membrane-bound [^{3}H]-PGE$_1$ was determined in methyl cellosolve–aquasol (1:6) with a Packard liquid scintillation counter. Duplicate experiments were run on each test compound at each of three concentrations.

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11,12-Secoprostaglandins. 4. 7-(N-Alkylmethanesulfonamido)heptanoic Acids

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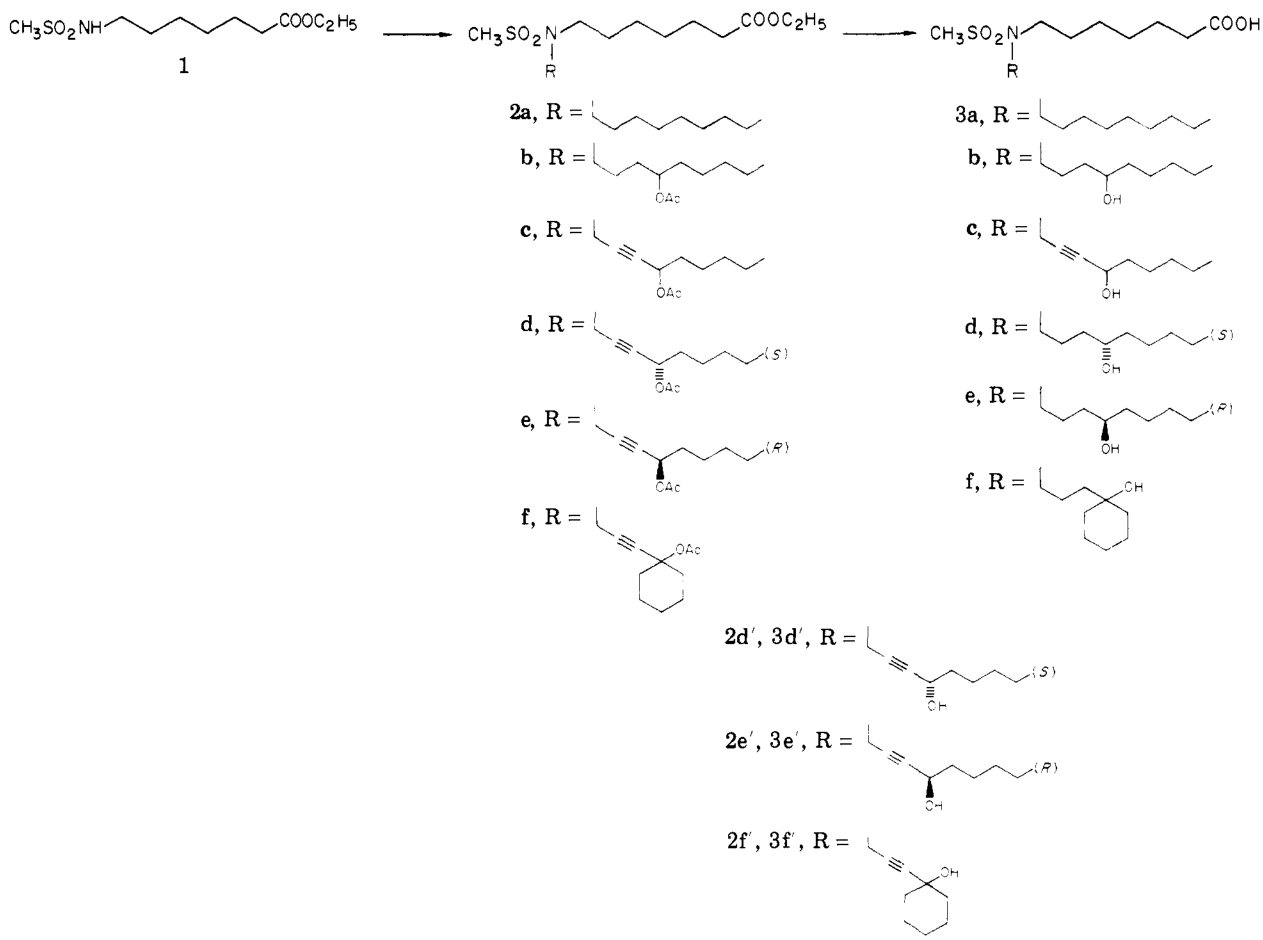
A series of 7-(*N*-alkylmethanesulfonamido)heptanoic acids has been prepared which represents an extension of our 8-aza-11,12-secoprostaglandin studies. The compounds mimic the natural prostaglandins in that they markedly stimulate cAMP formation in the mouse ovary assay.

Previous papers[1–3] in this series have described a group of 11,12-secoprostaglandin analogues that mimic the action of the natural prostaglandins in that they stimulate cAMP formation in the mouse ovary PG assay.[4] Some of these

Scheme I[a]



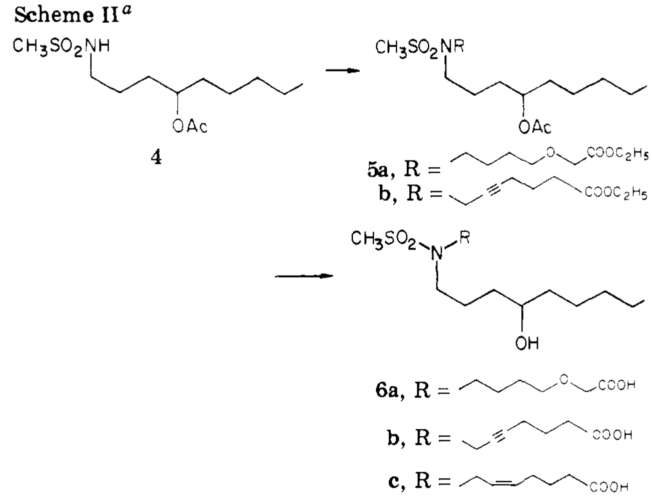
[a] See ref 11.

compounds also exhibit prostaglandin-like activities[1-3] in vivo. The apparent success of this approach prompted additional effort in this area of secoprostaglandins; thus this paper discloses the synthesis and biological activity of a series of 7-(*N*-alkylmethanesulfonamido)heptanoic acids (e.g., **3**, **6**, and **11**). The nitrogen atom located at position 8 in these molecules obviates the stereochemical problems at that position and the sulfonyl group can simulate[5] the carbonyl function located at position 9 in the natural prostaglandins.

Chemistry. The product carboxylic acids in Scheme I represented by structures **3a–c,d′–f′** were prepared by saponification of the corresponding acetoxy esters **2** using ethanolic sodium hydroxide. The carboxylic acids **3d–f** were prepared by hydrogenation of the corresponding unsaturated acids using 5% palladium on carbon as catalyst. The acetoxy esters **2** were prepared by alkylation of **1** with the appropriate acetoxyalkyl halide. In the case of **2d** and **2e** the alkylating agents were the *R* and *S* enantiomers of 1-bromo-4-acetoxy-2-nonyne.[1] Therefore, compounds **3d** and **3e** represent the pure stereoisomers. Compound **1** resulted from the alkylation of methanesulfonamide with ethyl 7-bromoheptanoate. Although the yield from this reaction was low, it was the most economical way to prepare this compound.

Scheme II depicts the procedure developed for making variations in the acid side chain of these secoprostaglandins. The product carboxylic acids, **6a,b**, were prepared by saponification of the corresponding acetoxy esters by the method described above. The carboxylic acid **6c** was prepared by catalytic hydrogenation of **6b** using a Lindlar catalyst which provided the depicted cis double

Scheme II[a]

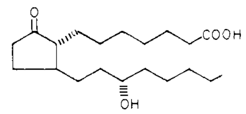
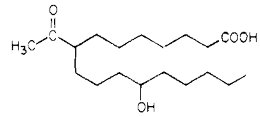
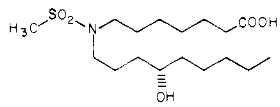


[a] See ref 11.

bond structure. The acetoxy esters **5a,b** were obtained by alkylation of **4** with the appropriate halo esters. Alkylation of methanesulfonamide with 1-bromo-4-acetoxynonane yielded intermediate **4**.

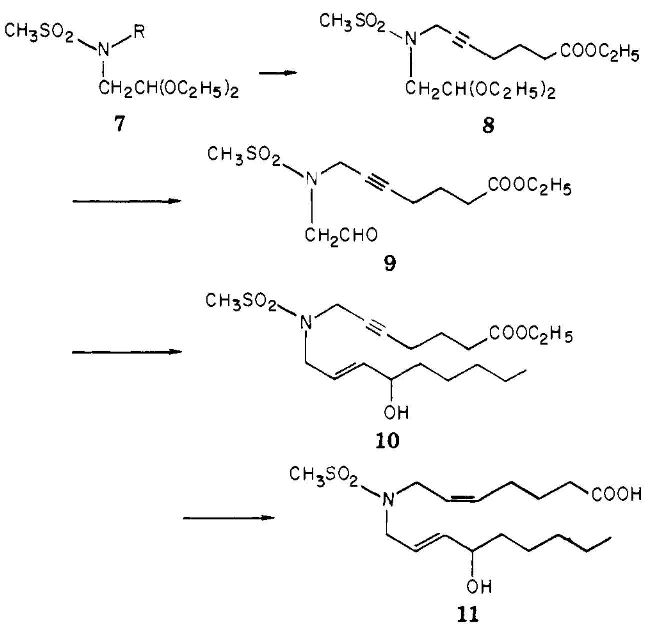
Scheme III illustrates the preparation of a seco analogue related to the "2-series" of natural prostaglandins. The double bonds in both chains have been introduced in their proper geometric configuration; however, no resolution of the racemate was attempted. Carboxylic acid **11** was obtained by saponification of **10**, using the method described above, followed by reduction of the triple bond to a cis double bond using a Lindlar catalyst. The Emmons

Table I[a]

	Mouse ovary PG assay, fold increase in cAMP, concn in μg/mL						
	0.01	0.05	0.1	1.0	10	25	100
PGE_1	8 ± 1 (n = 3)	25 ± 3 (n = 3)	29 ± 5 (n = 3)	54 ± 5 (n = 27)	60 ± 5 (n = 4)	62 ± 4 (n = 4)	62 ± 5 (n = 3)
				10	25	26	19
 12			1	2	11	14	23
 3d (S)			1 ± 0.5 (n = 3)	8 ± 1 (n = 5)	54 ± 4 (n = 4)	55 ± 10 (n = 4)	68 ± 9 (n = 3)

[a] See ref 11.

Scheme III[a]



[a] See ref 11.

reaction[6] between compound **9** and dimethyl (2-oxoheptyl)phosphonate afforded the corresponding ketone which was reduced at once using sodium borohydride in ethanol to give compound **10**. The slightly unstable aldehyde **9** was obtained by acid hydrolysis of the acetal **8**. Alkylation of **7** with ethyl 7-bromo-5-heptynoate[7] yielded the acetal **8**. Compound **7** was obtained by treatment of aminoacetaldehyde diethyl acetal with methanesulfonyl chloride.

Biological Activity. The prostaglandins of the E series have been shown to raise cAMP levels in cells of many types.[8] The dose-related stimulation by PGE_1 of cAMP formation in the mouse ovary is the basis for the primary assay used in these laboratories for the detection and measurement of prostaglandin-like activity.[4] In this assay, described in detail in the Experimental Section, mouse ovaries are first incubated with adenine-*8-^{14}C* to allow formation of intracellular ATP-^{14}C. Then, the test compound along with the phosphodiesterase inhibitor theophylline is added and incubation is continued. Reactions are finally terminated by the addition of trichloroacetic acid, and cAMP-^{14}C is isolated from the ovaries and measured. Results are expressed in this paper as fold increases in cAMP formation obtained by dividing the cAMP levels in treated ovaries by those levels found in untreated ovaries.

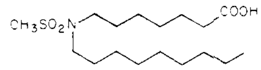
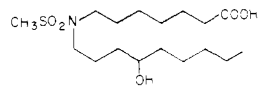
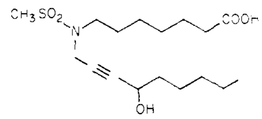
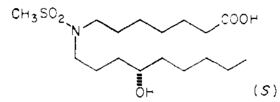
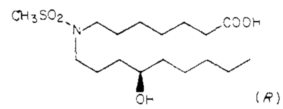
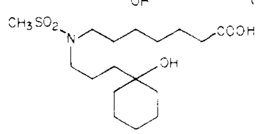
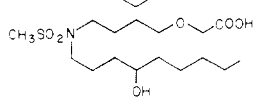
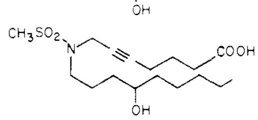
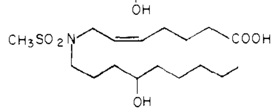
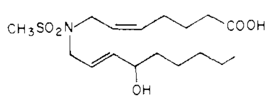
In Table I, 7-[N-[4-(S)-hydroxynonyl]methanesulfonamido]heptanoic acid (**3d**) is compared with PGE_1 and 11-deoxy-13,14-dihydro-PGE_1 for its ability to stimulate the formation of cAMP in mouse ovaries. Also included is 8-acetyl-12-hydroxyheptanoic acid (**12**), a representative compound from the first paper[1] of this series. Compound **3d** is a single enantiomer with the same configuration as the natural prostaglandins and it gives the greatest increase of cAMP of any compound in this series. The unnatural enantiomer, **3e**, is much less active and the racemate, **3b**, also is somewhat less active. The relatively high activity shown by compound **3d** further confirms the speculations on which this research is based.

Table II shows that the compound which lacks the 15-hydroxyl group (PG numbering), compound **3a**, has significant activity. This was also observed in the previous series.[2] Compound **3c**, the triple-bond analogue, gives intermediate cAMP-stimulating activity and compound **3f**, which has the cyclohexyl side chain, is very weakly active. Compounds **6a–c** which contain variations in the carboxy side chain all show decreased activity. Compound **11**, which is a member of the "2-series" of prostaglandins, was disappointingly poor in its ability to stimulate cAMP formation.

Results of the evaluation of the 7-(N-alkylmethanesulfonamido)heptanoic acids in vivo will be published elsewhere. A number of these compounds that have shown activity in vitro have shown some, but not all, of the characteristic actions of the E prostaglandins in whole animals. For example, certain members of this series inhibit collagen-induced platelet aggregation when administered orally to guinea pigs.[12] The ED_{50} of **3b** in this assay is 6.0 mg/kg; the ED_{50} of **3d**, its S enantiomer, is 5 mg/kg; and of **3e**, its R enantiomer, 8.2 mg/kg. The ED_{50} of PGE_1 (not active by oral administration) is 0.02 mg/kg ip.

Some of these compounds were evaluated as phosphodiesterase inhibitors and determined to be without effect; for example, compound **3b** did not inhibit beef heart

Table II[d]

No.		% yield[a]	R_f[b]	Formula	Mouse ovary assay, fold increase in cAMP, concn in μg/mL[c] 10	25	100
3a		16	0.55	$C_{17}H_{35}NO_4S$	13	14	15
3b		22	0.55	$C_{17}H_{35}NO_5S$	40	56	61
3c		32	0.58	$C_{17}H_{31}NO_5S$	21	21	36
3d		5	0.55	$C_{17}H_{35}NO_5S$	54	55	68
3e		11	0.55	$C_{17}H_{35}NO_5S$	23	25	45
3f		20	0.60	$C_{17}H_{33}NO_5S$	3	5	10
6a		24	0.65	$C_{16}H_{33}NO_6S$	24	27	38
6b		42	0.55	$C_{17}H_{31}NO_5S$	21	30	39
6c		41	0.55	$C_{17}H_{33}NO_5S$	16	18	37
11		8	0.59	$C_{17}H_{31}NO_5S \cdot H_2O$	11	19	27

[a] Overall yield for the synthesis. [b] Determined on SiO_2 plates with $CHCl_3$-CH_3OH-AcOH (94:5:1). [c] Fold increases of 2-3 of cAMP over controls are judged to be significant. [d] See ref 11.

cAMP phosphodiesterase when tested at 100 μg/mL vs. 0.4 mM cAMP.

Experimental Section

Reported boiling points are uncorrected. ^{1}H NMR spectra were obtained in $CDCl_3$ on a Varian A-60A spectrometer. Chemical shifts are reported as parts per million relative to Me_4Si as an internal standard. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. All new compounds have spectra consistent with the assigned structures.

Column chromatography was carried out on E. Merck silica gel 60, particle size 0.063–0.20 mm. Thin-layer chromatography (TLC) was used to monitor column fractions and to establish purity of products. It was performed on Analtech silica gel GF (thickness 250 μ). Spots were located with iodine vapor.

Chromatographed compounds were prepared for analysis and biological testing by being heated at 100 °C in oil pump vacuum for 4–6 h in order to remove the last traces of solvent.

When analyses are indicated only by the symbols of the elements, the analytical results obtained for these elements are within 0.4% of the theoretical values.

7-(*N*-Nonylmethanesulfonamido)heptanoic Acid (3a). (a) **Ethyl 7-Methanesulfonamidoheptanoate** (1). To a stirred suspension of NaH (1.32 g, 55 mmol) in benzene (50 mL) and DMF (50 mL) was added methanesulfonamide (4.75 g, 55 mmol) over 30 min. This mixture was heated on the steam bath for 1.5 h and then cooled to room temperature. Ethyl 7-bromoheptanoate (13 g, 55 mmol) was added and the reaction mixture was heated on the steam bath for 20 h. The cooled mixture was poured into water (200 mL), neutralized with HCl (dilute), and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and then distilled. There was obtained 7.1 g (51%) of 1, bp 165–168 °C (0.1 mm). Anal. ($C_{10}H_{21}NO_4S$) C, H, N.

(b) **Ethyl 7-(*N*-Nonylmethylsulfonamido)heptanoate (2a).** To a stirred suspension of NaH (0.24 g, 10 mmol) in benzene (15 mL) and DMF (15 mL) was added compound 1 (2.5 g, 10 mmol) over 30 min. Stirring was continued for 1 h at room temperature. There was added 1-bromononane (2.1 g, 10 mmol) and the mixture was heated for 4 h on the steam bath. The cooled mixture was poured into water, acidified with HCl (dilute), and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by chromatography over silica gel using 2% CH_3OH in $CHCl_3$ for elution. There was obtained 2.6 g (66%) of **2a** as a viscous oil. Anal. ($C_{19}H_{39}NO_4S$) H, N; C: calcd, 60.43; found, 59.96.

(c) **7-(*N*-Nonylmethanesulfonamido)heptanoic Acid (3a).** A solution of ester **2a** (2.8 g, 7.8 mmol) and NaOH (0.47 g, 11.8 mmol) in H_2O (2.5 mL) and C_2H_5OH (25 mL) was stirred 20 h at room temperature, poured into water (150 mL), and extracted with ether (100 mL). The aqueous layer was separated and carefully acidified with HCl (dilute). The oil that separated was extracted into ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The resulting oil was purified by chromatography over silica gel using 5% MeOH in $CHCl_3$ for elution. There was obtained 1.3 g (47%) of **3a** as a viscous oil. Anal. ($C_{17}H_{35}NO_4S$) C, H, N.

7-[*N*-(4-Hydroxynonyl)methanesulfonamido]heptanoic Acid (3b). (a) Ethyl 7-[*N*-(4-Acetoxynonyl)methanesulfonamido]heptanoate (2b). Using exactly the procedure described for **2a**, compound 1 (6.8 g, 27 mmol) was alkylated with 1-chloro-4-acetoxynonane[1] (6.55 g, 29.8 mmol) to yield 6.0 g (51%) of **2b** as an oil. Anal. ($C_{21}H_{41}NO_6S$) C, H, N.

(b) 7-[*N*-(4-Hydroxynonyl)methanesulfonamido]heptanoic Acid (3b). The saponification of **2b** to **3b** was carried out as described for **2a** in 85% yield. The product was an oil. Anal. ($C_{17}H_{35}NO_5S$) C, H, N.

7-[*N*-(4-Hydroxy-2-nonynyl)methanesulfonamido]heptanoic Acid (3c). (a) Ethyl 7-[*N*-(4-Acetoxy-2-nonynyl)methanesulfonamido]heptanoate (2c). Using the procedure for the preparation of **2a**, compound 1 (6.8 g, 27 mmol) was alkylated with 1-bromo-4-acetoxy-2-nonyne[1] (7.77 g, 29.8 mmol) to yield 9.3 g (80%) of **2c** as an oil. Anal. ($C_{21}H_{37}NO_6S$) N; C: calcd, 58.44; found, 57.92; H: calcd, 8.64; found, 9.15.

(b) 7-[*N*-(4-Hydroxy-2-nonynyl)methanesulfonamido]heptanoic Acid (3c). This saponification was carried out as for **2a** to give 78% of **3c** as an oil. Anal. ($C_{17}H_{31}NO_5S$) C, H, N.

7-[*N*-[4-(*S*)-Hydroxynonyl]methanesulfonamido]heptanoic Acid (3d). (a) Ethyl 7-[*N*-[4-(*S*)-Acetoxy-2-nonynyl]methanesulfonamido]heptanoate (2d). Using the procedure described for **2a**, compound 1 was alkylated with 1-bromo-4-(*S*)-acetoxy-2-nonyne, $[\alpha]^{26}_D$ −70.1° (*c* 2.91, $CHCl_3$),[1] to give **2d**, $[\alpha]^{26}_D$ −48.8° (*c* 2.865, $CHCl_3$), in 23% yield. Anal. ($C_{21}H_{37}NO_6S$) C, H, N.

(b) 7-[*N*-[4-(*S*)-Hydroxynonyl]methanesulfonamido]heptanoic Acid (3d). The saponification of **2d** was carried out as described for **2a** to give 7-[*N*-[4-(*S*)-hydroxy-2-nonynyl]methanesulfonamido]heptanoic acid (**3d′**), $[\alpha]^{26}_D$ +1.64° (*c* 3.18, $CHCl_3$), in 85% yield. The reduction of **3d′** to **3d** was effected by hydrogenation of a cyclohexane–ethyl acetate (2:1) solution of **3d′** using 5% palladium on carbon as catalyst. The compound was purified by chromatography over silica gel using 4% MeOH in $CHCl_3$ to elute. There was obtained a 50% yield of **3d**, $[\alpha]^{26}_D$ +3.92° (*c* 2.44, $CHCl_3$). Anal. ($C_{17}H_{35}NO_5S$) C, H, N.

7-[*N*-[4-(*R*)-Hydroxynonyl]methanesulfonamido]heptanoic Acid (3e). Ethyl 7-[*N*-[4-(*R*)-Acetoxy-2-nonynyl]methanesulfonamido]heptanoate (2e). Using the procedure described for compound **2a**, compound 1 was allowed to react with 1-bromo-4-(*R*)-acetoxy-2-nonyne, $[\alpha]^{26}_D$ +71.5° (*c* 3.34, $CHCl_3$),[1] to give, after chromatography, a 72% yield of **2e**, $[\alpha]^{26}_D$ +46° (*c* 2.95, $CHCl_3$). Anal. ($C_{21}H_{37}NO_6S$) C, H, N.

(b) 7-[*N*-[4-(*R*)-Hydroxynonyl]methanesulfonamido]heptanoic Acid (3e). The saponification of **2e** was carried out as described for **2a** to give 7-[*N*-[4-(*R*)-hydroxy-2-nonynyl]methanesulfonamido]heptanoic acid (**3e′**), $[\alpha]^{26}_D$ −0.933° (*c* 3.3, $CHCl_3$), in 72% yield. Anal. ($C_{17}H_{31}NO_5S$) N; C: calcd, 56.48; found, 55.96; H: calcd, 8.64; found, 9.13. The reduction of **3e′** to **3e** was effected as described for **3d**. There was obtained a 42% yield of **3e**, $[\alpha]^{26}_D$ −3.0° (*c* 3.72, $CHCl_3$). Anal. ($C_{17}H_{35}NO_5S$) C, H, N.

7-[*N*-[3-(1-Hydroxycyclohexyl)propyl]methanesulfonamido]heptanoic Acid (3f). (a) Ethyl 7-[*N*-[3-(1-Acetoxycyclohexyl)-2-propynyl]methanesulfonamido]heptanoate (2f). Using the procedure described for **2a**, compound 1 was alkylated with 1-acetoxy-1-(3-bromo-1-propynyl)cyclohexane[1] to give **2f** in 63% yield. The compound was a viscous oil. Anal. ($C_{21}H_{31}NO_6S$) C, H, N.

(b) 7-[*N*-[3-(1-Hydroxycyclohexyl)propyl]methanesulfonamido]heptanoic Acid (3f). The saponification of **2f** was effected by the procedure described for **2a** to give **7-[*N*-[3-(1-hydroxycyclohexyl)propynyl]methanesulfonamido]heptanoic acid (2f′)** in 80% yield. Anal. ($C_{17}H_{29}NO_5S$) N, H; C: calcd, 56.80; found, 56.24. Hydrogenation was carried out as described for **3d**. There was obtained 80% of **3f** as an oil. Anal. ($C_{17}H_{33}NO_5S$) C, H, N.

4-[*N*-(4-Hydroxynonyl)methanesulfonamido]butoxyacetic Acid (6a). (a) *N*-(4-Acetoxynonyl)methanesulfonamide (4). Methanesulfonamide (7.6 g, 80 mmol) was added to a stirred suspension of NaH (1.92 g, 80 mmol) in DMF (120 mL) and benzene (60 mL) over 30 min. Stirring was continued at room temperature until evolution of hydrogen ceased. 1-Bromo-4-acetoxynonane (21.2 g, 80 mmol) was added and the reaction mixture was heated on the steam bath for 20 h. The cooled mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and distilled. Short-path distillation gave 11.6 g (52%) of **4**, bp 182–185 °C (0.1 mm). Anal. ($C_{12}H_{25}NO_4S$) C, H, N.

(b) 4-[*N*-(4-Acetoxynonyl)methanesulfonamido]butoxyacetate (5a). Compound 4 (6.0 g, 21.5 mmol) was added to a stirred suspension of NaH (0.57 g, 23.6 mmol) in DMF (50 mL) and benzene (25 mL) over 30 min. When the evolution of hydrogen ceased, ethyl 4-bromobutoxyacetate[9] (6.7 g, 28 mmol) was added and the mixture was heated on the steam bath for 20 h. The cooled reaction mixture was diluted with water and extracted with ethyl acetate; the organic phase was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The resulting oil was chromatographed over silica gel using $CHCl_3$ to elute the product. There was obtained 6.3 g (67%) of **5a** as a viscous oil. Anal. ($C_{20}H_{39}NO_7S$) C, H, N.

(c) 4-[*N*-(4-Hydroxynonyl)methanesulfonamido]butoxyacetic Acid (6a). Saponification of acetoxy ester **5a** was carried out by the procedure described for **2a**. There was obtained a 70% yield of **6a** as a viscous oil. Anal. ($C_{16}H_{33}NO_6S$) C, H, N.

7-[*N*-(4-Hydroxynonyl)methanesulfonamido]hept-5-ynoic Acid (6b). (a) Methyl 7-[*N*-(4-Acetoxynonyl)methanesulfonamido]hept-5-ynoate (5b). Using the procedure described for **5a**, compound 4 was allowed to react with methyl 7-chloro-5-heptynoate to give **5d** in 90% yield. The compound was an oil. Anal. ($C_{20}H_{36}NO_6S$) C, H, N.

(b) 7-[*N*-(4-Hydroxynonyl)methanesulfonamido]hept-5-ynoic Acid (6b). Saponification was carried out as described for **2a** to give a 90% yield of **6b**. The compound was an oil. Anal. ($C_{17}H_{31}NO_5S$) C, H; N: calcd, 3.87; found, 3.36.

7-[*N*-(4-Hydroxynonyl)methanesulfonamido]-*cis*-hept-5-enoic Acid (6c). An ethyl acetate (75 mL) solution of **6b** (3.6 g, 10 mmol) was hydrogenated at atmospheric pressure using a Lindlar catalyst. When the correct amount of hydrogen was absorbed, **6c** was isolated by filtration and evaporation of the solvent. The yield was 3.55 g (98%) of a viscous oil: NMR 0.90 (3 H, m, CH_3CH_2–), 2.85 (3 H, s, CH_3SO_2–), 5.55 (2 H, m, cis –HC=CH–). Anal. ($C_{17}H_{33}NO_5S$) C, H, N.

7-[*N*-(4-Hydroxy-2-*trans*-nonenyl)methanesulfonamido]-5-*cis*-heptenoic Acid Hydrate (11). (a) *N*-(2,2-Diethoxyethane)methanesulfonamide (7). Methanesulfonyl chloride (11.4 g, 100 mmol) was added dropwise to a stirred solution of 2,2-diethoxyethylamine (13.3 g, 100 mmol) and triethylamine (10.1 g, 100 mmol) in benzene (100 mL) and the resulting mixture was let stand for 20 h. The mixture was filtered and the filtrate was concentrated in vacuo. The resulting oil was purified by column chromatography over silica gel using ethyl acetate–hexane (1:1) for elution. There was obtained 15.3 g (72%) of **7** as a clear oil. Anal. ($C_7H_{17}NO_4S$) C, H, N.

(b) Ethyl 7-[*N*-(2,2-Diethoxyethyl)methanesulfonamido]hept-5-ynoate Hemihydrate (8). Compound 7 (2.1 g, 10 mmol), ethyl 7-bromo-5-heptynoate[7] (2.3 g, 10 mmol), and potassium carbonate (1.5 g, 11 mmol) were combined in DMF (10 mL) and stirred at room temperature for 4 h. This mixture was added to water (100 mL), acidified (dilute HCl), and extracted with ethyl acetate (2 × 75 mL). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by column chromatography over silica gel using ethyl acetate–hexane (3:7) to elute. There was obtained 2.0 g (55%) of **8** as a clear oil. Anal. ($C_{16}H_{29}NO_6S\cdot0.5H_2O$) C, H, N.

(c) Ethyl 7-[*N*-(Formylmethyl)methanesulfonamido]hept-5-ynoate (9). A solution of **8** (15 g), water (10 mL), and concentrated sulfuric acid (2 mL) in dimethoxyethane (100 mL) was heated at reflux for 2 h. The cooled solution was poured into half-saturated NaCl and the oil that separated was extracted into ether. The ether layer was dried (Na_2SO_4) and then concentrated to an oil which was purified by chromatography on silica gel using ethyl acetate–hexane (4:1) to elute. There was obtained 7.3 g (61%) of **9** as a heavy oil, which tended to darken if kept for very long. Anal. ($C_{12}H_{19}NO_5S$) C, H, N.

(d) Ethyl 7-[*N*-(4-Hydroxy-2-*trans*-nonenyl)methanesulfonamido]hept-5-ynoate (10). Dimethyl (2-oxoheptyl)-

phosphonate (2.2 g, 10 mmol) was added dropwise to a stirred suspension of NaH (240 mg, 10 mmol) in dry dimethoxyethane (15 mL). In a few minutes the entire reaction mixture solidified. After 0.5 h **9** (2.8 g, 10 mmol) in dimethoxyethane (5 mL) was added in one portion. The reaction mixture became stirrable although a precipitate was present. After 20 h the reaction mixture was poured into water (150 mL), acidified, and extracted with ethyl acetate (2 × 75 mL). The organic phase was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The resulting oil was dissolved in EtOH (15 mL) and cooled in an ice bath and sodium borohydride (380 mg, excess) was added in small portions. After 1.5 h the reaction mixture was poured into water (150 mL), carefully acidified (dilute HCl), and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification was effected by chromatography on silica gel using ethyl acetate–hexane (3:2) to elute. There was obtained 1.6 g (41%) of **10** as a clear oil: NMR δ 0.90 (3 H, m, CH_3CH_2–), 2.85 (3 H, s, CH_3SO_2–), 5.8 (2 H, m, trans –HC=CH–). Anal. ($C_{19}H_{33}NO_5S$) H, N; C: calcd, 58.88; found, 59.49.

(e) 7-[*N*-(4-Hydroxy-2-*trans*-nonenyl)methanesulfonamido]-5-*cis*-heptenoic Acid Hydrate (11). Compound 10 (1.5 g, 3.8 mmol) was saponified by the method described for **2a**. The acid thus obtained was hydrogenated by the procedure described for **6d**. Thus there was obtained 1.2 g (85%) of **11** as a pale yellow oil: NMR δ 0.90 (3 H, m, CH_3CH_2–), 2.85 (3 H, s, CH_3SO_2–), 5.5 (2 H, m, cis –HC=CH–), 5.8 (2 H, m, trans –HC=CH–). Anal. ($C_{17}H_{31}NO_5S{\cdot}H_2O$) C, H, N.

Mouse Ovary Prostaglandin Assay.[4] Virgin female mice over 70 days old (Charles River CD-1) were killed and the ovaries dissected and denuded of adhering fatty tissue. Three ovaries were weighed (15–25 mg) and placed in 2 mL of aerated Krebs–Ringer phosphate buffer, pH 7.2, containing 1 μCi of adenine-*8-^{14}C*. The tissues were incubated 1 h at 37 °C with moderate shaking to cause a pool of intracellular ATP-^{14}C to accumulate.

The following additions were then made: 0.2 mL of 0.05 M theophylline in 0.15 M NaCl and the test compound in 0.1 mL of Me_2SO. The ovaries were again incubated at 37 °C for 30 min. The reactions were terminated by the addition of 0.4 mL of 10% trichloroacetic acid, and 50 μL of a nucleotide mixture solution[10] was added to facilitate recovery of the labeled nucleotides. The incubation mixture was transferred to a glass homogenizer and the ovarian tissue was homogenized into the acidified incubation solution. The homogenate was centrifuged 1000g for 5 min and the cAMP-^{14}C was isolated from the supernatant fluid as described by Humes and co-workers[10] including the final paper chromatography step.

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Synthesis and Antimineralocorticoid Activities of Some 6-Substituted 7α-Carboalkoxy Steroidal Spirolactones

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Several analogues of the previously reported steroidal spirolactone 1a were synthesized. These analogues bear C-6 substituents and include the 6β-deuterio (**1c**), the 6β-bromo (**1d**), the 6β-methyl (**1e**), and the 6α-methyl (**7**) compounds. The 6β-hydroxy compound **1b**, a human and animal metabolite of **1a**, was also synthesized. On subcutaneous administration to adrenalectomized rats, all these compounds exhibited the ability to block the effects of administered deoxycorticosterone acetate (DCA) (MED ≤ 0.58 mg). Only **7** failed to show anti-DCA effects at the standard test level on oral administration. None was significantly superior in potency to the parent compound **1a**.

An earlier report[1] described the synthesis and antimineralocorticoid potency of **1a**, a steroidal spirolactone substituted in the 7α position with a carbomethoxy function. During the course of supplemental biological studies on **1a**, administered intragastrically as its potassium salt **2**, metabolism studies revealed that a principal biotransformation product in both animals and man was the 6β-hydroxy compound **1b**.[2] This communication describes the chemical synthesis and antimineralocorticoid potencies of both metabolite **1b** and of other compounds designed to determine the effects on potency of substitution in both 6α and 6β positions. These compounds include the 6β-deuterio (**1c**), the 6β-bromo (**1d**), the 6β-methyl (**1e**), and the 6α-methyl (**7**) derivatives. One other hydroxylated compound was also synthesized, namely **1g**, the 6β-hydroxy derivative of the corresponding C-7 isopropyl ester **1f**.

Synthesis. All target compounds were prepared through the intermediacy of either the enol ethers **3a** and **3c** or the enol acetate **3b**. These compounds reacted as typical 3,5-dien-3-ol systems and underwent substitution at C-6 when treated with appropriate electrophilic reagents.[3] Both **3a** and **3c** were prepared according to conventional procedures[4] by treatment of **1a** and **1f** with triethyl orthoformate in EtOH in the presence of *p*-TsOH at room temperature. Compound **3b** was prepared by