

well be the true conformation. Further work of this kind could well give more insight into the conformational dependence of ^{13}C - ^{15}N coupling constants and, hence, the conformation of alkylamines in solution.

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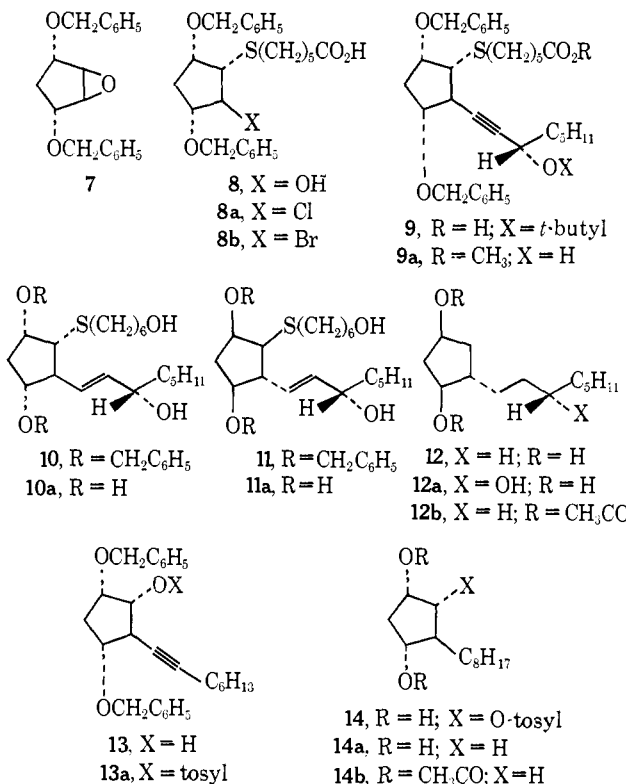
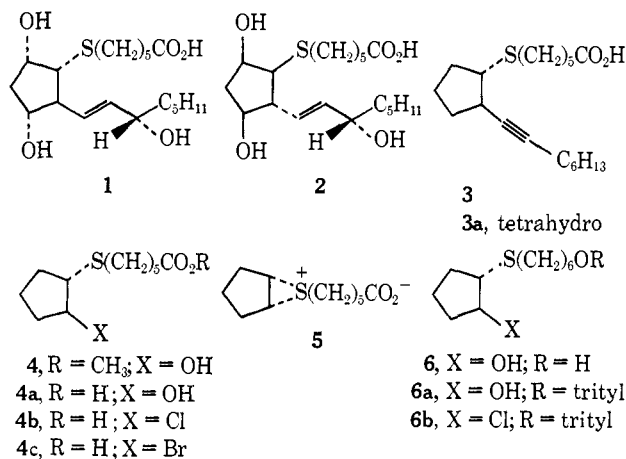
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Stereospecific Synthesis of 7-Thiaprostaglandins

Sir:

It has been amply demonstrated that 7-oxa derivatives of the prostaglandins¹⁻³ may function as either prostaglandin agonists or antagonists⁴ depending on the degree of hydroxyl substitution.⁵ It was felt that replacement of the ether oxygen by sulfur might have interesting biological consequences, in light of experiences, among others, in the steroid field,⁶ and when considering the well-known equivalence of oxybiotin and biotin in the nutrition of most biotin-requiring species.⁷

We wish to report a stereospecific synthesis of *nat*-7-thia-PGF_{1 α} (**1**), *ent*-15-*epi*-7-thia-PGF_{1 α} (**2**), and *rac*-7-thia-13-prostynoic acid (**3**),⁸ in which the *trans* geometry of the two side chains is established by substitution reactions involving episulfonium intermediates. The elaboration of the basic skeletal structure is exemplified by the synthesis of **3**, which is compatible with the additional functionality required for **1** and **2**. Reaction of cyclopentene oxide with methyl 6-mercaptohexanoate⁹ in the presence of sodium methoxide in methanol at 25° for 5 hr produced the *trans* hydroxy ester **4** (98%), which was hydrolyzed to the oily acid **4a**¹⁰ (98%) with 2% KOH in methanol at 25°. Treatment of **4a** with methanesulfonyl chloride in pyridine at 0° for 1 hr afforded the *trans* chloro acid **4b** in 82% yield, evidently formed by attack of chloride ion



(1) J. Fried, T. S. Santhanakrishnan, J. Himizu, C. H. Lin, S. H. Ford, B. Rubin, and E. O. Grigas, *Nature (London)*, **233**, 208 (1969).

(2) J. Fried, M. M. Mehra, W. L. Kao, and C. H. Lin, *Tetrahedron Lett.*, 2695 (1970).

(3) J. Fried, M. M. Mehra, and W. L. Kao, *J. Amer. Chem. Soc.*, **93**, 5594 (1971).

(4) (a) F. A. Kuehl, Jr., J. L. Humes, J. Tarnoff, V. J. Cirillo, and E. A. Ham, *Science*, **169**, 883 (1970); (b) S. Sato, M. Szabo, K. Kowalsky, and G. Burke, *Endocrinology*, **90**, 343 (1972); (c) G. Illiano and P. Cuatrecasas, *Nature (London), New Biol.*, **234**, 72 (1971); (d) A. Ozer and G. W. G. Sharp, *Amer. J. Physiol.*, **222**, 674 (1972); (e) M. A. Marrazzi and F. M. Matchinsky, *Prostaglandins*, **1**, 373 (1972); (f) R. G. McDonald-Gibson, J. D. Flack, and P. W. Ramwell, *Biochem. J.*, **132**, 117 (1973); (g) A. Ratner, M. C. Wilson, and G. T. Peake, *Prostaglandins*, **3**, 413 (1973); (h) H. S. Kantor, P. Tao, and H. C. Kiefer, *Proc. Nat. Acad. Sci. U. S. A.*, **71**, 1317 (1974).

(5) J. Fried, C. H. Lin, M. M. Mehra, W. L. Kao, and P. Dalven, *Ann. N. Y. Acad. Sci.*, **180**, 38 (1971).

(6) M. E. Wolff and G. Zanati, *J. Med. Chem.*, **12**, 629 (1969); **14**, 958 (1971); **15**, 368 (1972).

(7) A. White, P. Handler, and E. L. Smith, "Principles of Biochemistry," 4th ed., McGraw-Hill, 1970, 1034.

(8) Resolution of this acid was not attempted since (+)- and (-)-7-oxa-13-prostynoic acids possessed equal biological activity. Cf. ref 5.

(9) Prepared in 90% yield from 6-bromohexanoic acid and thiourea in DMSO (H. L. Pan and T. L. Fletcher, *Chem. Ind. (London)*, 546 (1968)), followed by methylation.

(10) All new products were characterized by nmr and mass spectra and gave correct elemental analyses.

on the expected mesylate (**4a**, X = OSO₂CH₃) via the episulfonium intermediate **5**.¹¹

Evidence for the formation of such a symmetrical intermediate was obtained as follows. 2-(1'-Hydroxyhexyl-6'-thio)cyclopentanol (**6**), prepared by a sequence of reactions analogous to that employed for **4**, was resolved via the diurethane obtained with (+)- α -phenethylamine isocyanate in boiling toluene for 24 hr and crystallization from ethyl acetate-hexane, mp 87-88°, [α]_D -62° (c 1.6).¹²

Reduction with LAH in THF gave (-)-**6** of unknown absolute configuration, [α]_D -21° (c 2.9), which was converted to the monitryl ether **6a** with trityl chloride (1.2 equiv) in pyridine, [α]_D -10° (c 0.65). Reaction with methanesulfonyl chloride in pyridine at 0° for 1 hr gave the chloro thioether **6b** devoid of significant optical activity ([α]_D +1°, c 1.1), indicating that racemization had taken place, most probably

(11) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **81**, 898 (1959).

(12) All rotations in chloroform at 25° unless indicated otherwise.

during substitution of the intermediate mesylate by chloride. In order to exclude the possibility that **6b** was not racemic but possessed low specific rotation, this compound was solvolyzed to revert to **6a** by applying it to silica gel tlc plates and allowing the plates to remain at 25° for 24 hr, followed by development with ethyl acetate containing 2% of methanol. The resulting diol **6** and the trityl ether **6a** showed $[\alpha]_D +0.3^\circ$ and $+0.2^\circ$, respectively, indicating that racemization had indeed taken place.¹³ The intermediacy of an episulfonium salt analogous to **5** in these reactions is thereby established and, therefore, also the trans stereochemistry of all subsequent products arising by nucleophilic substitution at the episulfonium carbon.¹⁴

The chloro acid **4b** was converted to *rac*-7-thia-13-prostynoic acid (**3**) in 50% yield, by first forming the sodium salt with sodium hydride in toluene, followed by reaction of the resulting slurry with 5 equiv of 1-octynyllithium in DME (prepared with *n*-BuLi in hexane) at 100° for 1 hr.¹⁵ Catalytic reduction of **3** with excess 10% Pd/C in ethyl acetate afforded the crystalline 7-thiaprostanoic acid **3a**, mp 40–41°.

The above procedure, when combined with methodology elaborated in this laboratory in conjunction with the synthesis of 7-oxaprostaglandins³ and prostaglandins,^{16,17} was successful also in the synthesis of **1** and **2**. Reaction of the epoxide **7** with the anion of methyl 6-mercaptohexanoate, followed by hydrolysis as described above, furnished the hydroxy acid **8**, mp 66–67°,¹⁸ in 75% yield, which was converted into the chloro acid **8a** and hence into the bromo acid **8b**.¹⁵ A suspension of the sodium salt of **8b** in toluene was treated with (*S*)-3-*tert*-butyloxy-1-octynyllithium^{3,5} in DME–hexane at 25° for 24 hr to form, after chromatography, in 33% yield the mixture of diastereomeric acids **9**,¹⁹ which after conversion into the methyl esters were debutylated with trifluoroacetic acid at 0° for 2 hr in 33% yield. The resulting hydroxy esters **9a** were reduced with LAH in boiling THF for 3 hr to yield, after chromatographic separation, 25% each of the diastereomeric alcohols **10** and **11**. The faster moving alcohol **10** had mp 62–64° (ethyl acetate–hexane), $[\alpha]_D +26.5^\circ$ (*c* 2.9), and the slower moving **11** had mp 52–54°, $[\alpha]_D -18.0^\circ$ (*c* 2.20). Debonylation of **10** and **11** was achieved in 63% yield by first con-

verting the alcoholic groups to their anions with sodium hydride in THF at 25°, followed by reduction with lithium in ammonia–THF at –78° for 3 hr, to furnish respectively **10a**, mp 99–100°, $[\alpha]_D +11.2^\circ$ (*c* 1.2), and **11a**, oil, $[\alpha]_D -6.0^\circ$ (*c* 0.4). A crucial step in this synthesis is the selective oxidation¹⁶ of the tetrols **10a** and **11a** with Pt in aqueous acetone in the presence of sodium bicarbonate, to furnish **1** and **2**, respectively, in 50% yield.²⁰ 7-Thia-PGF_{1 α} (**1**) had mp 94–96°, $[\alpha]_D +5.5^\circ$ (*c* 0.43 in CH₃OH). Its diastereomer **2**, oil, had $[\alpha]_D -4.4^\circ$ (*c* 0.27) –7.1° (*c* 1.1 in CH₃OH). Compounds **2** and **11a** showed greater mobility on tlc (ethyl acetate–methanol, 5:1) than **1** and **10a**, respectively.

The absolute configuration of **1** and **2** and of all intermediates was determined to be as shown in the structural formulas, as follows. The diol (–)-**11** was desulfurized and partially debenzylated with Raney nickel in alcohol for 6 hr followed by catalytic reduction with 10% Pd/C in ethanol. The resulting mixture of di- and triols **12** and **12a** was acetylated, and the acetates were separated by tlc. The faster moving component, **12b**, had a mass spectrum identical with, and a Cotton effect, CD, $\Delta\epsilon_{209}^{MeOH} -0.38$,²¹ opposite in sign to that of an authentic sample of the enantiomer of **12b** (**14b**) prepared from (+)-**13** of established absolute configuration^{3,5} by the following sequence. Compound (+)-**13** was converted into the tosylate **13a**, mp 55–56°, $[\alpha]_D +23.5^\circ$ (*c* 2.07), and the latter reduced with 10% Pd/C in moist ethyl acetate to the saturated diol tosylate **14**, mp 72–74°, $[\alpha]_D +35.8^\circ$ (*c* 1.85). LAH reduction of **14** in THF yielded, after tlc separation from contaminating triol, the oily diol **14a** $[\alpha]_D -30.6^\circ$ (*c* 1.75), which furnished the diacetate **14b** $[\alpha]_D -27.2^\circ$ (*c* 0.65), CD, $\Delta\epsilon_{210}^{MeOH} +0.31$.

7-Thia-13-prostynoic acid (**3**) is an inhibitor of the contraction of the gerbil colon, and of the stimulation of adenylate cyclase in the mouse ovary^{4a} caused by PGE₁, at levels similar to those effective for the 7-oxa analog. On the other hand, **3** and **3a** are five–ten times more active, $[I]_{50} = 15$ and $22 \mu M$, respectively, than the latter in inhibiting the placental prostaglandin 15-dehydrogenase,²² a vital regulator of PG-concentrations *in vivo*. Preliminary data obtained with the 7-thiaprostaglandins **1** and **2** show that **1** stimulates *c*-AMP synthesis in the mouse ovary (threefold over control at 20 μg), whereas **2**, which possesses unnatural configuration at four of the five chiral centers shows no activity at this dose. Similarly, **1** shows binding to a bovine corpus luteum “receptor”²³ with 1/10th the affinity of PGF_{1 α} , while **2** exhibits 1/100th the binding of **1**. Lastly, both **1** and **2** are inhibitors of the placental PG-15-dehydrogenase at $[I]_{50} = 5.2$ and $8.8 \mu M$, respectively.

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(13) Parallel results were obtained when the hydroxy acid (–)-**4a** obtained by oxidation of (–)-**6** with Pt/O₂ (*cf.* ref 16) was converted to the chloride (\pm)-**4b** and the latter solvolyzed back to (\pm)-**4a**.

(14) Independent evidence for the trans stereochemistry of the products arising by substitution with alkynyllithium reagents was adduced by examination of the 270-MHz nmr spectra of *trans*-2-ethylthiocyclohexanol (I) and 1-ethylthio-2-(1'-*n*-octynyl)cyclohexane (II) both prepared from cyclohexene oxide by the procedures described in this communication. Thus, the axial protons attached to C-1 and C-2 of I appear as sharp doublets of triplets: HCS, δ 2.37, $J_{ae} = 3.6$ Hz, $J_{aa} = 10.8$ Hz; HCO, δ 3.28, $J_{ae} = 4.8$ Hz, $J_{aa} = 9.6$ Hz. The axial proton HCS of II appears as a diffuse triplet at δ 2.38, $J_{as} = 9.0$ Hz. The other tertiary proton (CHC \equiv C) is not sufficiently separated from C \equiv CCH₂. From the identical chemical shifts, coupling constants and half widths of the resonances for HCS in I and II it is inferred that II possesses trans geometry.

(15) A variant of this procedure consisted of conversion of the chloro acid **4b** into the bromo acid **4c** with lithium bromide in boiling DME, followed by reaction with octynyllithium at 25°.

(16) J. Fried and J. C. Sih, *Tetrahedron Lett.*, 3899 (1973).

(17) J. Fried, C. H. Lin, J. C. Sih, P. Dalven, and G. F. Cooper, *J. Amer. Chem. Soc.*, **94**, 4342 (1972).

(18) The methyl ester of **8** could be isolated from this reaction by chromatography after remethylation, mp 37–39°.

(19) The inability to separate this mixture parallels previous experience with acetylenic diastereomers (*cf.* ref. 3, 17), which only become separable after reduction to the trans olefins.

(20) The procedure of ref 16 was modified so as to increase the amount of PtO₂ to eight times the weight of substrate and employing a reaction time of 4 hr.

(21) Utilization of the Cotton effect of the acetates for comparison of the chiralities of **12b** and **14b** was made necessary by the small size of the available sample **12**.

(22) J. Jarabak, *Proc. Nat. Acad. Sci. U. S.*, **69**, 533 (1972).

(23) W. S. Powell, S. Hammarström, and B. Samuelsson, *Eur. J. Biochem.*, **41**, 103 (1974).

thank the National Science Foundation (GP 33116) and the National Institutes of Health (Cancer Center Grant CA-14599) for the funds to purchase the nmr equipment used in this work. They are greatly indebted to Professor P. Ramwell, Georgetown University, for the gerbil colon assays, to Dr. F. A. Kuehl, Jr., Merck Laboratories, for the *c*-AMP and bovine receptor assays, and to Professor J. Jarabak, University of Chicago, for the PG-dehydrogenase inhibition studies.

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Theoretical Rayleigh Optical Activity of Hexahelicene

Sir:

The very large optical rotation and circular dichroism exhibited by hexahelicene suggests that it might show large Rayleigh optical activity (a difference in the Rayleigh scattered intensity in right and left circularly polarized light¹). Rayleigh optical activity has not yet been observed, although the Raman analog is now well established.²⁻⁴

In a recent article, Barron and Buckingham⁵ presented a simple two-group model in which Rayleigh and Raman optical activity arises through interference between light waves scattered independently from two groups held in a chiral structural unit. This contrasts with the Kirkwood dynamic-coupling theory of optical rotation⁶ in which an unscattered wave interferes with a forward-scattered wave that has suffered sequential scattering from the two groups. The Kirkwood theory was applied to hexahelicene⁷ by summing 15 pairwise interactions of benzenoid rings; the calculated specific rotation (3010°) agrees remarkably well with experiment (3750°) considering the complexity, and a recent X-ray study⁸ has shown that the correct absolute configuration is predicted. Despite the reservations about applying a two-group model to hexahelicene (on account of complete π -electron exchange between the benzenoid rings), the good optical rotation result encourages a calculation of the Rayleigh optical activity.

The components of the Rayleigh CID (circular intensity differential) parallel (Δ_z) and perpendicular (Δ_x) to the scattering plane are, for molecules much smaller than the wavelength of the light¹

$$\Delta_z = \frac{4(3\alpha_{\alpha\beta}G_{\alpha\beta}' - \alpha_{\alpha\alpha}G_{\beta\beta}' - \frac{1}{3}\omega\alpha_{\alpha\beta}\epsilon_{\alpha\gamma\delta}A_{\gamma\delta\beta})}{2c(3\alpha_{\gamma\delta}\alpha_{\gamma\delta} - \alpha_{\gamma\gamma}\alpha_{\delta\delta})} \quad (1a)$$

$$\Delta_x = \frac{2(7\alpha_{\alpha\beta}G_{\alpha\beta}' + \alpha_{\alpha\alpha}G_{\beta\beta}' + \frac{1}{3}\omega\alpha_{\alpha\beta}\epsilon_{\alpha\gamma\delta}A_{\gamma\delta\beta})}{c(7\alpha_{\gamma\delta}\alpha_{\gamma\delta} + \alpha_{\gamma\gamma}\alpha_{\delta\delta})} \quad (1b)$$

(1) L. D. Barron and A. D. Buckingham, *Mol. Phys.*, **20**, 1111 (1971).

(2) L. D. Barron, M. P. Bogaard, and A. D. Buckingham, *J. Amer. Chem. Soc.*, **95**, 603 (1973).

(3) L. D. Barron and A. D. Buckingham, *Nature (London)*, **241**, 113 (1973).

(4) L. D. Barron and E. D. Buckingham, *J. Chem. Soc., Chem. Commun.*, 152 (1973).

(5) L. D. Barron and A. D. Buckingham, *J. Amer. Chem. Soc.*, **96**, 4769 (1974).

(6) J. G. Kirkwood, *J. Chem. Phys.*, **5**, 479 (1937).

(7) D. D. Fitts and J. G. Kirkwood, *J. Amer. Chem. Soc.*, **77**, 4940 (1955).

where ω is the angular frequency, $\alpha_{\alpha\beta}$ is the polarizability tensor, $G_{\alpha\beta}'$ is the electric dipole-magnetic dipole distortion tensor, and $A_{\alpha\beta\gamma}$ is the electric dipole-electric quadrupole distortion tensor. According to Barron and Buckingham,⁵ the required products in eq 1 for two chirally arranged groups *i* and *j* with threefold or higher rotation axes are, neglecting the static and dynamic coupling between the groups

$$\alpha_{\alpha\beta}G_{\alpha\beta}' = \frac{1}{3}\omega\alpha_{\alpha\beta}\epsilon_{\alpha\gamma\delta}A_{\gamma\delta\beta} = -\frac{9}{2}\omega\alpha_i\alpha_j\kappa_i\kappa_j\epsilon_{\beta\gamma\delta}R_{ij\gamma}u_{ja}u_{ia}u_{j\beta}u_{i\delta} \quad (2a)$$

$$\alpha_{\alpha\alpha}G_{\beta\beta}' = 0 \quad (2b)$$

$$\alpha_{\alpha\beta}\alpha_{\alpha\beta} = \alpha_{i\alpha\beta}\alpha_{i\alpha\beta} + \alpha_{j\alpha\beta}\alpha_{j\alpha\beta} + 2\alpha_{i\alpha\beta}\alpha_{j\alpha\beta} \quad (2c)$$

$$\alpha_{i\alpha\beta}\alpha_{j\alpha\beta} = 3\alpha_i\alpha_j + 3\alpha_i\alpha_j\kappa_i\kappa_j(3u_{ia}u_{ja}u_{i\beta}u_{j\beta} - 1) \quad (2d)$$

where u_i is the principal axis of the *i*th group, α_i and κ_i are its mean polarizability and polarizability anisotropy, and $R_{ij} = R_i - R_j$.

The centers of the six benzenoid rings in hexahelicene are placed on a right-handed cylindrical helix $X = a \cos \theta$, $Y = a \sin \theta$, and $Z = b\theta$ at $\theta = 30, 90, 150, 210, 270$, and 330° . The radius vector of the *i*th benzenoid ring is

$$R_{i\alpha} = I_\alpha a \cos \theta_i + J_\alpha a \sin \theta_i + K_\alpha b \theta_i \quad (3)$$

where **I**, **J**, **K** are unit vectors along the internal axes, *X*, *Y*, *Z*, of the molecule. The principal axis of the *i*th group is

$$u_{i\alpha} = (a^2 + b^2)^{-1/2}(I_\alpha b \sin \theta_i - J_\alpha b \cos \theta_i + K_\alpha a) \quad (4)$$

These geometrical relations are derived more fully in a recent article on the optical rotation of oriented hexahelicene.⁹ If a bond length of 1.40 Å is adopted, the radius *a* is 2.42 Å. An X-ray analysis of hexahelicene¹⁰ reports a distance $2\pi b = 3.05$ Å between the closest pair of nonbonded carbon atoms in the terminal rings.

By summing independently the numerators and denominators of eq 1 over all 15 pairs of benzenoid rings, it is found that the resulting expressions are functions of $\theta_{ij} \equiv \theta_i - \theta_j$ only

$$\Delta_z = \frac{2\pi b \sum_{i>j=1}^6 [2(1 - \cos \theta_{ij}) + \gamma^2 \theta_{ij} \sin \theta_{ij}](1 + \gamma^2 \cos \theta_{ij})}{3\lambda \left[-3(1 + \gamma^2)^2 + \sum_{i>j=1}^6 (1 + \gamma^2 \cos \theta_{ij})^2 \right]} \quad (5a)$$

$$\Delta_x = \frac{8\pi\kappa^2 b \sum_{i>j=1}^6 [2(1 - \cos \theta_{ij}) + \gamma^2 \theta_{ij} \sin \theta_{ij}](1 + \gamma^2 \cos \theta_{ij})}{\lambda \left[3(1 + \gamma^2)^2(20 - 7\kappa^2) + 7\kappa^2 \sum_{i>j=1}^6 (1 + \gamma^2 \cos \theta_{ij})^2 \right]} \quad (5b)$$

(8) D. A. Lightner, D. T. Hefelfinger, T. W. Powers, G. W. Frank, and K. N. Trueblood, *J. Amer. Chem. Soc.*, **94**, 3492 (1972).

(9) L. D. Barron, *J. Chem. Soc., Faraday 2*, in press.

(10) I. R. Mackay, J. M. Robertson, and J. G. Sime, *Chem. Commun.*, 1470 (1969).