2 (15.9 g, 0.1 mol) in 80 ml of tetralin with 21.8 g (0.1 mol) of diphenyl disulfide at 200° with stirring. The thiophenol formed during the reaction was continuously allowed to distill over. After the reaction was complete (about 4 h), tetralin was removed by distillation using a water aspirator. The remaining oil, **3**, was then distilled, bp 78–82° (0.05 mm), to yield 13.8 g (89%).

1,4-Dimethyl-5-nitroisoquinoline (4). A solution of 10.1 g (0.1 mol) of potassium nitrate in 50 ml of concentrated H_2SO_4 was added slowly from a dropping funnel to a solution of 15.7 g (0.1 mol) of **3** in 60 ml of concentrated H_2SO_4 kept at 0°. After the addition, the mixture was heated at 60° for 2 h and then poured slowly over crushed ice. The solution was made alkaline with NH_4OH; the resulting yellow precipitate was filtered, washed with water, dried, and crystallized from ethanol to yield 15.6 g (77%), mp 150–151°. Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

4-Methyl-5-nitroisoquinoline-1-carboxaldehyde (5). A solution of 10.1 g (0.05 mol) of **4** in 200 ml of dioxane was treated with 5.55 g (0.05 mol) of selenium dioxide (freshly resublimed) and the mixture was refluxed for 3 h. The precipitated selenium was removed by filtration, and the filtrate was flash evaporated. The residue was dissolved in dilute HCl and filtered, the filtrate was brought to pH 1.5 with solid $NaHCO_3$, and the mixture was again filtered through Celite. The clear solution was then alkalinized with a solution of Na_2CO_3. The precipitate was filtered, washed with water, dried, and crystallized from benzene and cyclohexane to yield 7.6 g (71%), mp 141–143°. Anal. ($C_{11}H_8N_2O_3$) C, H, N.

4-Methyl-5-nitro-1-formylisoquinoline Ethylene Acetal (6). To 10.8 g (0.05 mol) of **5** in 300 ml of benzene was added 0.5 g of *p*-toluenesulfonic acid and 10 ml of ethylene glycol. The mixture was refluxed with stirring for 24 h using a Dean-Stark trap to remove the water formed during condensation. The mixture was then washed with 25 ml of 10% $NaHCO_3$ solution followed by 25 ml of water. The benzene layer was dried ($MgSO_4$) and removed under vacuum, and the residue was recrystallized from ethanol to yield 10.3 g (87%), mp 114–115°. Anal. ($C_{13}H_{12}N_2O_4$) C, H, N.

4-Methyl-5-amino-1-formylisoquinoline Ethylene Acetal (7). Compound **6** (6.4 g, 0.025 mol) was dissolved in 250 ml of ethanol and 0.65 g of Pd/C (10%) was added. The mixture was hydrogenated at 50 psi for 1 h and then filtered to remove the catalyst. The ethanol was removed under vacuum and the residue was recrystallized from benzene to yield 4.6 g of **7** (80%), mp 130–131°. Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

4-Methyl-5-amino-1-formylisoquinoline Thiosemicarbazone (8). To 2.3 g (0.01 mol) of **7** in 50 ml of ethanol was added 5 ml of concentrated HCl and 0.91 g (0.01 mol) of thiosemicarbazide. The mixture was refluxed for 1.5 h; the precipitate of the hydrochloride salt of the desired compound was collected by filtration, washed with ethanol, and dried. The hydrochloride salt was then dissolved in 500 ml of boiling water and filtered into a flask containing 50 ml of 10% Na_2CO_3 solution. The yellow precipitate which formed was filtered, washed with water and ethanol, and dried to yield 2.2 g (81%), mp 216–218° dec. Anal. ($C_{12}H_{13}N_5S$) C, H, N.

4-Methyl-5-nitro-1-formylisoquinoline Thiosemicarbazone (9). To 1.08 g (0.05 mol) of compound **5** in 20 ml of ethanol was added a solution of 0.46 g (0.05 mol) of thiosemicarbazide dissolved in 10 ml of H_2O. The resulting solution was heated for 5 min and then cooled. The yellow precipitate was filtered, washed with water and ethanol, and then dried to yield 1.2 g (83%), mp 233–234° dec. Anal. ($C_{12}H_{11}N_5O_2S$) C, H, N.

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(Vinylaryloxy)acetic Acids. A New Class of Diuretic Agents. 4. Various [(2-Substituted and 2,2-disubstituted vinyl)aryloxy]acetic Acids

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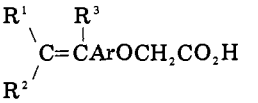
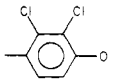
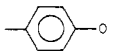
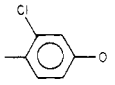
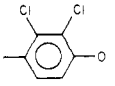
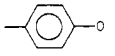
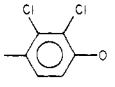
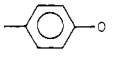
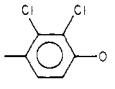
A variety of [(2-substituted and 2,2-disubstituted vinyl)aryloxy]acetic acids was synthesized in which the substituents were primarily electron-withdrawing groups. These compounds were tested in dogs for their saluretic and diuretic properties. Many of the compounds exhibited significant activity; however, they were generally less potent than those reported in the three earlier papers in this series.

The three earlier papers in this series disclosed 2,2-diacylvinyl- (**1a**),[1] 2-acylvinyl- (**1b**),[2] and 2-nitrovinyl- (**1c**)[3] substituted aryloxyacetic acids, many of which possess a high order of saluretic and diuretic activity. These studies prompted the extension of the investigation to include other [(2-substituted and 2,2-disubstituted vinyl)aryloxy]acetic acids, in which the substituents are electron-withdrawing groups such as carboxy, carbethoxy, carbamoyl, cyano, sulfamoyl, and alkylsulfonyl.

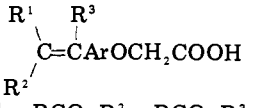
Chemistry. The [(2,2-disubstituted vinyl)aryloxy]acetic acids presented in Table I were generally prepared by the process outlined below involving the ammonium acetate or piperidine acetate catalyzed Knoevenagel condensation of ethyl formylaryloxyacetates (**2a**) or their corresponding

Table I. [(2,2-Disubstituted vinyl)aryloxy]acetic Acids



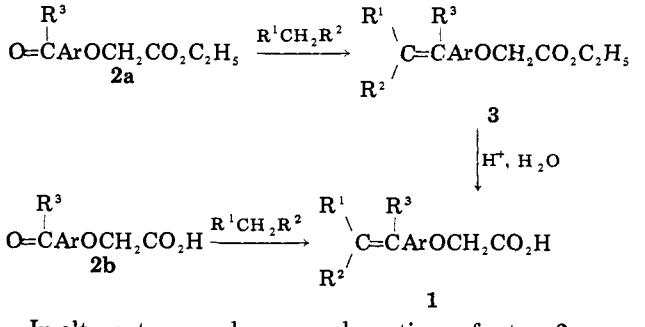
No.	ArO	R^3	R^1	R^2	Mp, °C	Recrystn solvent	Synthetic method	% yield	Formula	Analyses[a]
4		H	H	H	182-184	BuCl	C-4	12	$C_{10}H_8Cl_2O_3$	C, H, Cl
5		H	CN	CN	171-172	CH_3CN	A	97	$C_{12}H_8N_2O_3$	C, H, N
6		H	CN	CN	173-174	AcOH	A	100	$C_{12}H_7ClN_2O_3$	C, H, N
7		H	CN	CN	178-179	AcOH	A	95	$C_{12}H_6Cl_2N_2O_3$	C, H, N
8		CH_3	CN	CN	164-165	AcOH-H_2O	A	67	$C_{13}H_8Cl_2N_2O_3$	C, H, N
9		H	CN	$CONH_2$	263.5	AcOH	A	100	$C_{12}H_8Cl_2N_2O_4$	C, H, N
10		H	CN	$CO_2C_2H_5$	179-180	CH_3CN	A	98	$C_{14}H_{13}NO_5$	C, H, N
11		H	CN	CO_2H	262-263	EtOH	C-1	70	$C_{12}H_7Cl_2NO_5$	C, H, N
12		H	CN	SO_2NH_2	232-235	AcOH	A	62	$C_{11}H_8ClN_2O_5S$	C, H, N
13		H	$CONH_2$	$CONH_2$	270 dec	AcOH	A	54	$C_{12}H_{10}Cl_2N_2O_5$	C, H, N
14		H	$CO_2C_2H_5$	$CO_2C_2H_5$	94-97	BuCl	A	66.5	$C_{16}H_{18}O_7$	C, H
15		H	$CO_2C_2H_5$	$CO_2C_2H_5$	127-130	BuCl	A	52	$C_{16}H_{16}Cl_2O_7$	C, H, Cl
16		H	CH_3SO_2	CH_3SO_2	217-219	EtOAc-hexane	B	50	$C_{12}H_{12}Cl_2O_7S$	C, H, S
17		H	CH_3CO	$C_6H_5SO_2$	200-201	EtOAc-hexane	B	61	$C_{18}H_{14}Cl_2O_6S$	C, H, S
18		H	$C_6H_5O_2C$	$C_6H_5O_3S$	178-180	CH_3NO_2	A	46	$C_{23}H_{16}Cl_2O_8S$	C, H, Cl
19		H			225	EtOH	C-2	13	$C_{16}H_{15}Cl_2NO_4$	C, H, N
20		H	H	CN	157-158	C_6H_6	C-3	48	$C_{11}H_7Cl_2NO_3$	*b*

[a] Compounds were analyzed for the elements indicated and were within ±0.4% of calculated values. [b] C: calcd, 48.56; found, 49.13. H: calcd, 2.59; found, 2.73. N: calcd, 5.15; found, 5.04.



1a, R^1 = RCO; R^2 = RCO; R^3 = H
b, R^1 = RCO; R^2 = R; R^3 = H
c, R^1 = NO_2; R^2 = R; R^3 = H

carboxylic acids (**2b**) with activated methylene compounds. The esters (**3**) were hydrolyzed under aqueous acidic conditions.



In alternate procedures, condensations of esters **2a** were catalyzed by aqueous NaOH (with cyanoacetic acid) or NaOEt (with 3-quinuclidinone). The Wittig reaction of ethyl (2,3-dichloro-4-formylphenoxy)acetate with triphenylcyanomethylenephosphorane led to **20**.

Structure–Activity Relationships. Compounds **4–20** were evaluated in dogs for their saluretic and diuretic properties. The results obtained on intravenous administration are seen in Table II.

The importance of nuclear substituents on structure **1** is seen in compounds **5**, **10**, and **14**, which lack nuclear halogen and, like analogous compounds in the ethacrynic acid series, possess little activity. Introduction of a 3-chloro substituent has little effect (compare compound **5** with **6**). However, introduction of a chloro substituent in both the 2 and 3 positions produces a marked increase in activity; compound **7** is much more active than **5** and **6**.

The nature of the electron-withdrawing groups on the terminal vinyl carbon atom (i.e., R^1 and R^2) is most important. When R^1 and R^2 are H (**4**) little activity is seen. Introduction of cyano at R^1 makes a dramatic increase in activity (**20**), and the effect is even greater when R^1 and R^2 are both cyano (**7**). The compound where R^1 is cyano but R^2 is carbamoyl (**9**) is weaker than **7**, and the one where R^2 is carboxy (**11**) is much weaker.

Table II. Intravenous Activity in Dogs

Compd	Dose,[a] mg/kg	μequiv/min excreted[b] (control period/drug period) Na+	K+	Cl-	Urine vol,[b] ml/min, control/drug
4	10	21/34	10/29	3/2	1/1
5	10	3/64	17/10	12/45	2/2
6	10	5/14	32/34	3/14	5/2
7	10	31/736	24/100	3/665	2/5
8	10	21/123	23/38	10/125	3/2
9	10	42/180	20/35	13/88	3/4
10	25	35/79	36/43	8/16	1/1
	10	10/25	26/29	12/25	2/2
11	10	13/38	28/32	10/29	1/1
13	10	6/195	27/86	1/145	1/3
14	25	14/44	16/45	9/20	1/1
15	5	16/313	39/113	8/261	1/4
	1	17/200	42/54	0/198	2/2
16	25	25/31	44/48	30/34	4/3
17	10	44/183	33/58	16/166	1/3
19	10	31/172	11/70	1/115	3/4
20	10	23/448	30/59	9/484	3/6

[a] The compounds were administered as Na salts in H_2O. [b] The procedure is described in ref 1. Control values are averages of data from two 15-min clearance periods prior to dosage. Response values are averages of data from two consecutive 15-min periods during which Na^+ excretion was maximal; these periods usually occurred between 15 and 45 min after dosage. Changes in glomerular filtration rate during these experiments were minimal and did not show consistent trends. The data are selected from single representative experiments performed on three or four dogs.

The compounds where R^1 and R^2 are both carbamoyl (**13**) or ethoxycarbonyl (**15**) exhibit modest activity. Other combinations of R^1 and R^2, i.e., compounds **16** and **17**, are less potent. Interestingly, the cyclic structure **19** is quite active.

Only one compound was prepared where R^3 was not H; this compound (**8**) where $R^3 = CH_3$ was considerably weaker than the analogous compound where $R^3 = H$ (**7**).

Compounds **12**, **18**, and **20** were evaluated for their oral diuretic and saluretic effects in dogs and the results are presented in Table III. Compounds **12** and **18**, which represent further combinations of R^1 and R^2 substituents, could not be tested intravenously due to lack of solubility. In the oral protocol these compounds exhibited weak but real activity. Compound **20**, one of the most active ones in the intravenous assay, was quite diuretic and saluretic at 5 mg/kg. (This effect is equivalent to that produced by ethacrynic acid at a dose between 0.3 and 1 mg/kg.)

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, the analytical results for these elements are within 0.4% of theoretical values. The following synthetic intermediates were prepared as described in the cited references: cyanomethanesulfonamide,[4] bis(methylsulfonylmethane),[5] diphenyl sulfoacetate.[4]

General Procedures for the Preparation of 4-[(Disubstituted vinyl)phenoxy]acetic Acids (Table I). Method A. A 100-ml flask fitted with a Dean-Stark constant water separator was charged with the 4-formyl- (or 4-acetyl-) phenoxyacetic acid[1,2] (0.02 mol), the desired malonic acid derivative (0.024 mol), acetic acid (10 ml), toluene or benzene (50 ml), and NH_4OAc (100 mg). The mixture was refluxed for 2 h during which time the requisite amount of H_2O separated. The reaction mixture was cooled; the product was filtered and then recrystallized from the appropriate solvent. Compounds **4–7**, **12–15**, and **18** were prepared by this method.

Method B. A 100-ml flask fitted with a Dean-Stark constant water separator was charged with ethyl (2,3-dichloro-4-formylphenoxy)acetate (0.01 mol), the desired malonic acid derivative (0.01 mol), toluene (50 ml), and piperidine acetate (100 mg). The mixture was refluxed for 2–3 h until the requisite amount of H_2O had been collected in the trap. Upon cooling, the ester was collected and hydrolyzed in a mixture of AcOH (15 ml) and 5% aqueous HCl (7 ml) heated on a steam bath for 1 h. Upon dilution with H_2O (25 ml) the product separated and was then recrystallized from the appropriate solvent. Compounds **16** and **17** were prepared by this method.

Table III. Oral Activity in Dogs[a]

Compd	Dose, mg/kg	No. of dogs	Av equiv/6 h excreted Na+	K+	Cl-	Av urine vol, ml/6 h
12	10	6	6	4	6	276
18	10	6	6	2	6	363
20	5	4	12	4	17	588
Ethacrynic	1	10	21	5	26	560
acid	0.3	12	8	2	10	459
Placebo		35	2	1	2	180

[a] Oral tests were carried out on a colony of trained female mongrel dogs weighing 8–10 kg. All dogs received 100 ml of water the previous day and were fasted overnight. On the day of the test, 250 ml of water was administered orally, followed by 500 ml of water (orally) 1 h later. One hour after the last oral priming dose of water, bladders were emptied by catheterization and the study was commenced by administration of compound or placebo. Compounds were given in gelatin capsules and the animals were maintained in metabolism cages for collection of spontaneously voided urine. Spontaneous urine was combined with bladder urine collected by catheterization at the end of 6 h. Urine volumes were measured, and aliquots were analyzed for sodium, potassium, and chloride content by standard methodology. Values are reported as geometric means.

Miscellaneous Methods (C). Each of the following procedures was specifically directed toward the synthesis of one compound.

C-1. (2,3-Dichloro-α-cyano-4-carboxymethoxy)cinnamic Acid (11). A solution of cyanoacetic acid (1.52 g, 0.01 mol) in H_2O (20 ml) was neutralized with 5% NaOH and then added to a vigorously stirred solution of ethyl (2,3-dichloro-4-formylphenoxy)acetate (2.77 g, 0.01 mol) in a warm mixture of EtOH (100 ml) and H_2O (20 ml). A solution of 5% aqueous NaOH was added to the reaction mixture and stirring was continued for 5 min. Then the reaction was acidified with HCl and cooled in an ice bath to yield **11** which was recrystallized to constant melting point. Anal. ($C_{14}H_{11}Cl_2NO_5$) C, H, N.

C-2. 2-(2,3-Dichloro-4-carboxymethoxy)benzylidene-3-quinuclidinone (19). To a solution of NaOEt prepared from sodium (910 mg, 0.04 g-atom) in EtOH (35 ml) was added 3-quinuclidinone (4.8 g, 0.038 mol) and ethyl (2,3-dichloro-4-formylphenoxy)acetate (8.3 g, 0.03 mol). The reaction was refluxed for 1 h and treated with H_2O (200 ml) and 5% NaOH (50 ml). After an additional hour at reflux, the EtOH was distilled at reduced pressure and the reaction was acidified with AcOH. The product was collected and recrystallized. Anal. ($C_{16}H_{15}Cl_2NO_4$) C, H, N.

C-3. [2,3-Dichloro-4-(2-cyanovinyl)phenoxy]acetic Acid (20). A mixture of ethyl (2,3-dichloro-4-formylphenoxy)acetate (5.54 g, 0.02 mol) and triphenylcyanomethylenephosphorane (6.02 g, 0.02 mol) in C_6H_6 was refluxed in a nitrogen atmosphere for 5 h. The C_6H_6 was distilled at reduced pressure and the residue was extracted with boiling hexane (2 × 250 ml) which upon cooling deposited the ester as white crystals. Hydrolysis was effected in 50% H_2O–EtOH (400 ml) with $NaHCO_3$ (3.4 g) at reflux for 1 h. The sodium salt was collected and dissolved in hot H_2O (200 ml) and the resulting solution acidified with HCl. The product was recrystallized to constant melting point. Anal. ($C_{11}H_7Cl_2NO_3$) H, Cl; C: calcd, 48.56; found, 49,13.

C-4. (2,3-Dichloro-4-vinylphenoxy)acetic Acid (4). Step A. 2,3-Dichloro-4-acetylphenol. A stirred solution of 2,3-dichloroanisole (71 g, 0.40 mol) and AcCl (48 g, 0.60 mol) in CH_2Cl_2 (300 ml) was cooled to 5 °C and treated with $AlCl_3$ (80 g, 0.60 mol) in portions over a 0.5-h period. The reaction mixture was

stirred at 5 °C for 2 h; then the CH_2Cl_2 and two additional 175-ml charges of CH_2Cl_2 were distilled from the reaction. $AlCl_3$ (80 g, 0.60 mol) and CH_2Cl_2 (200 ml) were added to the reaction which was warmed slowly to reflux, refluxed for 2.5 h, then quenched in ice (600 g) and concentrated HCl (75 ml), extracted with Et_2O (800 ml), washed with H_2O, back extracted into 5% NaOH (3 × 100 ml), and acidified with HCl. The product was filtered, rinsed with water, dried, and used in step B without further purification.

Step B. (2,3-Dichloro-4-acetylphenoxy)acetic Acid. In an N_2 atmosphere Na (3.79 g, 0.165 g-atom) was dissolved in EtOH (450 ml). 2,3-Dichloro-4-acetylphenol (30.75 g, 0.15 mol) and ethyl bromoacetate (30.06 g, 0.18 mol) were added; the reaction was refluxed for 2 h, heated with 5% KOH (350 ml), and refluxed an additional hour, and the EtOH was distilled. The aqueous solution was acidified with HCl, extracted into Et_2O (4 × 300 ml), and dried (Na_2SO_4), and the Et_2O was evaporated to dryness. Recrystallization from xylene (500 ml) gave 32.2 g (85%) of the product: mp 154–156 °C. Anal. ($C_{10}H_8Cl_2O_4$) C, H, Cl.

Step C. [2,3-Dichloro-4-(1-hydroxyethyl)phenoxy]acetic Acid. To a stirred, ice-cooled suspension of (2,3-dichloro-4-acetylphenoxy)acetic acid (10.5 g, 0.04 mol) in H_2O (350 ml) was added a solution of KBH_4 (4.0 g, 0.074 mol) in H_2O (200 ml) over a period of 1 h. The reaction mixture was acidified with HCl and the product was collected and recrystallized: mp 145–147° (from H_2O). Anal. ($C_{10}H_{10}Cl_2O_4$) C, H, Cl.

Step D. Compound 4. Absolute EtOH (4.6 g) in a round-bottomed flask was cooled in a dry ice bath and then treated with P_2O_5 (5.7 g). The flask was warmed slightly and [2,3-dichloro-4-(1-hydroxyethyl)phenoxy]acetic acid (5.3 g) was added. The reaction mixture was heated 3 h on a steam bath and treated with ice water, the product was extracted into Et_2O and dried over $MgSO_4$, and the solvent was evaporated. The residue was purified by recrystallization. Anal. ($C_{10}H_8Cl_2O_3$) C, H, Cl.

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Synthesis and Antimineralocorticoid Activities of Some 7α-Cyano and 7α-Alkoxycarbonylamino Steroidal Spirolactones

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The synthesis and antimineralocorticoid potencies of several steroidal spirolactones bearing novel nitrogenous substituents in the 7α position are reported. These substituents include the cyano, the isocyanato, and the alkoxycarbonylamino groupings. The nitrile **1b** and the *N*-carbomethoxy compound **1h** showed good antimineralocorticoid potency (MED ≤ 0.79 mg) on subcutaneous administration to adrenalectomized rats.

We have recently reported[1] that substitution of a carboalkoxy function in the 7α position of the steroidal spirolactone (e.g., **1a**) yielded a series of compounds possessing strong antimineralocorticoid potency on both subcutaneous and oral administration to adrenalectomized rats. This finding prompted us to survey the effects on potency brought about by other types of functionality in this position. This communication describes the synthesis and antimineralocorticoid potencies of those structures bearing the cyano, the isocyanato, and the alkoxycarbonylamino groups in this 7α position. Although our earlier publication reported only esters at this position, the substituents reported herein are all nitrogen bearing. In addition, the isocyanato and the cyano groups have a linear geometry and, thus, depart quite drastically from the branched-type substituents heretofore described.

Synthesis. Dienones **2a** and **2b**[2] served as convenient starting materials for the synthesis of the 7α-cyano compounds in the normal and 19-nor series, respectively. Michael addition to this system was effected by treating these steroids with 1 equiv of KCN in the presence of 1 equiv of HOAc in aqueous 98% Me_2SO on the steam bath. This reaction was run in a pressure bottle to prevent the escape of any HCN generated during the course of the reaction. Although this procedure gave only modest to poor yields of **1b** (38%) and **1c** (17%), the use of only 1 equiv of KCN effectively suppressed the formation of any bis adduct previously noted in this type of system.[1,3] A minimum amount of H_2O and only 1 equiv of HOAc were employed to minimize the possibility of any hydrolysis of the nitrile group during the reaction.[4]

The stereochemistry of the cyano group in **1b** was determined by its NMR and CD spectra according to the methods described earlier.[1] The NMR spectrum shows the equatorial proton on C-7 as a complex multiplet centered at about 3.03 ppm. This represents a shift of approximately 0.2 ppm downfield from the chemical shift of the C-7 proton in the 7α-carboalkoxy series but such a shift is not unreasonable because of the greater electronegativity of –CN relative to $-CO_2R$.[5] Were this proton in an axial position as in the epimeric 7β-cyano compound, the C-7 proton would be expected to appear at higher field.[6]

The CD spectrum of **1b** showed it to have a molecular ellipticity (θ) of −2389°. Like **1a**, this value is considerably more positive than θ for **1d** (−4110°)[1] and, therefore, according to the octant rule, the stereochemistry of this substituent is clearly α.[7]

Two derivatives of **1b** were also synthesized. The C-1 unsaturated nitrile **4** was prepared by treatment of **1b** with dichlorodicyanobenzoquinone in refluxing benzene. For purposes of oral administration, the water-soluble potassium salt of the γ-hydroxy acid corresponding to **1b** was also prepared (**3**).

The isocyanate **1g** was synthesized from the previously reported mixed anhydride **1e**[1] by treatment of this