

Fig. 2.

tion which is compatible with the chemical evidence for the 13α -configuration.

A fundamental analysis⁶ of the rotatory dispersion of optically active 1,3-cyclohexadienes has revealed that the skewness imposed on such diene systems by structural factors constitutes the major element of asymmetry responsible for the Cotton effect, its contribution to optical activity far outweighing that of adjacent asymmetric centers. In addition, it has been derived theoretically and demonstrated experimentally⁶ that the direction of the Cotton effect so produced depends upon the sense of helicity of the diene, a left-handed helix producing a negative effect. On the basis of this rule, the negative Cotton effect of I requires that its dienic system form a left-handed helix. It is apparent from Dreiding models that this requirement is met not only by the 13β -configuration of I, but also by one (I-A)⁷ of two possible conformations with 13α (the other one, I-B, predicts a positive Cotton effect). Since the first of these possibilities is contrary to the available chemical evidence, we feel that the second one with its 13α -configuration is likely to be correct.

An analogous situation obtains in (-)- α -phellandrene (III), our only other case (out of eleven compounds studied so far) of a seemingly wrong prediction of the sign of a Cotton effect from the helicity rule.⁸ Here, a positive Cotton effect is expected if the isopropyl group has the quasi-equatorial conformation III-A usually assumed to be the preferred one. The observed negative effect suggests that the alternative conformation III-B with a quasi-axial isopropyl group is in fact correct; in this case the diene system assumes the required left-handed helicity.

It seems significant that both in III-B and in I-A the protons of an alkyl group (17-methyl in I, isopropyl in III) are spatially close to the center of the unsaturated system. This suggests some type of interaction which stabilizes an otherwise unfavorable conformation.^{9,10} A special condition of the protons on C-17 of I is actually suggested by n.m.r.

(6) A. Moscovitz, E. Charney, U. Weiss and H. Ziffer, *J. Am. Chem. Soc.*, **83**, 4661 (1961).

(7) Models of I-A actually show an almost planar diene; it is plausible to assume, however, that in reality this system is more strongly twisted to avoid serious crowding of the hydrogen atoms at C-4 and C-5.

(8) The absolute configuration of III appears well established; cf., *inter alia*, the discussion by K. Freudenberg and W. Lwowski, *Ann.*, **587**, 213 (1954), and literature quoted there.

(9) Cf. also the case of isomenthone: (a) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., New York, N. Y., 1960, pp. 106, 107; (b) C. Djerassi, *et al.*, *J. Am. Chem. Soc.*, **83**, 3334 (1961).

(10) The positive Cotton effect observed for II clearly eliminates a possible "folded" conformation resembling I-A (left-handed helix). In II the absence of an alkyl group at C-9 precludes the stabilizing interaction assumed for I-A and III-B, and hence the extended conformation (cf. I-B) with a right-handed helix prevails.

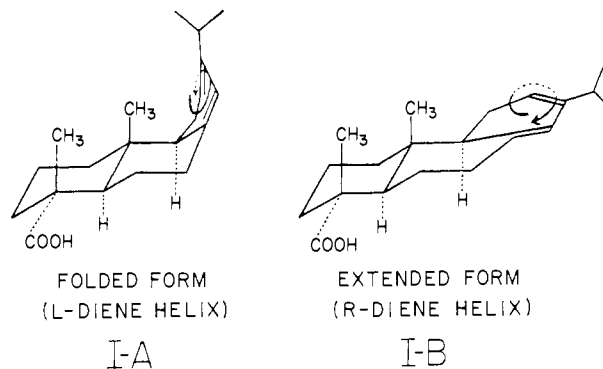


Fig. 3.

data.³ The signal caused by them is shifted ~ 0.17 p.p.m. downfield from its position in thirteen related compounds, including, e.g., neoabietic acid ($\Delta^{7(18),8(14)}$) and pimaric acid ($\Delta^{8(14)}$). Hence, this shift appears to be due to a specific interaction, possible only in I, between the methyl protons and the entire diene, rather than to the presence of the $\Delta^{8(14)}$ bond, isolated or conjugated.¹¹

While this interpretation is permissive rather than decisive, it removes the otherwise unresolved discrepancy between chemical evidence and rotational data. It also emphasizes the importance of making due allowance for conformational influences not immediately obvious.

We wish to thank Dr. R. V. Lawrence, Naval Stores Research Laboratory, Olustee, Florida, for samples of resin acids, and several colleagues for helpful discussions.

(11) The downfield shift³ in compounds with a Δ^{13} bond (e.g., palustric acid) is normal for a double bond at this distance and hence not relevant (cf. J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958)).

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OPTICAL ACTIVITY IN SKEWED DIENES

Sir:

In connection with our interest in dissymmetric chromophores,^{1,2} we have considered the optical activity associated with skewed dienes.³ It will be recognized that butadiene would be optically active in any of its nonplanar forms and that comparable dissymmetric diene conformations may be achieved permanently when the conjugated moiety is part of a rigidly fixed ring system, e.g., in lumisterol (I).

(1) K. Mislow, M. A. W. Glass, A. Moscovitz and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 2771 (1961).

(2) A. Moscovitz, *Tetrahedron*, **13**, 48 (1961).

(3) While this manuscript was in preparation, the publication of R. Deen and H. J. C. Jacobs, *Koninkl. Nederl. Akademie Van Wetenschappen Amsterdam*, **64**, 313 (1961), came to our attention. From both theoretical and experimental considerations (see also R. Deen, Thesis, Leiden, September, 1961), these authors conclude that "an asymmetrically situated butadiene system will either in itself or due to its environment bring about optical activity correlated with its longest wavelength transition." The present work is in agreement with and supports this conclusion.

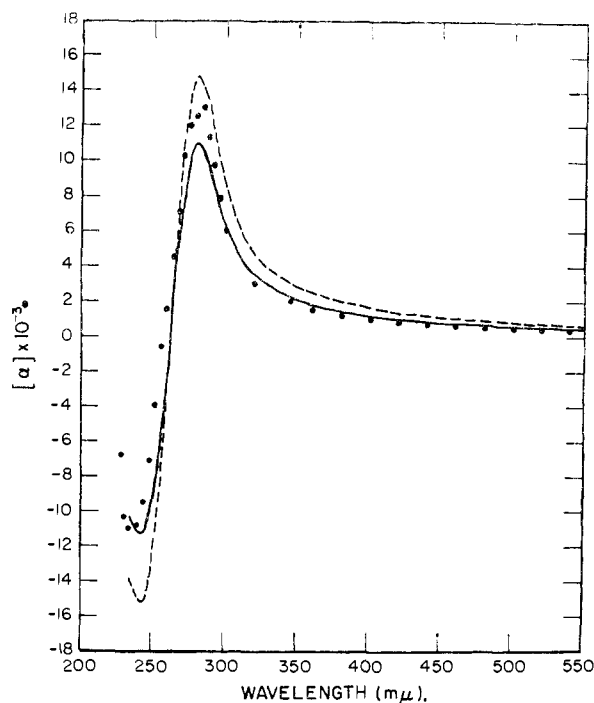


Fig. 1.—Cotton effect of rotatory dispersion of (+)-*trans*-9-methyl-1,4,9,10-tetrahydronaphthalene: experimental ($c = 0.0073$, cyclohexane); - - - - computed with $(\eta^2 + 2)/3$ correction for refractive index of solvent; ——— computed without solvent correction.

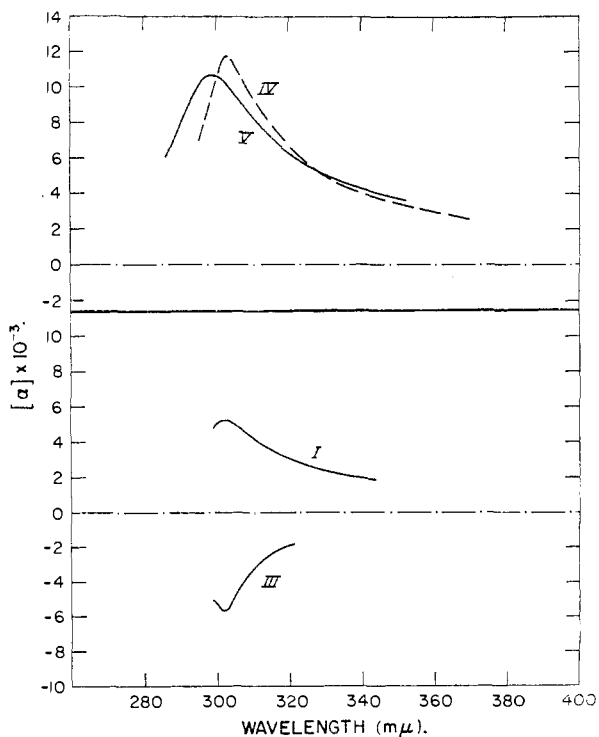


Fig. 2.—Rotatory dispersion of ergosterol and its stereoisomers in alcohol.

The contribution to the observed rotatory dispersion associated with such inherently dissymmetric chromophores usually will outweigh^{1,2} any contributions associated with asymmetrically dis-

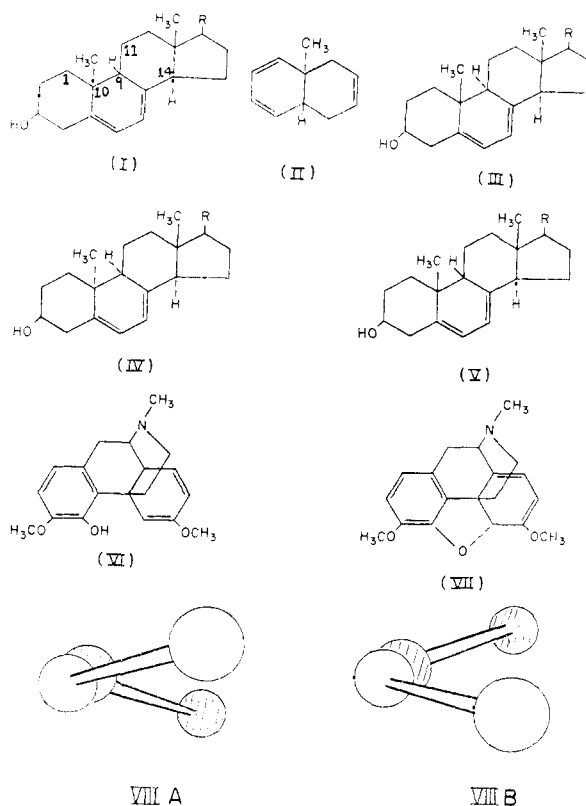


Fig. 3.

posed substituents, such as alkyl groups. Hence the Cotton effect observed in the vicinity of the diene absorption will be to a large extent a reflection of the relative orientation of the double bonds of the chromophore and is therefore stereochemically significant.

To demonstrate this point, we have synthesized (+)-*trans*-9-methyl-1,4,9,10-tetrahydronaphthalene (II) of known absolute configuration and measured its rotatory dispersion curve in cyclohexane. At the same time, we have calculated the partial rotatory dispersion curve for the lowest singlet diene transition on the assumption that from the point of view of optical activity, the molecule may be treated simply as a *cis* butadiene whose conjugated bonds are not coplanar, but rather are fixed at an angle of 17.5° with respect to each other, as suggested by a Dreiding model. The method of calculation was similar to the one we employed for hexahelicene.^{2,4} Care was taken to ensure that the rotational strength as computed is invariant to the choice of origin of coordinates, and the necessary shape factor was obtained from a Kronig-Kramers transform of the relevant absorption band.

The agreement between the computed and experimental results (Fig. 1) seems sufficiently good to bear out our contentions.⁵ We therefore feel justified in enunciating the following rule: A strong (reduced rotational strength⁶ ~ 25 or greater) posi-

(4) A. Moscovitz, Ph.D. Thesis, Harvard University, March, 1957.

(5) Such a comparison of partial and experimental curves is deemed valid because the roughly equal magnitude of the experimental peak and trough are indicative of a relatively small background rotation.

(6) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Company, Inc., New York, N. Y., 1960, p. 170.

tive Cotton effect associated with the lowest frequency *cisoid* diene absorption band (~ 260 – 280 μ in polycyclic compounds) means the presence of a *cisoid* diene chromophore twisted in the sense of a righthanded helix (VIII A). A strong negative Cotton effect is indicative of the lefthanded twist (VIII B).

As further test of the theory, the four stereoisomers: ergosterol (III), lumisterol₃ (I), pyrocalciferol (IV), and isopyrocalciferol (V) were investigated. The Cotton effects found (see Fig. 2) are in agreement with the predictions from the above rule, provided that the Dreiding models for (IV) and (V) are adjusted to relieve the interatomic hydrogen repulsions at C11 and C1. On the other hand, attempted analysis of the contributions by the three asymmetric carbon atoms (C9, C10, C14) adjacent to the chromophore on a "classical" basis runs into an irreconcilable contradiction: the inverse sign of the Cotton effect of (I) and (III), antipodal at both C9 and C10 but equal at C14, suggests that the former pair is in control, C14 contributing little; however, the similar Cotton effects of (IV) and (V), likewise antipodal to each other at both C9 and C10 but equal at C14, would lead to the precisely opposite conclusion of a negligible influence of C9 and C10 and a very strong one of C14. This discrepancy (also noted by Deen and Jacobs³) shows clearly that it is the skew sense of the diene that controls the sign of the rotatory dispersion in this spectral region. The rule we have stated thus provides a method for the conformational analysis of these compounds in a case where "classical" considerations fail.

The powerful influence of the skewed diene is further demonstrated in the case of thebainone methyl enolate (VI) where a positive Cotton effect is observed corresponding to the righthanded skew sense predicted from the models. This, to our knowledge, is the only compound in the (–)-codeine series that exhibits a long-wave-length positive rotatory dispersion curve.⁷ In thebaine (VII) the skew sense of the diene is such as to predict a strong negative Cotton effect, as observed.

(7) J. M. Bobbitt, U. Weiss and D. D. Hanessian, *J. Org. Chem.*, **24**, 1582 (1959).

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NOVEL GONADOTROPHIN INHIBITORS IN THE 19-NORSTEROID SERIES

Sir:

The inhibition of pituitary gonadotrophin secretion has been one of the most promising approaches in the search for an effective antifertility agent. The anovulatory response¹ to 17 α -ethynyl-19-nor-4-androstene-17 β -ol-3-one² (I), and 17 α -ethynyl-

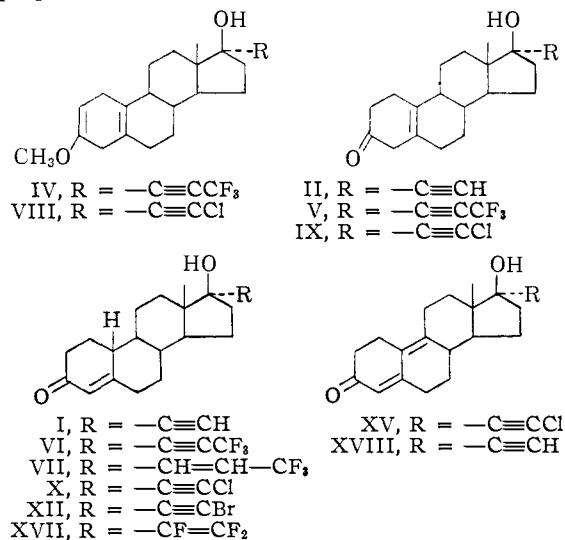
(1) G. Pincus, *Vitamins and Hormones*, **17**, 307 (1959), Academic Press, New York, N. Y., and references cited.

(2) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954).

19-nor-5(10)-androstene-17 β -ol-3-one³ (II), has been shown to be mediated *via* suppression of pituitary gonadotrophin secretion.

We wish to report a number of compounds exhibiting greatly increased gonadotrophin inhibition over previously known hormonal agents.

Reaction of 1,4-dihydroestrone-3-methyl ether III,⁴ with trifluoropropynylmagnesium bromide (prepared from ethylmagnesium bromide and excess



trifluoropropyne⁵ in tetrahydrofuran solution) affords 17 α -trifluoropropynyl-3-methoxy-19-nor-2,5-(10)-androstadiene-17 β -ol (IV). Hydrolysis of the enol ether function in IV with a mixture consisting of aqueous acetic acid, dioxane and ethanol affords 17 α -trifluoropropynyl-19-nor-5(10)-androstene-17 β -ol-3-one (V), m.p. 137–140°; $\alpha^{24}_D + 100$ (dioxane). (*Anal.* Found: C, 68.77; H, 7.00; F, 17.3), while hydrolysis with *p*-toluenesulfonic acid in acetone yields 17 α -trifluoropropynyl-19-nor-4-androstene-17 β -ol-3-one (VI), m.p. 128–132°; $\alpha^{26}_D - 21$ (chloroform), ultraviolet $\lambda_{\text{max}}^{\text{MeOH}}$ 238 μ , ϵ 15,000 (*Anal.* Found: C, 68.30; H, 7.00.)

Hydrogenation of V at 40 psi. with Lindlar catalyst followed by treatment with *p*-toluenesulfonic acid in acetone affords 17 α -trifluoropropenyl-19-nor-4-androstene-17 β -ol-3-one (VII), m.p. 138–142°; $\alpha^{24}_D + 44$ (chloroform), $\lambda_{\text{max}}^{\text{MeOH}}$ 239 μ , ϵ 15,800 (*Anal.* Found: C, 68.47; H, 7.60).

Addition of chloroethynyllithium (prepared *in situ* from *cis*-dichloroethylene and methyllithium)⁶ to III affords 17 α -chloroethynyl-3-methoxy-19-nor-2,5(10)-androstadiene-17 β -ol (VIII), m.p. 112–115°; $\alpha^{26}_D + 69$ (dioxane). (*Anal.* Found: C, 72.85; H, 8.15.) Hydrolysis as above produces 17 α -chloroethynyl-19-nor-5(10)-androstene-17 β -ol-3-one (IX), m.p. indef. ca. 160°; $\alpha^{26}_D + 86$ (dioxane). (*Anal.* Found: C, 71.63; H, 7.65) and 17 α -chloroethynyl-19-nor-4-androstene-17 β -ol-3-one (X), m.p. 198–201°; $\alpha^{26}_D - 49$ (chloroform), ultraviolet $\lambda_{\text{max}}^{\text{MeOH}}$ 240 μ , ϵ 15,000 (*Anal.* Found: C, 72.27; H, 7.57; Cl, 9.90.)

(3) F. B. Colton, U. S. Patent 2,725,389.

(4) F. B. Colton, L. N. Nysted, B. Riegel and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957).

(5) W. R. Hasek, W. C. Smith and V. A. Engelhardt, *ibid.*, **82**, 543 (1960).

(6) H. G. Viche, *Chem. Ber.*, **92**, 1950 (1959).