpha]_{700}$ −46°, $[\alpha]_{589}$ −122°, $[\alpha]_{367.5}$ −1232°, $[\alpha]_{355}$ −1185° (infl.), $[\alpha]_{305}$ +575°, $[\alpha]_{295}$ −46° (infl.), $[\alpha]_{280}$ −782°.

Isohelenalin (VIII) (G. Büchi). R. D. (Fig. 1) in dioxane (c 0.0825), 25°: $[\alpha]_{700}$ −139°, $[\alpha]_{589}$ −208°, $[\alpha]_{360}$ −1705°, $[\alpha]_{357.5}$ −1695°, $[\alpha]_{347.5}$ −1833°, $[\alpha]_{310}$ +327°, $[\alpha]_{380}$ −1589°.

Dihydroisohelenalin (IX) (G. Büchi). R. D. (Fig. 5) in dioxane (c 0.098), 25°: $[\alpha]_{700}$ −4°, $[\alpha]_{589}$ +5°, $[\alpha]_{320}$ +1720°, $[\alpha]_{285}$ −3420°.

Tetrahydrohelenalin (X) (G. Büchi). R. D. (Fig. 5) in dioxane (c 0.08), 24°: $[\alpha]_{700}$ +23°, $[\alpha]_{589}$ +41°, $[\alpha]_{320-322.5}$ + 1150°, $[\alpha]_{280}$ −925°.

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(28) It was shown in refs. 18 and 22 that the methyl group on the double bond did not influence the rotatory dispersion curve of Δ^4-3-ketosteroids.

(29) The striking difference in ease of hydrogenation between geigerin and isophotosantonic lactone, on the one hand, and desacetylneotenulin, on the other, may conceivably be rationalized by invoking the above argument concerning the configuration of these three substances. Whereas geigerin and isophotosantonic lactone[13] are reportedly converted to the respective dihydroderivatives on shaking with palladium catalysts in ethanol, desacetylneotenulin remains unaffected under these conditions (unpublished observations by K. Rabindran).

(30) For experimental procedure and errors see footnote 34 in ref. 18. The only difference between the current and earlier measurements was that in the present work a mechanically oscillating polarizer [H. Rudolph, *Proc. Instrum. Soc. Amer.*, Sept. 1956 (paper No. 56-3-1)] was employed which resulted in a saving of time. We are greatly indebted to the various investigators listed in the experimental section for supplying us with samples. Where no source is listed, the specimen came from the collection of W. H. The data are presented in the manner recommended in ref. 19.

Desacetyldihydroalloisotenulin (XI). R. D. (Fig. 4) in dioxane (c 0.102), 25°: $[\alpha]_{700}$ −7°, $[\alpha]_{589}$ −2°, $[\alpha]_{327.5}$ +1441°, $[\alpha]_{285}$ −1853°.

(8S, 9S)-(+)-Δ^4-9-methyl-8-hydroxy-3-octalone (XII) (V. Prelog). R. D. (Fig. 3) in dioxane (c, 0.152), 25°: $[\alpha]_{700}$ +111°, $[\alpha]_{589}$ +161°, $[\alpha]_{405}$ +340° (sh.), $[\alpha]_{370}$ −16°, $[\alpha]_{362.5}$ +54°, $[\alpha]_{357.5}$ −14°, $[\alpha]_{342.5}$ +737°, $[\alpha]_{340}$ +692°, $[\alpha]_{275}$ +4550°.

(8S, 9R)-(−)-Δ^4-9-methyl-8-hydroxy-3-octalone (XIII) (V. Prelog). R. D. (Fig. 3) in dioxane (c 0.104), 25°: $[\alpha]_{700}$ −100°, $[\alpha]_{589}$ −125°, $[\alpha]_{410-412.5}$ −345° (infl.), $[\alpha]_{380}$ −442° (sh.), $[\alpha]_{365}$ −258°, $[\alpha]_{357.5}$ −316°, $[\alpha]_{352.5}$ −160°, $[\alpha]_{315}$ −1980°, $[\alpha]_{312.5}$ −1900°, $[\alpha]_{280}$ −3390°.

Δ^{14}-Cholesten-3β-ol-16-one benzoate (XIV) (K. Tsuda). R. D. (Fig. 3) in dioxane (c 0.10), 25°: $[\alpha]_{700}$ +77°, $[\alpha]_{589}$ +97°, $[\alpha]_{360}$ +1332°, $[\alpha]_{305}$ −845°, $[\alpha]_{290}$ −555°.

Desacetylneotenulin (XVII) (D. H. R. Barton, W. Herz). R. D. (Fig. 2) in dioxane (c 0.085), 24°: $[\alpha]_{700}$ −41°, $[\alpha]_{589}$ −48°, $[\alpha]_{337.5}$ +318°, $[\alpha]_{290}$ −800°.

Geigerin (XVIII) (G. W. Perold). R. D. (Fig. 2) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ −52°, $[\alpha]_{589}$ −30°, $[\alpha]_{357.5}$ −499°, $[\alpha]_{352.5}$ −481°, $[\alpha]_{345}$ −623°, $[\alpha]_{330}$ −376° (infl.), $[\alpha]_{300}$ +180°, $[\alpha]_{275}$ −175°.

Dihydrogeigerin (XIX) (G. W. Perold). R. D. (Fig. 5) in methanol (c 0.085), 24°: $[\alpha]_{700}$ +46°, $[\alpha]_{589}$ +102°, $[\alpha]_{312.5}$ +2720°, $[\alpha]_{275}$ −2827°, $[\alpha]_{255}$ −2144°.

Isophotosantonic lactone (XX) (D. H. R. Barton). R. D. (Fig. 2) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ +56°, $[\alpha]_{589}$ +117°, $[\alpha]_{405}$ +224°, $[\alpha]_{370}$ −74°, $[\alpha]_{360}$ +26°, $[\alpha]_{352.5}$ −48°, $[\alpha]_{275}$ +2836°.

DETROIT, MICH.
TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE, PUBLIC HEALTH SERVICE]

Structures Related to Morphine. VIII. Further Syntheses in the Benzomorphan Series*[1,2]

EVERETTE L. MAY AND EDWARD M. FRY

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2,5,9-Trimethyl-6,7-benzomorphan (VIII) has been synthesized from 3,4-lutidine methiodide (V) and benzylmagnesium chloride or from β-tetralone, while the hydroxy derivative (X) results from V and *p*-methoxybenzylmagnesium chloride. Compound VIII has also been converted to X *via* nitration, reduction, and diazotization and has been degraded to 1,2-dimethylnaphthalene.

Compound X, a close chemical relative of the potent analgesic racemorphan (IIIb) is an effective analgesic in mice with relatively low toxicity.

Recent studies in our laboratories have shown that 2,5-dimethyl-6,7-benzomorphan (IVa)[3] and the phenolic congener (IVb)[4] possess lower analgesic activity and lower toxicity than *N*-methylmorphinan (IIIa) and racemorphan (IIIb)[5,6] respectively. Stereochemically, structure IV simulates structure III except at carbon 9 (carbon 14 in III). The introduction of a methyl substituent at position 9 would complete this stereochemical approximation, and might be expected to enhance the analgesic effectiveness of IV. The present report is concerned with such an alteration of IV, the synthesis of 2,5,9-trimethyl 6,7-benzomorphan (VIII) and the hydroxy analog (X), compounds in which the C-methyl groups may be regarded as fragments of ring C of III. Attempts were first made to synthesize VIII by the sequence of reactions employed in the preparation of IVa.[3] However, the Knoevenagel reaction with 5-dimethylamino-3-methyl-3-phenyl-2-pentanone, a key step in this scheme of reactions, failed.[2] We then turned our attention to the synthesis developed by Grewe[5] for the morphinans (III and analogs)[6] which is outlined in Fig. 1. Transposing to our own case would merely involve substituting 3,4-lutidine methiodide (V) for 2-methyl-5,6,7,8-tetrahydrohydroisoquinoline methiodide (I).

In 1909 Freund and Bode[7] reported the formation of unstable dihydropyridines when pyridine methiodides and Grignard reagents were brought to reaction in ether. When we utilized benzylmagnesium chloride and V in this manner, a readily autoxidizable dihydro derivative (VI) was obtained. It was quickly distilled at 0.5 mm. and hydrogenated (palladium–barium sulfate) to the more stable tetrahydro compound (VII) which was cyclized (after distillation) to VIII with 85% phosphoric acid. The overall yield of VIII, based on 3,4-lutidine methiodide, was 20%. No attempt was made to characterize VI and VII. Similarly 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (X) resulted from *p*-methoxybenzylmagnesium chloride

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) The benzomorphan nomenclature was proposed by Dr. J. A. Barltrop [*J. Chem. Soc.*, 399 (1947) and private communication (1956).]

(2) Paper VII, E. L. May, *J. Org. Chem.*, **22**, 593 (1957).

(3) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955).

(4) N. B Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

(5) R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948); R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949).

(6) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949).

(7) M. Freund and G. Bode, *Ber.*, **42**, 1746 (1909).