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Synthesis and Biological Properties of Some Novel Heterocyclic Homoprostanoids

A. Douglas Bender,* Charles E. Berkoff, William G. Groves, Linda M. Sofranko, George R. Wellman, Jih-Hua Liu, Peter P. Begosh, and Joseph W. Horodniak

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. *Received May 19, 1975*

In the search for prostaglandin-like structures capable of exerting specific and desirable biological properties, a variety of simple heterocyclic homoprostanoidal derivatives was synthesized from readily available stearic acid derivatives. Compounds **5b** and **5e** were found to be more than 100 times as potent as PGE_1 and PGE_2 in a tracheal chain bioassay and, like **6**, **9**, and **12**, inhibited PGE_2-induced diarrhea. Derivatives **6** and **7a** showed significant PG-synthetase inhibitor activity.

The lack of tissue specificity and the rapid metabolic destruction of the natural prostaglandins have resulted in the search for analogs possessing more desirable biological profiles. Limitations in ready access to these relatively complex structures have imposed additional burdens on their development as potentially useful therapeutic agents.[1]

Encouraged by recent publications indicating the extent to which the chemistry of the natural prostaglandins (especially that of the cyclopentane ring) may be modified without sacrificing biological activity,[2-9] we elected to exploit the ready availability of oleic acid and its 9,10-bifunctionalized (stearic acid) derivatives and their facile conversion to the corresponding heterocyclic homoprostanoidal derivatives.[10] We were additionally attracted to these relatively simple heterocyclic ring systems because of their conformational similarity to the cyclopentane ring of the natural prostaglandins and by our developing appreciation of the state of the art of drug design;[11] calculated estimates of the partition coefficients of the compounds described compared favorably with those of the corresponding PGE and PGF derivatives. The recent disclosure of the modest PGE_2-like activity of certain bis(oxa)prostaglandins[9] prompts us to present our finding at this time.

Chemistry. Oleic acid (**1**) yields two isomeric 9,10-dihydroxyoctadecanoic acids depending on the mode of synthesis.[12] The higher melting erythro isomer **2** results from treatment of oleic acid with basic permanganate. The lower melting threo isomer **3** is readily obtained when oleic acid is oxidized using hydrogen peroxide under acidic conditions. Esterification yields the corresponding methyl esters **8** and **4** also having characteristic melting points.[12]

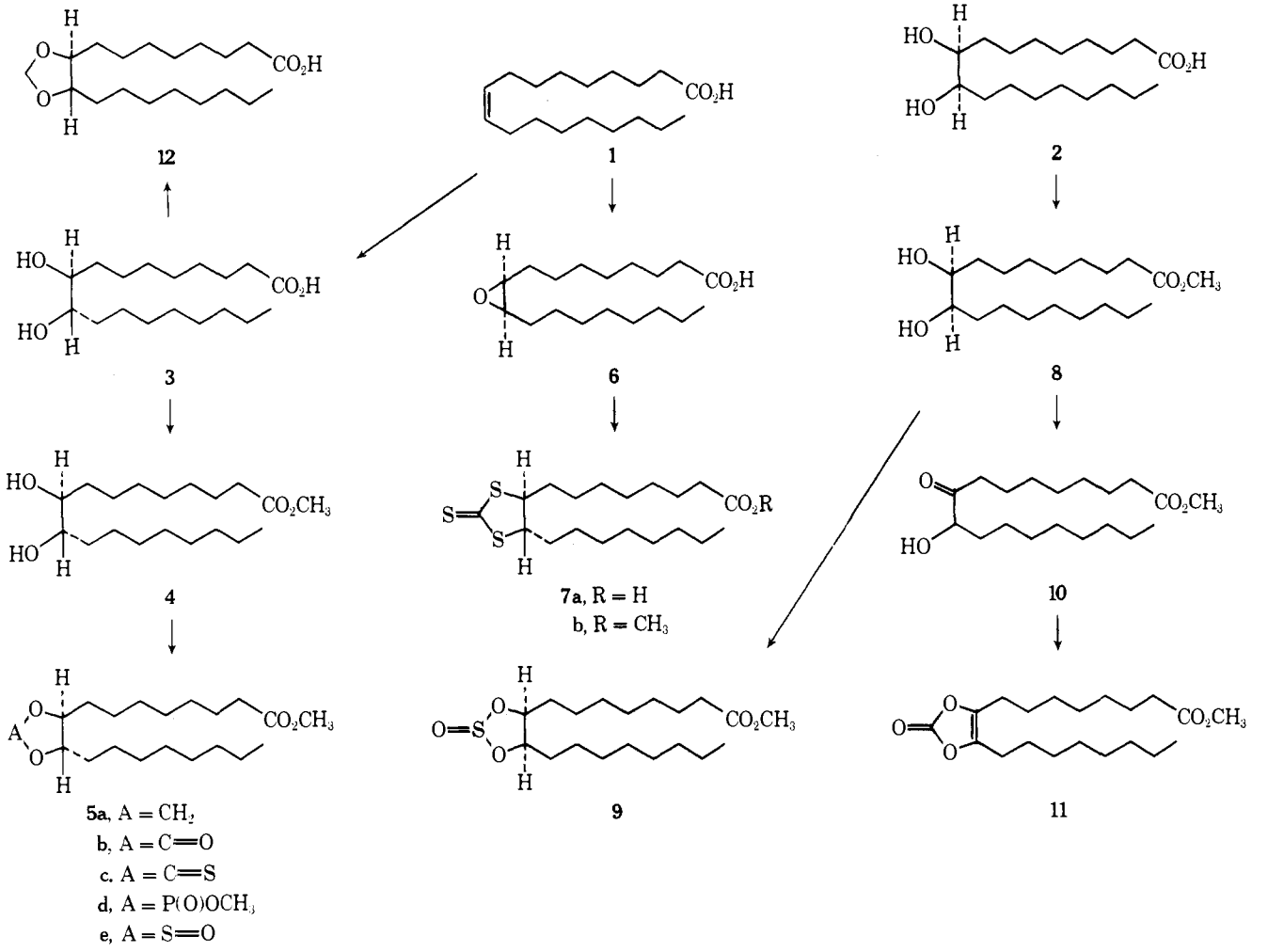
The threo ester **4** was chosen for conversion to heterocycles **5a–e** because the resulting compounds would bear a trans configuration of the ring hydrogen atoms and thus correspond to the natural prostaglandins. Accordingly, reaction of **4** with paraformaldehyde and orthophosphoric acid gave the dioxolane **5a**. Treatment of **4** with phosgene, thiophosgene, phosphorus oxychloride–methanol, and thionyl chloride afforded the corresponding homoprostanoids **5b–e**.

Oleic acid (**1**) was transformed to the cis epoxide[13] **6** using *m*-chloroperbenzoic acid. Reaction with potassium methylxanthate gave a mixture of the trans acid **7a** and the trans ester **7b**. The trans geometry follows from the work of Overberger and Drucker who obtained *trans*-4,5-dimethyl-1,3-dithiolone-2-thione from *cis*-2,3-epoxybutane and potassium methylxanthate.[14]

The NMR spectra of **5b–d** were quite similar; a broad peak near δ 4.5 was assigned to the ring protons. The cyclic sulfite **5e**, however, exhibited two multiplets in this region, one at δ 4.55 and the other at δ 4.01. In their NMR studies of simple cyclic sulfites Pritchard and Lauterbur have shown that the double-bonded oxygen lies out of the plane of the ring.[15] Protons that are cis relative to this oxygen are shifted downfield compared to those that bear a trans relationship to the oxygen. Thus, the NMR spectrum of **5e** is consistent with a cyclic sulfite having a trans arrangement of the protons. A coupling constant of 8.20 Hz for the ring protons (i.e., a dihedral angle of about 160°) indicates the noncoplanarity of the carbon and ring oxygen atoms.[16] It was not determined which of the two possible trans compounds, **5e** or **5d**, was or whether or not it was a 1:1 mixture of the two possible trans diastereoisomers.

An isomeric cyclic sulfite was similarly prepared from *erythro*-9,10-dihydroxyoctadecanoic acid. The NMR spectrum of this compound (**9**) showed only a single ring proton absorption at δ 4.52 corresponding closely to the downfield absorption seen in **5e**. Hence, the probable structure of **9** is

Scheme I



that where the ring protons and double-bonded oxygen are in the all-cis configuration.

Oxidation of 8 using BF_3–Me_2SO as described by Cohen and Tsuji afforded methyl 9(10),10(9)-ketohydroxyoctadecanoate (**10**).[17] Reaction of **10** with phosgene, followed by acid treatment, gave 11.

The structures shown in Scheme I are intended to indicate relative and not absolute configuration.

Results

Two compounds, **5b** and **5e**, were more potent and more effective than the natural prostaglandins PGE_1 and PGE_2 in relaxing the guinea pig tracheal chain (see Table I). None of the other compounds were active in this test including **9**, the cis isomer of **5e**.

5b did not protect guinea pigs against the bronchospastic effect of an acetylcholine aerosol at doses of 0.01 and 1.0 mg/kg sc. Both **5b** and **5e** were tested (iv) in anesthetized cats for effects on total lung resistance. In doses up to 1 mg/kg neither compound produced bronchodilation nor was any effect on blood pressure or heart rate observed. PGE_2 produced definitive bronchodilation at 5 μg/kg iv in the same cats.

Only *threo*-9,10-dihydroxystearic acid (3) inhibited acid secretion. This diol decreased acid output by about 50% at 10–20 mg/kg (sc) primarily by a reduction in secretion volume. An oral dose of 50 mg/kg was no more effective. In contrast, the PGE's produced maximal or near-maximal inhibition at very low (sc) doses.

None of the test compounds caused diarrhea in mice following doses up to 40 mg/kg (sc). PGE_2, on the other hand, was a very potent diarrheal agent (ED_{50} about 0.1 mg/kg sc).

Table I. Guinea Pig Tracheal Chain Relaxation

Compd	Concn range for act., μg/ml	Range of av max % relaxation
5b	0.004–0.5	24–26
5e	0.004–2.5	21–37
9	Up to 12.5	0
PGE_1	0.5–2.5	24–25
PGE_2	2.5	11

Two compounds, **5b** and **12**, were tested as inhibitors of passive cutaneous anaphylaxis at 10 mg/kg ip but were found to be devoid of activity. PGE_1 and PGE_2, on the other hand, were very active in this test at doses of 0.75 and 1.5 mg/kg ip, respectively (unpublished results).

Several compounds showed antidiarrheal effects in these tests. Compounds **5b, 5e, 6, 9,** and **12** were the most effective, producing 36–57% inhibition at the peak dose; in general, no dose–response relationship was evident (see Table II). **5e** and its cis isomer **9** were approximately as potent as polyphloretin phosphate (ED_{50} 25.5) although the maximum obtainable response was less; they were less potent than 7-oxa-13-prostynoic acid.[18]

Compound **7a** showed substantial activity as an inhibitor of prostaglandin synthetase (see Table III). It was about twice as potent as phenylbutazone and some nine times as

Table II. Inhibition of PGE_2-Induced Diarrhea in Mice

Compd	Dose, mg/kg sc	Percent change, diarrhea incidence						
		80	40	20	10	5	1	0.2
5b			−14	0	−36	0		
5e			−8	−54	−31	−15		
6			−43	−43	−43	−14		
9			0	−57	−29	−14		
12			−14	0	−36	0		
7-Oxa-13-prostynoic acid[a]						−100	−100	−15
PPP[b]		−68	−65	−36	−26	−4		

[a] Administered iv. [b] Polyphloretin phosphate administered ip.

Table III. Inhibition of Prostaglandin Biosynthesis

Compd	ID_{50}
5b	1000 μM = 15% inhibition
5e	1000 μM = 20% inhibition
6	2000–4000 μM
7a	390 μM
12	1000 μM = 30% inhibition
Indomethacin	2 μM
Phenylbutazone	875 μM
Aspirin	3700 μM

potent as aspirin. 6 was also active and about equipotent with aspirin. Three compounds (**5b, 5e,** and **12**) showed weak activity. Many of the compounds, particularly the methyl ester derivatives, could not be evaluated in this assay because of their insolubility.

Summary and Conclusions

The preliminary biological results presented in this communication demonstrate that PG-related activity can indeed be found in readily accessible compounds which represent a significant structural departure from the natural prostaglandins. Two of the derivatives prepared, **5b** and **5e,** produced significant relaxant activity in the guinea pig tracheal chain assay as does PGE_2. While these compounds were more than 100 times as potent as PGE_1 and PGE_2 in this in vitro test, however, neither showed statistically significant activity on preliminary in vivo evaluation. The complete lack of in vitro activity of the cis isomer of compound 5e (**9**) in this assay would appear to parallel the preferred trans configuration of the natural prostaglandins.

Unlike the natural PG's none of the compounds described exerted notable antisecretory effects in the pylorus-ligated rat model, and none caused diarrhea in untreated mice. Several derivatives (**5b, 5e, 6,** and **12**) were found to inhibit PGE_2-induced diarrhea in the mouse, and these may be acting by competitive PG antagonism. It was especially interesting to note the equivalent antidiarrheal effects of **5e** and **9**, since the cis isomer **9** does not affect tracheal smooth muscle while the trans isomer **5e** exerts significant relaxation. This indicates that selective antiprostaglandin effects may be obtained with **9** while **5e** produces both prostaglandin-like and antiprostaglandin effects. Of further interest is the PG-synthetase inhibitory activity shown by some of the compounds where, in particular, **6** and **7a** were found to be as potent as standard nonsteroidal antiinflammatory agents; their further pharmacological evaluation is clearly indicated.

Experimental Section

Chemical. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Boiling points and melting points are uncorrected. NMR spectra were determined on a Perkin-Elmer R-32 spectrometer in $CDCl_3$ and reported in parts per million relative to Me_4Si. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Column chromatography was performed on a 3.5 × 25 cm glass column packed with 70–325 mesh silica gel (E. Merck, Darmstadt, Germany). The polarity of the eluent (ether–pentane) was adjusted so that the R_f of the major spot on silica gel TLC was 0.2–0.5. The eluent from the column was then monitored by TLC and purest fractions were combined. No attempts were made to optimize yields. Elemental analyses were determined by the Analytical Department of Smith Kline & French Laboratories and, unless indicated to the contrary, were within ±0.4% of theoretical values. NMR, ir, and mass spectra were obtained for all compounds and were completely consistent with assigned structures.

Preparation of 9,10-Dihydroxystearic Acid Methyl Esters (4 and 8). *threo*-9,10-Dihydroxystearic acid (**3**) (Alfred Bader Chemicals) (31.4 g) was dissolved in methanol (500 ml) and heated under reflux with AG 50W-X8 resin (Bio-Rad) (25 g) for 12 hr. The mixture was filtered and the solvent removed under reduced pressure. Recrystallization of the solid residue from hexane gave **4** (26 g, 80%), mp 65–69° (lit.[12] 71°). Similarly, *erythro*-9,10-dihydroxystearic acid[12] gave the corresponding methyl ester **8**, mp 100–103° (lit.[12] 105°).

Preparation of (8ξ-*trans*)-9,11-Dioxa-1a-homoprostan-1-oic Acid (12) and Methyl Ester (5a). *threo*-9,10-Dihydroxystearic acid (**3**) (6.4 g) and paraformaldehyde (3.6 g) were dissolved together in orthophosphoric acid (60 ml) and the solution was heated at 100° for 4 hr. The reaction mixture was cooled and extracted with ether. The combined ether extracts were concentrated under reduced pressure yielding **12** contaminated with **3** and other minor products as a viscous oil: NMR δ 4.95 (m, 2, methylenedioxy protons). Anal. ($C_{19}H_{36}O_4$) C: calcd, 69.47; found, 67.50. Esterification as described for **4** gave after chromatography **5a** (2.1 g, 30% from **3**) as an oil: mass spectrum *m/e* 341 $(M - 1)^+$; NMR δ 3.70 (s, 3, OCH_3), 5.03 (s, 2, methylenedioxy protons); ir 1740 cm^{-1} (ester). Anal. ($C_{20}H_{38}O_4$) C, H.

Preparation of (8ξ-*trans*)-10-Oxo-9,11-dioxa-1a-homoprostan-1-oic Acid Methyl Ester (5b). Methyl *threo*-9,10-dihydroxystearate (**4**) (1.75 g) was dissolved in chloroform (50 ml) and pyridine was added (1 ml). A solution of phosgene (1 g) in toluene (12.5 ml) was added dropwise to this solution. The solution was stirred for 2 hr whereupon an additional amount of phosgene (0.2 g) in toluene (2.5 ml) was added and the stirring continued an additional 1.5 hr. The reaction mixture was washed with H_2O and dried over Na_2SO_4. The solvent was removed and the oil chromatographed giving **5b** (0.55 g, 31%) as an oil:[19] NMR δ 4.30 (m, 2, ring protons); ir 1800 cm^{-1} (carbonate). Anal. ($C_{20}H_{36}O_5$) C, H.

Preparation of (8ξ-*trans*)-10-Thioxo-9,11-dioxa-1a-homoprostan-1-oic Acid Methyl Ester (5c). Toluene (100 ml) was used to dissolve **3** (3.3 g). Commercial thiocarboxyldiimidazole (2.0 g) was added and the mixture heated under reflux for 1 hr, cooled to 25°, and stirred an additional 1.5 hr. The reaction mixture was washed with aqueous HCl (3.6 *N*) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue chromatographed giving **5c** (1.0 g, 25%): NMR δ 4.52 (m, 2,

ring protons); ir 1280 cm^{-1} (thiocarbonate). Anal. ($C_{20}H_{36}SO_4$) C, H, S.

Preparation of (8ξ-*trans*)-10-Methoxy-10-oxo-9,11-dioxa-10-phospha-1a-homoprostan-1-oic Acid Methyl Ester (5d). Pyridine (100 ml) was used to dissolve 3 (8 g). The solution was cooled to 0° and $POCl_3$ (4 g) added slowly. The temperature was maintained at 0° for 1 hr whereupon the solution was diluted with MeOH (10 ml). After an additional 1 hr, the solution was concentrated and chromatographed giving **5d** (5.1 g, 52%) as an oil: NMR δ 4.20 (m, 2, ring protons); ir 1725 cm^{-1} (ester). Anal. ($C_{20}H_{39}O_6P$) C, H, P.

Preparation of (8ξ-*trans*)-10-Oxo-9,11-dioxa-10-thia-1a-homoprostan-1-oic Acid Methyl Ester (5e). Ether (250 ml) was used to dissolve 4 (3.5 g). The solution was cooled to 0° and thionyl chloride (2.4 g) was added in one portion. Nitrogen was bubbled through the solution for 2 hr at 0° to remove HCl. The solution was concentrated and chromatographed to give **5e** (2.2 g, 60%): NMR δ 4.01 and 4.55 (m, 1, ring protons); ir 1210 cm^{-1} (S=O). Anal. ($C_{19}H_{36}SO_5$) C, H, S.

Preparation of (8ξ-*trans*)-10-Thioxo-9,11-dithia-1a-homoprostan-1-oic Acid (7a) and Methyl Ester (7b). A solution of potassium methylxanthate was made by dissolving 85% KOH (40 g) in MeOH (150 ml) and CS_2 (57 g). The volume was adjusted to 170 ml by the addition of more MeOH. A portion of this solution (13.5 ml) was added to a solution of 6[13] (3.7 g) in MeOH (100 ml). The solution stood for 2 weeks at 25° and deposited some inorganic material. The mixture was filtered and neutralized to pH 7 using concentrated HCl. The solution was concentrated and chromatographed first giving **7b** (0.35 g, 7%): NMR δ 3.90 (m, 2, ring protons); ir 1740 cm^{-1}. Anal. ($C_{20}H_{39}O_2S_3$) C, H; S: calcd, 23.77; found, 22.53. The acid **7a** was eluted later and the fractions were combined and concentrated. The residue was crystallized from ether–hexane giving **7a** (0.5 g, 10%): mp 47–50°; NMR δ 3.95 (m, 2, ring protons); ir 1700 cm^{-1} (ester). Anal. ($C_{19}H_{34}O_2S_3$) C, H, S.

Preparation of (8ξ-*cis*)-10-Oxo-9,11-dioxa-10-thia-1a-homoprostan-1-oic Acid Methyl Ester (9). The sulfite **9** was prepared from 8 by the same procedure used to prepare **5e** from 4: NMR δ 4.52 (m, 2, ring protons). Anal. ($C_{19}H_{36}SO_5$) C, H.

Preparation of 10-Oxo-9,11-dioxa-1a-homoprost-8(12)-en-1-oic Acid Methyl Ester (11). 9(10),10(9)-Ketohydroxystearic acid (**10**)[20] was converted to the methyl ester as described for the preparation of **4**. A solution of this ester (10 g) in benzene (200 ml) and pyridine (80 ml) was cooled to 0°. A solution of phosgene in benzene (80 ml of a 12.5% solution) was added dropwise and the solution was warmed to 25° and stirred for 18 hr. Hexane (300 ml) was added and the solids were removed by filtration. The filtrate was washed with 5% HCl and H_2O and dried over Na_2SO_4. Removal of the solvent gave the crude chlorocarbonate. A portion of this material (8.5 g) was heated under reflux with *p*-toluenesulfonic acid (1 g) whereupon pyridine (0.5 ml) was added at 10°. The solids were removed by filtration and the filtrate was concentrated to yield a dark oil. The oil was distilled (0.025 mm at 190°) giving a brown oil (3.35 g). Column chromatography gave 11 (1.68 g, 22%) as an oil: NMR δ 3.64 (OCH_3); ir 1820 cm^{-1} (carbonate). Anal. ($C_{20}H_{34}O_5$) C, H.

Biological. Guinea Pig Tracheal Chain Relaxation (in Vitro). Guinea pig tracheal chains were prepared and used according to the method of Castillo and deBeer[21] and subsequently modified by Wardell et al.[22] Drug response was expressed as a percent of the maximum possible responsiveness of each tissue. Maximum responsiveness for relaxation was obtained by adding a supramaximal dose of papaverine (10 mg/ml) to the bath at the end of each experiment.

Inhibition of Acetylcholine Bronchoconstriction in Conscious Guinea Pigs.[22] Male Hartley guinea pigs ranging in weight from 300 to 400 g were exposed to a 1% acetylcholine (Ach) aerosol. Control and drug-treated animals were separate groups and were exposed only once to the acetylcholine aerosol. The time interval between initiation of the Ach aerosol and prostration was measured. Bronchodilator pretreatment inhibits the Ach-induced bronchospasm. Maximum aerosol exposure time was 420 sec.

Effect on Total Lung Resistance in the Anesthetized Cat.[22] Male cats weighing about 3 kg were anesthetized with pentobarbital sodium, 30 mg/kg ip. The right femoral artery was catheterized for recording blood pressure; the left femoral vein was catheterized for injections. The cats were allowed to breath spontaneously. Test compounds were given after an equilibration period, and drug effect was calculated as the percentage of the maximum decrease in total lung resistance (produced by administration of a supramaximal dose of isoproterenol at the end of each experiment). Drug-induced effects on diastolic blood pressure and heart rate were calculated as percent change from control values in the same animal.

Pylorus-Ligated Rats. Male Carworth Farms rats ranging in weight from 290 to 380 g were food deprived with free access to water 18 hr prior to testing. Under ether anesthesia, the pyloric portion of the stomach was exposed and ligated. The incision was closed and each animal received a subcutaneous (sc) injection of either test compound or vehicle (saline–phosphate buffer) at a dose volume of 10 ml/kg. Later (2 hr) the animals were sacrificed, the stomach was removed, and the gastric contents were collected. After centrifugation the gastric juice volumes, pH's, and titratable acidities were determined. Reference compounds were PGE_1 and PGE_2 (Ono Pharmaceuticals, Osaka, Japan).

Passive Cutaneous Anaphylaxis in Rats. The backs of unanesthetized rats were shaved and 0.1 ml of diluted antiserum [produced previously in a separate group of rats by injecting 5 ml of $Al(OH)_3$ (~50 mg/ml) + 1 mg of egg albumin (ip) and collecting blood 10 days later] sufficient to produce an average wheal of approximately 12 × 12 mm was injected intradermally at four sites. After 45–51 hr, test compounds were injected ip and followed 5 min later by 0.5 ml (iv) of saline containing 5 mg of Evans Blue dye and 5 mg of egg albumin. Later (30 min) the animals were killed, the dorsal skin was deflected, and the extent of cutaneous anaphylaxis (bluing) was measured from two axes of each of the four wheals and averaged for each animal. Control animals received an equivalent volume of vehicle only. The mean average wheal size of each drug-treated group was compared to the mean average wheal size of the control group for that day. The percent inhibition was calculated from the difference in mean average wheal size.

Antagonism of Mouse Diarrhea Induced by PGE_2. Male CF_1 mice ranging in weight from 15 to 30 g were allowed to acclimate for 30 min with free access to food and water. When the compounds were administered, the water was removed. Test compounds were given sc to the experimental animals 15 min prior to an ip injection of 180 μg/kg of PGE_2. The control group received vehicle (saline + 0.1 ml of absolute alcohol) sc at 5 ml/kg followed by an ip injection of PGE_2 15 min later. Each animal was examined for diarrhea every 15 min for 1 hr postdrug. Reference compounds were polyphloretin phosphate (Aktiebalaget Leo, Halsingborg, Sweden) and 7 oxa-13-prostynoic acid (Professor Josef Fried, University of Chicago). Single injections of test compound were also given to separate groups of otherwise untreated mice to determine whether the test compounds themselves induced diarrhea.

Prostaglandin Synthetase Inhibition. The formation of adrenochrome was followed spectrophotometrically by the procedure described by Takeguchi and Sih.[23] Reaction tubes were preincubated at 25° for 5 min with all components except for arachidonic acid (AA). They were then heated to 37.5° and the AA was added. The formation of the adrenochrome color was followed at 520 nm. Compounds were run first at 1000 μM; the ID_{50} was determined for active compounds. Indomethacin (Merck Sharp & Dohme, West Point, Pa.), phenylbutazone, and aspirin were used as reference compounds.

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Synthesis and Antitumor Activity of 2-Deamino- and N^2-(γ-Hydroxypropyl)actinomycin D[1]

Stanley Moore, Michio Kondo, Michelle Copeland, Johannes Meienhofer,*

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110, and the Children's Cancer Research Foundation† and Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts 02115

and Randall K. Johnson

Drug Research and Development, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland 20014.
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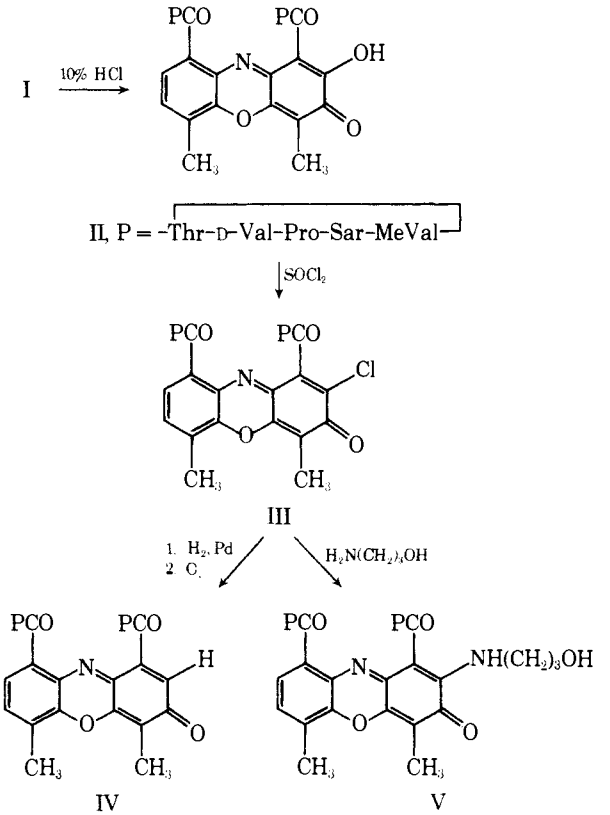
2-Deamino- and N^2-(γ-hydroxypropyl)actinomycin D were synthesized by modification of the parent actinomycin D molecule at the 2 position of the phenoxazinone moiety. The common intermediate was 2-deamino-2-chloroactinomycin D. Catalytic hydrogenation of this material afforded the 2-deamino derivative while treatment with γ-hydroxypropylamine yielded the N^2-(γ-hydroxypropyl) derivative. These 2-substituted actinomycin D derivatives were less potent in microbiological assays than the parent compound. Evaluation of activity in vivo against three murine tumor systems indicated that optimal dose levels of 2-deaminoactinomycin D were 50 times greater than toxic dose levels of actinomycin D. N^2-(γ-Hydroxypropyl)actinomycin D exhibited antitumor activity similar to the parent compound.

Among clinically used antitumor agents actinomycin D (I) (Figure 1) is one of the few possessing curative effects against two different tumors,[2,3] i.e., Wilms' tumor[4] and gestational choriocarcinoma.[5] Unfortunately, its spectrum of antitumor activity in man is relatively narrow and its administration difficult due to its high toxicity. The development of modified actinomycins possessing a broader range of activity and/or lower toxicity is thus highly desirable.[6]

We wish to report syntheses of 2-deaminoactinomycin D (IV) and N^2-(γ-hydroxypropyl)actinomycin D (V) (Figure 1). The 2-amino function seems to play a role in the biological activity of actinomycins.[7,8] Consequently, many 2-substituted derivatives have been prepared and evaluated.[9-12] Although a few N^2-alkyl derivatives exhibited low antibacterial activity (ca. 10% that of actinomycin D), most other 2-substituted derivatives were completely inactive, including 2-deamino-2-hydroxyactinomycin[13] and 2-deamino-2-chloroactinomycin.[13,14] These results suggested that the 2-amino group is essential for actinomycin activity. Conclusive proof, however, required synthesis and evaluation of actual 2-deaminoactinomycin in which the 2-amino group would be replaced by hydrogen. Rationale for the preparation of V was twofold: (a) the lower homolog N^2-(β-hydroxyethyl)actinomycin[11] exhibited some antibacterial activity and appears to interact with double-stranded DNA,[8] and (b) the cytotoxic agent acrolein, which may contribute to the antitumor activity of cyclophosphamide,[15] could perhaps be liberated from V along with actinomycin D by enzymatic processes in vivo.

The synthetic route to these derivatives is outlined in Scheme I. 2-Deamino-2-hydroxyactinomycin D (II) was produced by treatment of actinomycin D (I) with 10% HCl for 4.5 hr at 60°.[13] This derivative was converted to 2-deamino-2-chloroactinomycin D (III) by reaction of I with

Scheme I



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