Of some thirty *Senecio* alkaloids of known structures,[7] jacobine is now the first member of the family whose stereochemistry is completely formulated with the absolute configuration also established. The stereochemical correlation of this alkaloid with other members of the *Senecio* family (in particular, seneciphylline,[8] integerrimine[7] and senecionine[7]) will be undertaken.[9,10,11]

(8) S. Masamune, *Chem. and Ind.*, 21 (1959).

(9) Satisfactory analyses and ultraviolet and infrared spectra were obtained for all the new compounds described herein.

(10) The author is deeply indebted to Dr. R. B. Bradbury, Swinburne Technical College, Australia, for his helpful suggestions and generous gifts of natural products, without which this work would not have been completed.

(11) This investigation was supported by a grant (RG-6646) from the National Institute of Health, Public Health Service.

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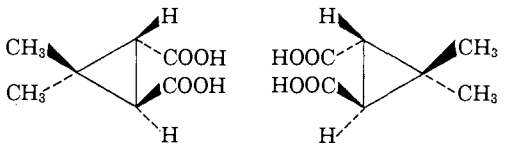
CYCLOPROPANES. VII. THE ABSOLUTE CONFIGURATION OF *trans*-CARONIC AND *cis* AND *trans*-UMBELLULARIC ACIDS[1]

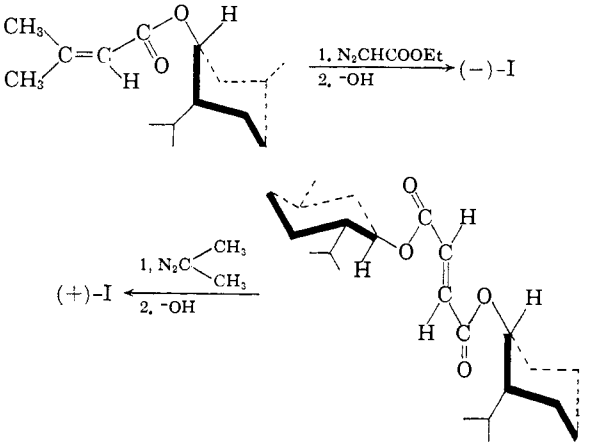
Sir:

It was shown recently that the addition of diazodiphenylmethane to (−)-menthyl acrylate and (−)-menthyl methacrylate resulted in partial asymmetric syntheses.[2] On the basis of the Prelog[3]–Cram[4] model[5] the absolute configurations were assigned tentatively to the 2,2-diphenylcyclopropanecarboxylic acids that were obtained. We wish to report evidence in support of the use of this model, and to assign absolute configurations to *cis* and *trans*-umbellularic acids.



I

The absolute configuration of *trans*-caronic acid has been previously established[6] and has the configuration shown above. This fact provides one with the means of determining whether the Prelog–Cram model can be used for establishing absolute configurations by the addition of diazo derivatives to α,β-unsaturated menthyl esters. Using this model one would predict that the addition of diazodimethylmethane to (−)-dimenthyl fumarate would produce (+)-I in excess, whereas the addition of ethyl diazoacetate to (−)-menthyl β,β-dimethylacrylate should yield (−)-I predominantly. This prediction has been verified experimentally (*vide infra*) and provides cogent support for the use of the Prelog–Cram model.



Ethyl diazoacetate (4.8 g., 0.042 mole) was added slowly to (−)-menthyl β,β-dimethylacrylate[7] (10.0 g., 0.042 mole) at 130–140°. The reaction mixture was distilled to remove unreacted acrylate (7.3 g.) which was treated once more with an equivalent amount of ethyl diazoacetate to yield a total of 2.4 g. (65%) of crude adduct.[8] The adduct was subjected to complete saponification[9a] to yield pure caronic acid (27%),[9b] $[\alpha]^{20}D$ − 5.05° (ethanol), m.p. 205–207°, whose infrared spectrum was identical with an authentic sample.[10] The observed optical rotation corresponds to 15.9% asymmetric synthesis.[10]

To a xylene solution of dimethyldiazomethane[11] was added a solution of (−)-dimethyl fumarate (31.4 g.) in xylene at 0–5° to yield, upon removal of solvent, an oily product. The oil (10.0 g.) was heated with copper powder (1.0 g.) at 160–170° until nitrogen evolution ceased and the product distilled to yield 5.3 g. (56%) of the adduct ester. Complete saponification[9a] yielded *trans*-caronic acid (0.20 g., 25%),[12] m.p. 206–212°, $[\alpha]^{20}D$ + 2.0° (ethanol). This corresponds to 6.3% asymmetric synthesis.

Ethyl diazoacetate (5.0 g.) was added slowly to (−)-menthyl α-isopropylacrylate[13] (11.3 g.) at 80° until nitrogen evolution ceased. The addition product was saponified[9a] and the mixture of *cis* and *trans* acids separated to yield 1.25 g. (14.7%) of *cis*-umbellularic acid, m.p. 107–110°, $[\alpha]^{16}D$ − 5.4° ($CHCl_3$), whose infrared spectrum was identical with that of an authentic sample.[14] This represents 6% asymmetric synthesis.

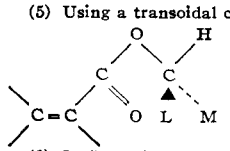
(1) This work was supported, in part, by a grant from the National Science Foundation.

(2) F. J. Impastato, L. Barash and H. M. Walborsky, THIS JOURNAL, **81**, 1514 (1959).

(3) V. Prelog, *et al.*, *Helv. Chim. Acta*, **36**, 308 (1953).

(4) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1952).

(5) Using a transoidal coplanar configuration for the



system and a staggered orientation of the asymmetric center such that two substituents (L and M) or (H and M) flank the carbonyl and the third is in the plane of the coplanarity.

(6) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 470 (1954), established absolute configuration of chrysanthemum-carboxylic acid. Chrysanthemum-carboxylic acid has been degraded to caronic acid (see H. Staudinger and L. Ruzicka, *Helv. Chim. Acta.*, **7**, 201 (1924)).

(7) M.p. 35–36°, $[\alpha]^{18}D$ −80.4° (ethanol); it gave the correct elemental analysis, as did all other new substances reported here.

(8) A fraction b.p. 160–168° at 0.6 mm. was collected. Complete fractionation was avoided. The yield is based on recovered (−)-menthyl β,β-dimethylacrylate.

(9) (a) As evidenced by the absence of carbonyl absorption at 1720 cm.$^{-1}$ in the neutral fraction. (b) The *cis* isomer was not isolated.

(10) A. Fredga and Å. Skiström, *Arkiv. Kemi*, **8**, 433 (1955).

(11) P. C. Guha and D. K. Sankaran, *Ber.*, **70**, 1688 (1937).

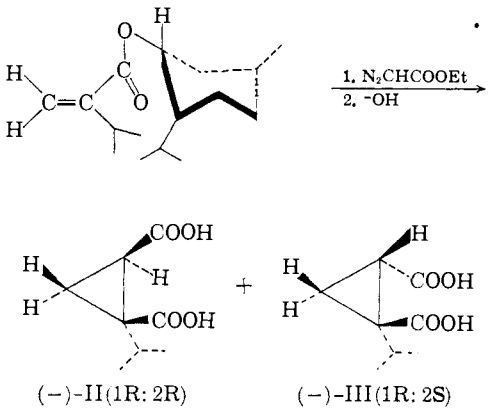
(12) The infrared spectrum showed slight contamination by fumaric acid.

(13) B.p. 64–65° at 0.1 mm., $n^{18}D$ 1.4648, $[\alpha]^{16}D$ −81.6° (ethanol).

(14) H. N. Rydon, *J. Chem. Soc.*, 829 (1936).

The *trans*-umbellularic acid was isolated in 56.5% (4.38 g.) yield, m.p. 189–190°, $[\alpha]^{16}D$ − 5.2° (acetone); its infrared spectrum was identical with that of an authentic sample. This represents 2.7% asymmetric synthesis.[15]

On the basis of the above asymmetric syntheses the following absolute configurations are assigned to (−)-*cis* (II) and (−)-*trans* (III)-umbellularic acid. The establishment of the absolute configuration of *cis*-umbellularic acid enables one now to assign absolute configurations to (−)-umbellulone, (+)-thujane, (+)-sabinene and their derivatives.[16a,b,c]



(−)-II(1R: 2R) (−)-III(1R: 2S)

(15) An authentic sample was resolved to give optically pure acid, m.p. 155° and $[\alpha]^{16}D$ −194.0°.

(16) (a) Based on the correlations described in J. L. Simonson's "The Terpenes," Vol. 11, 1–60, 533, Cambridge Press, England, 1949. (b) Prof. James H. Brewster has kindly informed me that his method of predicting $[M]_D$ values gives, when applied to the thujane terpenes, configurations consistent with our findings. His calculations indicate that the 2-methyl group in (+)-isothujone is *trans* to the 5-isopropyl group contrary to the assumption made in (a). (c) Confirmation of the assignment given by Brewster is found in the work of L. Tschugaev and W. Fomin (*Compt. rend.*, **151**, 1088 (1910)), who showed that (+)-α-thujane has a lower index of refraction and density than (+)-β-thujane, which indicates that the methyl and isopropyl groups in (±)-α-thujane, and therefore in (+)isothujone, are *trans*.

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RECEIVED AUGUST 3, 1960

16,16-DIFLUOROESTRONE DERIVATIVES. A NEW SERIES OF CHOLESTEROL LOWERING AGENTS

Sir:

In recent years, attempts have been made[1] to synthesize steroidal compounds (related to the natural estrogens) which might alter blood cholesterol and phospholipid levels without exhibiting undesirable estrogenic activity. Compounds of this type could be expected to find therapeutic use in the treatment of atherosclerosis.

We wish to report here the synthesis of a series of 16,16-difluoroestrone derivatives, several members of which display remarkably diminished uterotrophic activity, as compared to estradiol-17β, together with substantial serum cholesterol lowering properties. Thus, 16,16-difluoroestrone 3-methyl ether (I) possesses a hypocholesterolemic: uterotrophic activity ratio about 800 times that of estradiol-17β in rodents on a normal diet (*vide infra*).

The fluorination of active methylene compounds by perchloryl fluoride was first described in 1958,[2] and this reagent subsequently has been used to fluorinate steroids at the C-2,[3a–f] C-4,[3c] C-6,[3c,3g] and C-21[3c,3d] positions. In these syntheses, steroidal β-dicarbonyl compounds,[3b,3d–3f] enamines,[3a,3c] enol ethers[3c] and enol acetates[3g] have been used to advantage.

We now have found that 16-formylestrone 3-methyl ether[4] when treated with perchloryl fluoride in *tert*-butyl alcohol containing potassium *tert*-butoxide, at room temperature, furnishes directly 16,16-difluoroestrone 3-methyl ether (I) (m.p. 126–128°; $^{5}[\alpha]D$ + 167°; λ_{max}^{Nujol} 5.63, 6.22, 6.35, 6.68, 7.98, 8.44 μ). This represents the first reported example of α-fluorination of the cyclopentanone system by perchloryl fluoride, and the first reported insertion of a *gem*-difluoro grouping into the steroid nucleus by fluorination of a β-dicarbonyl system.[6]

Zinc and acetic acid reduction of I proceeded smoothly to give estrone 3-methyl ether. Cleavage of the methyl ether group of I, using hydriodic acid–acetic acid, gave 16,16-difluoroestrone (II) (m.p. 173–175°; $[\alpha]D$ + 161°; λ_{max}^{Nujol} 2.88, 5.64, 6.20, 6.66 μ). Reduction of I with sodium borohydride in 2-propanol furnished 16,16-difluoroestradiol 3-methyl ether (III) (m.p. 123–127°; $[\alpha]D$ + 71°; λ_{max}^{Nujol} 2.92, 6.20, 6.36, 6.68, 7.98 μ).

Conversion of I to 16,16-difluoro-17α-ethynylestradiol 3-methyl ether (IV) (m.p. 141–143°; $[\alpha]D$ + 20°; λ_{max}^{Nujol} 2.96, 3.08, 4.76, 6.22, 6.34, 6.56, 8.1 μ) was accomplished by the sodium acetylide–dimethyl sulfoxide procedure.[7] Catalytic reduction of IV using palladized strontium carbonate in pyridine gave 16,16-difluoro-17α-vinylestradiol 3-methyl ether (V) (m.p. 132–137°; $[\alpha]D$ + 37°; λ_{max}^{Nujol} 2.86, 6.22, 6.34, 6.68, 8.12, 8.58 μ). Finally, reaction of I with methylmagnesium iodide in tetrahydrofuran–ether furnished 16,16-difluoro-17α-methylestradiol 3-methyl ether (VI) (m.p. 143–145°; $[\alpha]D$ + 38°; λ_{max}^{Nujol} 2.85, 6.22, 6.32, 6.66, 8.10, 8.55 μ).

(1) *Cf.* G. P. Mueller, W. F. Johns, D. L. Cook and R. A. Edgren, THIS JOURNAL, **80**, 1769 (1958).

(2) C. E. Inman, E. A. Tyczkowski, R. E. Oesterling and F. L. Scott, *Experientia*, **14**, 355 (1958); C. E. Inman, R. E. Oesterling and E. A. Tyczkowski, THIS JOURNAL, **80**, 6533 (1958).

(3) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958); (b) H. M. Kissman, A. M. Small and M. J. Weiss, THIS JOURNAL, **81**, 1262 (1959); **82**, 2312 (1960); (c) S. Nakanishi, K. Morita and E. V. Jensen, *ibid.*, **81**, 5259 (1959); (d) J. Edwards and H. J. Ringold, *ibid.*, **81**, 5262 (1959); (e) A. H. Nathan, J. C. Babcock and J. A. Hogg, *J. Org. Chem.*, **24**, 1395 (1959); THIS JOURNAL, **82**, 1436 (1960); (f) A. H. Nathan, B. J. Magerlein and J. A. Hogg, *J. Org. Chem.*, **24**, 1517 (1959); (g) R. M. Bloom, V. V. Bogert and R. Pinson, *Chem. and Ind.* 1317 (1959).

(4) J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936).

(5) All melting points were taken on the Kofler block. All rotations were measured in dioxane solution. Satisfactory analyses have been obtained for all the new compounds described herein.

(6) The conversion of a 21-ethoxalyl-20-ketosteroid to the 21,21-difluoro-20-ketone, using perchloryl fluoride, has been reported recently (ref. 3c and 3d) and the further fluorination of the 21,21-difluoro-20-keto system to the 21,21,21-trifluoro compound also has been described (ref. 3c). Enamines of Δ4-3-ketosteroids have been reported (ref. 3c) to yield 4,4-difluoro-3-keto-Δ5-steroids with perchloryl fluoride.

(7) J. A. Campbell, J. C. Babcock and J. A. Hogg, THIS JOURNAL, **80**, 4717 (1958).