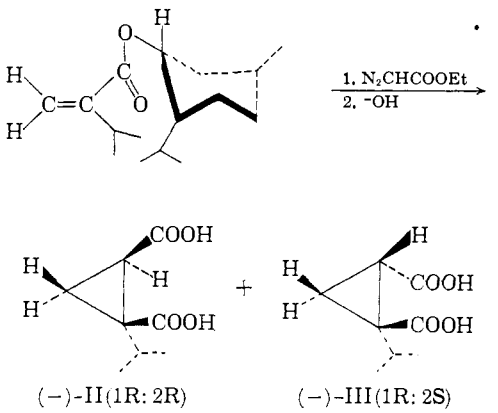
The *trans*-umbellularic acid was isolated in 56.5% (4.38 g.) yield, m.p. 189–190°, $[\alpha]^{16}D$ − 5.2° (acetone); its infrared spectrum was identical with that of an authentic sample. This represents 2.7% asymmetric synthesis.[15]

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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## 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°; $\lambda_{max}^{Nujol}$ 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°; $\lambda_{max}^{Nujol}$ 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°; $\lambda_{max}^{Nujol}$ 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°; $\lambda_{max}^{Nujol}$ 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°; $\lambda_{max}^{Nujol}$ 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°; $\lambda_{max}^{Nujol}$ 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.

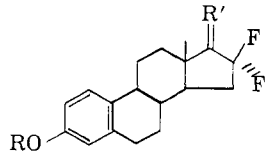
(6) The conversion of a 21-ethoxalyl-20-ketosteroid to the 21,21-difluoro-20-ketone, using perchloryl fluoride, has been reported recently (ref. 3c and 3d) and the further fluorination of the 21,21-difluoro-20-keto system to the 21,21,21-trifluoro compound also has been described (ref. 3c). Enamines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

The hypocholesterolemic activity of compounds I-VI was determined in adult, male rats (Charles River), fed stock diet *ad lib.*

The compounds were suspended in peanut oil and injected subcutaneously for four days. Total serum cholesterol was determined by the method of Zak[8] and the results are presented in the accompanying table.

The estrogenic potencies were obtained by the uterotrophic response in the sexually immature mouse[9] following subcutaneous administration.[10]




RESULTS OBTAINED USING ESTRADIOL-17$\beta$ AS STANDARD

| Compound | Serum cholesterol lowering activity standard = 1 | Uterotrophic activity standard = 1 | R | R' |
|---|---|---|---|---|
| I | 0.42 (0.13–0.93) | 0.0005 | $CH_3$ | =O |
| II | 2.0 (1.8–2.7) | 0.0001–0.006[11] | H | =O |
| III | 0.88 (0.73–1.0) | 0.0011 | $CH_3$ | OH, H |
| IV | 4.3 (2.5–6.2) | 0.02–0.03 | $CH_3$ | OH, C≡CH |
| V | 0.65 (0.63–0.66) | 0.0005–0.0045[11] | $CH_3$ | OH, $CH=CH_2$ |
| VI | ~1.0 | 0.0004–0.0023[11] | $CH_3$ | OH, $CH_3$ |

(8) B. Zak, *Tech. Bull. Registry Med. Technologists*, **27**, 71 (1957).

(9) Carworth Farms, strain CF-1.

(10) We wish to express our gratitude to Dr. Milton Eisler and Mr. Arthur Watnick for the uterotrophic assays.

(11) The large range is a result of non-parallel slopes shown by the dose-response curves.

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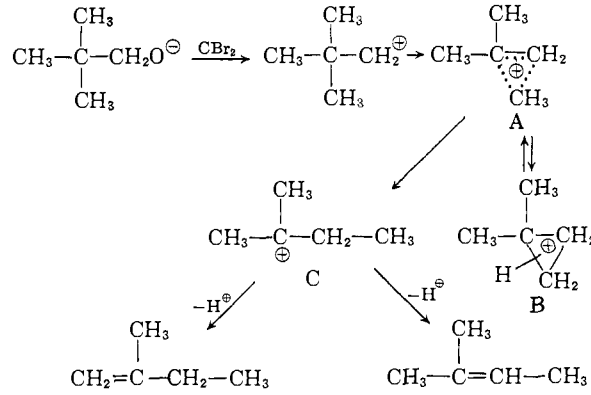
## PROTONATED CYCLOPROPANE INTERMEDIATES IN THE NEOPENTYL CARBONIUM ION SYSTEM

*Sir:*

It was suggested[1] recently that protonated cyclopropanes might be important transient storage configurations for certain carbonium ions, particularly those involved in Wagner–Meerwein rearrangements. The neopentyl carbonium ion system was chosen for a critical test.

To learn whether appreciable storage in the form of a protonated cyclopropane occurred, this reaction was carried out with 1,1-dideuterioneopentyl alcohol. If equilibration between A and B occurs at rates competitive with conversion to *t*-amyl cation, then $(CH_3)_3CCD_2OH$ would be converted to $(CH_3)_2C^{\oplus}\text{-}CH_2\text{-}CD_2H$ and $(CH_3)_2C^{\oplus}\text{-}CD_2\text{-}CH_3$,




and the olefins would have deuterium on both $C_3$ and $C_4$. On the other hand, if B is not a storage form for this amyl cation, only $(CH_3)_2C^{+}\text{-}CD_2\text{-}CH_3$ would be produced and the olefins would be labeled on $C_3$ only.

Reduction of trimethylacetic acid with lithium aluminum deuteride provided the 1,1-dideuterioneopentyl alcohol. De-oxidation of this neopentoxide ion was carried out with aqueous potassium hydroxide and bromoform. The two $C_5$ olefins were separated with vapor phase chromatography to provide the pure compounds which were examined with infrared and proton magnetic resonance spectroscopies. None of these examinations yielded evidence for deuterium labeling on $C_4$ of either olefin.

The infrared spectrum of 2-methyl-2-butene showed a sharp vinyl deuterium absorption[2,3] at 4.48 $\mu$ and was devoid of additional absorption bands up to 5.5$\mu$, consistent with $C_3$ labeling only. The 2-methyl-1-butene showed C-D absorptions between 4.55 $\mu$ and 4.75 $\mu$, yielding no additional information regarding $C_3$ and $C_4$ labeling.

Proton magnetic resonance spectra does not reveal vinyl hydrogen in the 2-methyl-2-butene or =C-CHD— in the 2-methyl-1-butene. With respect to the 2-methyl-2-butene the evidence is not strong, because the sample was small, and the vinyl hydrogen absorption of undeuterated olefin is of low intensity. The other olefin shows exactly the spectrum[4] expected for 2-methyl-3,3-dideuterio-1-butene, a quartet of vinyl hydrogens at 185.4 c.p.s. with relative intensity 2.0, a triplet of allylic methyl hydrogens at 68.2 c.p.s. with relative intensity 3.0, and a quintet of alkyl methyl hydrogens at 40.8 c.p.s. with relative intensity 3.0, all $J$ values falling between 1.1 and 1.4 c.p.s. No other absorptions were evident, particular care being used to search the 70 to 80 c.p.s. region where allylic methylene proton absorptions were anticipated.

The evidence cited supports the conclusion that the 1,1-dideuterioneopentyl carbonium ion system yields rearranged olefins with deuterium labeling on $C_3$ only, thus excluding as significant intermediates any species in which the migrating methyl and the original methylene groups are equivalent, such as protonated cyclopropanes, etc.

(1) P. S. Skell and I. Starer, THIS JOURNAL, **82**, 2971 (1960).

(2) E. G. Hoffmann, *Ann.*, **618**, 276 (1958).

(3) P. S. Skell and R. G. Allen, THIS JOURNAL, **81**, 5383 (1959); also other unpublished work from this laboratory.

(4) 40 Mc. equipment; tetramethylsilane internal reference.