was filtered, and the filtrate was evaporated to an oil, which was purified by thin-layer chromatography (silica gel, 150 g, eluent: ethyl acetate). The material (**31**) was obtained (7 mg) was crystallized from methylene chloride–ether: mp 139–140 °C (lit.[15] mp 140–141 °C); CIMS, m/e 278 ($M^+ + 1$).

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Registry No. **5**, 632-20-2; **6**, 79006-99-8; **7**, 82679-67-2; **8**, 82679-57-0; **9**, 79006-98-7; **13a**, 82730-04-9; **13b**, 82730-05-0; **14a**, 82679-56-9; **14b**, 82730-06-1; **15a**, 82679-60-5; **15b**, 82730-07-2; **17**, 82730-08-3; **18**, 82679-62-7; **19**, 82679-61-6; **20**, 82730-10-7; **21** (isomer 1), 82730-13-0; **21** (isomer 2), 82730-14-1; **21** (amino derivative isomer 1), 82730-11-8; **21** (amino derivative isomer 2), 82730-12-9; **22**, 78905-28-9; **23**, 80024-26-6; **23** amino derivative, 82730-15-2; **24**, 2104-89-4; **24**·HCl, 5619-04-5; **25**, 82679-63-8; **26** (isomer 1), 82679-64-9; **26** (isomer 2), 82730-16-3; **28**, 82730-17-4; **29**, 82730-18-5; **30**, 82679-65-0; **31**, 82679-66-1; **32**, 82730-09-4; methyl acetoacetate, 105-45-3; *p*-nitrobenzyl bromide, 100-11-8; *p*-nitrobenzyl-D-threonine, 78963-69-6; *trans*-cinnamaldehyde, 14371-10-9; azidoacetyl chloride, 30426-58-5; D-threonine methyl ester, 82679-55-8; benzyl D-threonine-*p*-toluenesulfonate, 82679-59-2; D-threonine benzyl ester, 82679-58-1; phenoxyacetyl chloride, 701-99-5.

Synthesis of Optically Active Spirohydantoins by Asymmetric Induction. Hydantoin Formation from Amino Nitriles and Chlorosulfonyl Isocyanate

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Conversion of 6-chloro- or 6-fluoro-2,3-dihydro-4*H*-1-benzopyran-4-one with optically active (*S*)-α-methylbenzylamine in the presence of $TiCl_4$ to the ketimine followed by treatment in EtOH with HCN gas gives excellent yields of crystalline, enantiomerically pure (4*S*)-4-cyano-2,3-dihydro-6-chloro(or 6-fluoro)-4-[(*S*)-(1-phenylethyl)amino]-4*H*-1-benzopyran. These sterically hindered amino nitriles react smoothly with chlorosulfonyl isocyanate to give, after hydrolysis, the hydantoins (4*S*)-2,3-dihydro-6-chloro(or 6-fluoro)-3′-[(*S*)-1-phenylethyl]spiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione. The α-methylbenzyl groups can be removed by aqueous HBr/acetic acid to give the unprotected spirohydantoins.

Compounds that inhibit the enzyme aldose reductase are of potential value in the therapy of chronic complications of diabetes mellitus because they inhibit the conversion of glucose to sorbitol. Formation of sorbitol, for instance in lens and nerve, is believed to contribute to certain late-stage complications (e.g., cataracts and neuropathy) in diabetics. We have previously reported on potent in vitro and in vivo aldose reductase inhibitory activity is spirohydantoins derived from 1-tetralones, 1-indanones, 4-thiochromanones, and 4-chromanones.[1] In the chroman series the biological activity was found to reside predominantly in the *S* enantiomers, and one of these compounds, (4*S*)-2,3-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (**17a**; CP-45,634; USAN, sorbinil), is currently undergoing clinical evaluation.[1,2] Although this compound has been obtained by resolution of its racemic form with brucine,[3] certain congeners could not be obtained by standard resolution techniques. This prompted us to examine alternative synthetic approaches to these spirohydantoins involving asymmetric induction, and the results of these studies are reported here.

Our initial strategy envisioned as the first step the addition of HCN to an imine prepared from an optically active benzylamine derivative; this was to be followed by hydrolysis and debenzylation of the amino nitrile to the amino acid, in analogy to published asymmetric induction syntheses,[4,5] and conversion to the hydantoin, as shown in Scheme I.

Indeed, treatment of 2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-one[3] (**1**) with (*R*)-(+)-α-methylbenzylamine in the presence of $TiCl_4$[6] gave the imine **2** (attempts to form **2** by using molecular sieves or toluenesulfonic acid in place of $TiCl_4$ were unsatisfactory and led to substantial dimerization of the ketone). Treatment of a solution of **2** in EtOH with HCN precipitated the crystalline and diastereomerically pure 4*R* amino nitrile **3** in very good yield. However, attempted hydrolysis of **3** under acidic conditions[4,5] gave ketone **1** instead of the expected **4**, presumably via a stabilized benzylic carbonium ion intermediate at C-4. Initial attempts to convert **3** into a hydantoin or a potential hydantoin precursor were also unsuccessful: treatment of **3** with $(NH_4)_2CO_3$ in aqueous EtOH[7] at 65 °C caused partial conversion to ketone **1**, as did treatment of **3** with KNCO in glacial AcOH[8] or with NaNCO in trifluoroacetic acid.[9] Similar results were obtained in acylation experiments with **3** and CS_2,[10] phosgene, or methyl or ethyl chloroformate.[11] No reaction occurred between **3** and CO_2[7] or methyl isocyanate. Presumably, steric hindrance around the benzylic amine nitrogen is too severe in all of these cases.

This problem was solved by the use of highly reactive chlorosulfonyl isocyanate,[12] which reacted cleanly with **3** in CH_2Cl_2 to give, after treatment with water, the iminohydantoin **11**. Hydrolysis of **11** with aqueous acid resulted in the hydantoin **12** (Scheme II). Attempts to remove the α-methylbenzyl group from **12** by hydrogenation failed under a variety of conditions, a finding con-

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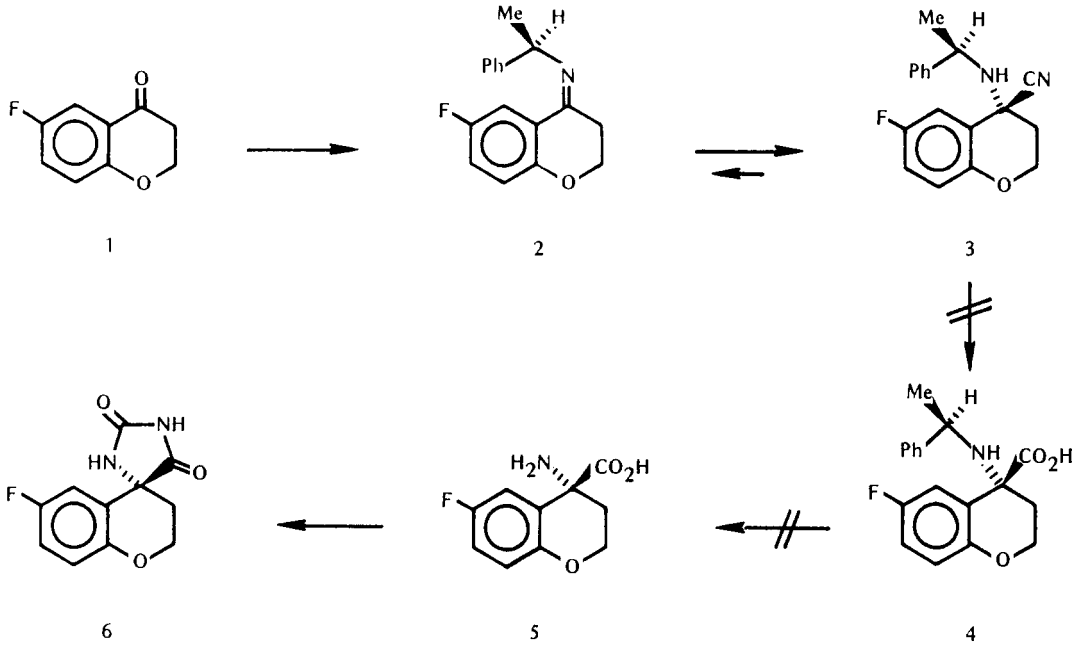
Scheme I



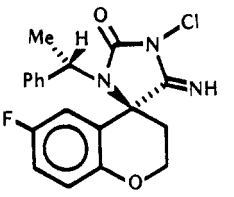
sistent with the known resistance of *N*-benzyl amides toward hydrogenation.[13] Even sodium in liquid ammonia, which had been reported to remove the *N*-benzyl group from a 2-piperidinone derivative,[13] failed to give any trace of the debenzylated hydantoin **6**. However, treatment with 48% aqueous HBr in acetic acid finally succeeded in removing the benzyl group. This reagent, which had been used in the N-debenzylation of urea-type biotin intermediates,[14] gave the target hydantoin **6** in fair yield. Comparison with authentic material[3] established that **6** had the 4*R* configuration.

An analogous reaction sequence starting with (*S*)-(−)-α-methylbenzylamine and **1** led to the desired biologically active 4*S* enantiomer of **6** (**17a**, sorbinil), and use of 6-chloro-2,3-dihydro-4*H*-1-benzopyran-4-one in place of the fluoro compound gave its 6-chloro congener **17b** (Scheme III).

NMR spectra of intermediate **3** showed only a single diastereomer, and the isolated yields of the pure enantiomers[15] after the HCN addition step have been as high as 82%; these results compare favorably with yields of 9–58% and optical purities of 22–58% reported by Harada et al.[5] in the asymmetric synthesis of amino acids by HCN addition to Schiff bases. It is likely that the HCN addition step from **2** to **3** is reversible[16,17] and that the high optical purity of **3** is achieved in our case by allowing the pure enantiomeric adduct (the less soluble diastereomer) to crystallize out of the reaction mixture. Attempts to prove this mechanism by HPLC analysis of the mother liquor of **3** failed due to the chemical instability of **3** under our HPLC conditions.

As an extension of this work, an exploration of the scope of the hydantoin-forming reaction (Scheme IV) was undertaken. Treatment of aminoacetonitrile hydrochloride (**18**) with chlorosulfonyl isocyanate in the presence of triethylamine, followed by hydrolysis, gave the unsubstituted hydantoin **19**, which proved difficult to isolate owing to its water solubility. On the other hand, phenylglycinonitrile (**20**) was readily converted to phenylhydantoin (**22**) in good, isolated yield. Interestingly, the ureido acid **21** was a major byproduct in this reaction presumably from incomplete cyclization.

The isolation of the intermediates **11** and **21** allows speculation concerning the mechanism of the hydantoin-forming reaction. The initial adduct of amino nitrile **3** and chlorosulfonyl isocyanate is presumably **7** (Scheme II),[12] which could hydrolyze to **8**[12] or cyclize to **10**. The intermediate **11**, isolated after hydrolysis of **7**, with water could arise from **8**[18] or **10**, whereas intermediate **9** (analogous to intermediate **21** and not actually isolated in the synthesis of **12**) most likely arises from **8**. Thus, while there are several potential pathways toward hydantoin **12**, it is likely that **7** and **8** are intermediates. On one occasion we isolated a product which has been assigned the *N*-chlorohydantoinimine structure **23**. This compound, which precipitated when the enantiomer of intermediate **7** was heated immediately with aqueous HCl, could be formed by loss of SO_2 from a precursor such as **10**. Further treatment of **23** with aqueous HCl led to formation of the enantiomer of hydantoin **12**.



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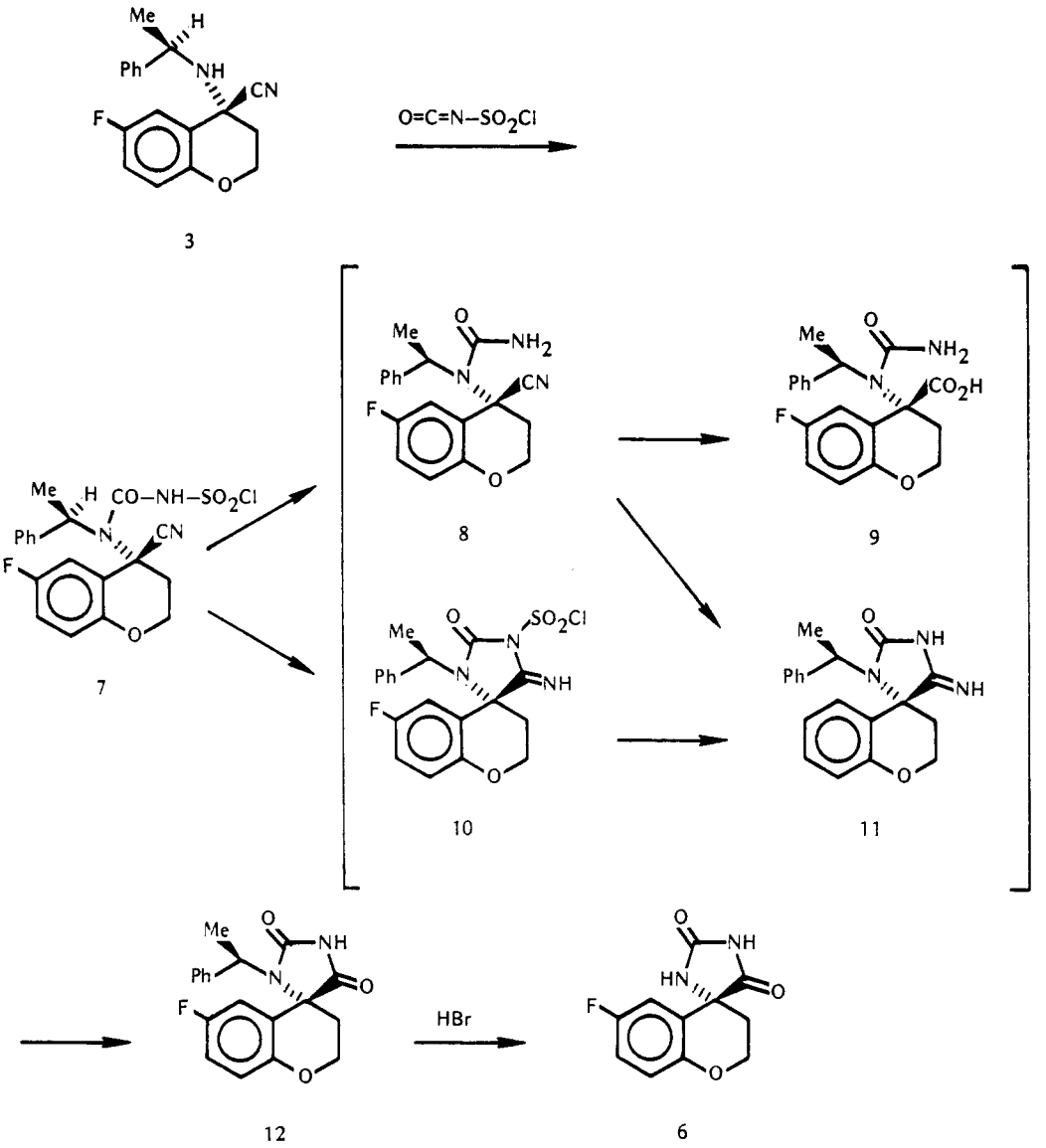
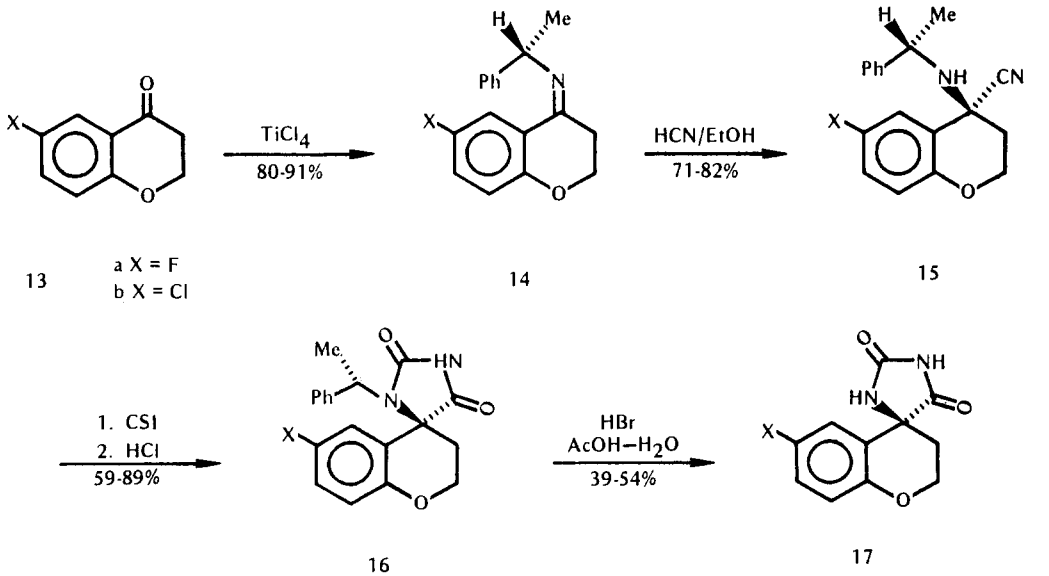
In summary, our studies indicate that chlorosulfonyl isocyanate is a uniquely useful reagent for the formation of hydantoins from sterically hindered acid- and base-labile

(13) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.*, **6**, 587 (1958).
(14) M. W. Goldberg and L. H. Sternbach, U.S. Patent 2 489 238.
(15) Attempts to establish the enantiomeric purity of **3** with the use of chiral shift reagents were unsuccessful; reagents such as tris [3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium(III) failed to cause line shifts, presumably due to extreme steric hindrance around the amine nitrogen. However, the physical characteristics of **3**, **15a**, and **15b** and of their subsequent reaction products gave no indication of enantiomeric contamination.
(16) R. Kuhn and J. C. Jochims, *Chem. Ber.*, **96**, 983 (1963).
(17) K. Weinges, G. Graab, D. Nagel, and B. Stemmle, *Chem. Ber.*, **104**, 3594 (1971).
(18) J. Knabe and W. Wunn, *Arch. Pharm. (Winkeim, Ger.)*, **313**, 538 (1980).

Scheme II



Scheme III

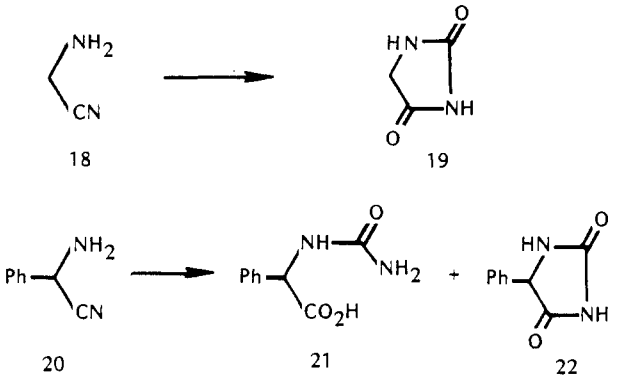


amino nitriles such as **3** and that biologically active chiral hydantoins are readily accessible by the sequence shown in Scheme III.

Experimental Section

(*R*)-2,3-Dihydro-6-fluoro-4-[(1-phenylethyl)imino]-4*H*-1-benzopyran (2). A flame-dried three-necked flask fitted with

Scheme IV



a mechanical stirrer, dropping funnel, N_2 inlet, and thermometer was charged with 4.98 g (0.03 mol) of 2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-one (1)[2] and 120 mL of dry benzene. The pale orange solution was cooled to 0 °C, and to it was added a solution of 3.63 g (0.03 mol) of (*R*)-(+)-α-methylbenzylamine (Aldrich, 98%) and 6.06 g (8.35 mL, 0.06 mol) of triethylamine in 15 mL of dry benzene. While the temperature was kept below 10 °C, a solution of 2.84 g (1.64 mL, 0.015 mol) of $TiCl_4$ in 15 mL of benzene was added dropwise over 15 min. The red-brown suspension was allowed to warm to room temperature and stirred for 24–48 h. At this time, if IR analysis of an aliquot showed the presence of a carbonyl band, then another 1.42 g (0.0075 mL) of $TiCl_4$ in 10 mL of benzene and 1.81 g (0.015 mol) of (*R*)-(+)-α-methylbenzylamine were added, and stirring was continued for another 18 h. The suspension was filtered through a coarse sintered-glass funnel charged with Celite, and the orange filter cake was washed well with benzene. The filtrate was concentrated in vacuo to a red-brown oil, triturated with 200 mL of petroleum ether, and filtered. The filtrate was concentrated to yield 3.4–7.1 g (42–88%) of **2** as a clear pale yellow oil: IR 1650 cm^{-1}; MS, *m/e* 269; NMR (T-60A, $CDCl_3$–Me_4Si) δ 1.5 (d, 3 H), 2.6 (t, 2 H), 4.1 (t, 2 H), 4.7 (q, 1 H), 6.6–7.6 (m, 8 H), 7.9 (dd, 1 H).

In general, the yields were increased by using larger amounts of benzene in the reaction mixture and by employing vigorous stirring. Attempts to form **2** with molecular sieves[19] or toluenesulfonic acid[20] in place of $TiCl_4$ led to low yields of **2** and significant self-condensation of ketone **1**.

In a modified procedure, 0.83 g (5 mmol) of **1**, 2.44 mL (15 mmol) of (*S*)-(−)-α-methylbenzylamine (Aldrich, 98%), and 0.375 mL (2.5 mmol) of $TiCl_4$ in 60 mL of benzene gave, after initial cooling followed by 24 h at room temperature, 1.07 g (80%) of **14a**, the *S* isomer of **2**; spectral data of **14a** were identical with those of **2**.

Similarly, 5 g (0.027 mol) of 6-chloro-2,3-dihydro-4*H*-1-benzopyran-4-one, 10.6 mL (0.082 mol) of (*S*)-(−)-α-methylbenzylamine, and 1.5 mL (0.0137 mol) of $TiCl_4$ in 275 mL of dry benzene gave after 24 h 7.1 g (91%) of (*S*)-6-chloro-2,3-dihydro-4-[(1-phenylethyl)imino]-4*H*-benzopyran (**14b**) as a pale yellow viscous oil: IR 1640 cm^{-1}; MS, *m/e* 287/285; NMR (T-60A, $CDCl_3$–Me_4Si) δ 1.5 (d, 3 H), 2.7 (t, 2 H), 4.2 (t, 2 H), 4.75 (q, 1 H), 6.8 (d, 1 H), 7.1–7.5 (m, 6 H), 8.2 (d, 1 H).

(*R*)-4-Cyano-2,3-dihydro-6-fluoro-4-[(*R*)-(1-phenylethyl)amino]-4*H*-1-benzopyran (3). An HCN generator (a three-necked flask containing a 50% H_2SO_4 solution and fitted with a dropping funnel containing an aqueous NaCN solution) was connected by Tygon tubing via a $CaCl_2$ drying tube to the inlet tube of the main reaction vessel (a three-necked round-bottomed flask with a magnetic stirrer and a perfusion capillary tube which could be lowered below the solvent surface). Throughout the reaction a gentle N_2 stream was passed through the HCN generator, through the reaction flask, and finally through a neutralizing trap containing 5 N NaOH. The reaction flask was charged with 0.538 g (2 mmol) of **2** in 10 mL of absolute EtOH and cooled to −10 °C. HCN was generated by adding dropwise over 10 min a solution of 2.45 g of NaCN (0.05 mol) in 10 mL of H_2O to a vigorously stirred mixture of 2.7 mL (0.05 mol) of concentrated H_2SO_4 and 2.7 mL of H_2O. The HCN generator was warmed to 80 °C for 5 min and allowed to cool under N_2 perfusion of the entire system for another 10 min. The N_2 perfusion was then discontinued, the reaction flask was kept at 0 °C for 1 h, and the crystalline product, which normally started to precipitate midway through the perfusion, was filtered and dried to yield 0.395 g (72%) of **3**: mp 126–129 °C dec; IR 2210 cm^{-1}; MS, *m/e* 296; ^1H NMR (XL-100, $CDCl_3$–Me_4Si) δ 1.45 (d, 3 H), 1.3–2.1 (m, 3 H), 3.7–4.4 (m, 3 H), 6.6–7.5 (m, 8 H). Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.95; H, 5.78; N, 9.46. Found: C, 73.04; H, 5.84; N, 9.43.

In a similar procedure 1.5 g (5.6 mmol) of **14a** in 25 mL of absolute EtOH was perfused with HCN gas (from 3.65 g of KCN in 12 mL of H_2O and 6 mL of 50% H_2SO_4) to give 1.353 g (82%) of **15a**, the *S,S* enantiomer of **3**; mp 131–133 °C dec. Anal. Found: C, 73.01; H, 5.88; N, 9.45.

With the same procedure, 1.01 g (3.53 mmol) of **14b** in 15 mL of EtOH, with 1.73 g (35.3 mmol) of NaCN in 8 mL of H_2O and 4 mL of 50% H_2SO_4, was converted to 781 mg (71%) of (*S*)-6-chloro-4-cyano-2,3-dihydro-4-[(*S*)-(1-phenylethyl)amino]-4*H*-1-benzopyran (**15b**): mp 146–148 °C dec; IR 2210 cm^{-1}; MS, *m/e* 312/314; ^1H NMR (XL-100, $CDCl_3$–Me_4Si) δ 1.45 (d, 3 H), 1.6–2.1 (m, 3 H), 3.7–4.4 (m, 3 H), 6.75 (d, 1 H), 7.15–7.55 (m, 7 H). Anal. Calcd for $C_{18}H_{17}ClN_2O$: C, 69.11; H, 5.48; N, 8.96. Found: C, 69.36; H, 5.62; N, 9.05.

(*R*)-6-Fluoro-3′-[(*R*)-1-phenylethyl]spiro[4*H*-1-Benzopyran-4,4′-imidazolidine]-2′,5′-dione (12). To a solution of 100 mg (0.34 mmol) of **3** in 4 mL of CH_2Cl_2 was added 48 mg (0.34 mmol) of chlorosulfonyl isocyanate. After being stirred 10 min at room temperature, the clear solution was concentrated in vacuo to a pale yellow foam. After addition of 3 mL of 1 N HCl the suspension was stirred for 10 min at room temperature, followed by heating on a steam bath for 1 h. After approximately 15 min on the steam bath the reaction became homogeneous, and then a precipitate formed. After the mixture cooled to room temperature, the solid was filtered, washed with water, and dried to give 69 mg (59%) of **12**, mp 226–228 °C. Reheating the filtrate for 1 h gave a second crop of 15 mg (13%). An analytical sample was recrystallized from EtOH–H_2O: mp 227–229 °C; IR 1760, 1715, 1700 cm^{-1}; ^1H NMR (XL-100, $CDCl_3$–Me_4Si) δ 1.8 (d, 3 H), 2.0–2.6 (m, 2 H), 4.15–4.8 (m, 3 H), 6.35–6.5 (m, 1 H), 6.85–6.95 (m, 2 H). Anal. Calcd for $C_{19}H_{17}FN_2O_3$: C, 67.05; H, 5.04; N, 8.23. Found: C, 66.79; H, 5.18; N, 8.38.

Similarly, 0.25 g (0.84 mmol) of **15a** and 0.074 mL (0.84 mmol) of chlorosulfonyl isocyanate in 10 mL of CH_2Cl_2, followed by treatment with 7.5 mL of 1 N HCl, gave 0.168 g (59%) of 16a, the *S,S* enantiomer of **12**, as a white crystalline solid, mp 225–228 °C. Anal. Found: C, 66.83; H, 5.30; N, 8.02.

In a similar procedure, 0.5 g (1.6 mmol) of **15b** and 0.14 mL (1.6 mmol) of chlorosulfonyl isocyanate gave ultimately 0.509 g (89%) of (*S*)-6-chloro-2,3-dihydro-3′-[(*S*)-1-phenylethyl]spiro-[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (**16b**) as a white solid: mp 268–270 °C; NMR (T-60A, $CDCl_3$/Me_2SO-Me_4Si) δ 1.7 (d, 3 H), 2.0–2.4 (m, 2 H), 2.8 (br s), 4.1–4.9 (m, 3 H), 6.7–7.5 (m, 8 H). Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.95; H, 4.80; N, 7.85. Found: C, 63.66; H, 4.98; N, 7.67.

(*R*)-6-Fluoro-2,3-dihydrospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (6). To a suspension of 0.34 g (1 mmol) of **12** in 8 mL of glacial AcOH was added 15 mL of 48% aqueous HBr. After the mixture was heated 2 h at 120–130 °C (oil bath temperature) TLC (EtOAc–hexane, 1:1; visualization with phosphomolybdate spray/charring) showed two new spots [**6**, R_f 0.45; (α-bromoethyl)benzene, R_f 0.95] in addition to starting material (R_f 0.75) and a trace of origin material (possibly the amino acid **5**). After the reaction mixture cooled, the solvents were removed in vacuo to give an amber liquid which was dissolved in 50 mL of EtOAc, washed twice with H_2O, dried with $MgSO_4$, filtered, and evaporated to an amber oil (0.19 g). This residue was triturated with CH_2Cl_2 to give 91 mg (39%) of **6** as a white solid: mp 233–235 °C (lit.[3] mp 241–243 °C; mixture melting point with authentic material 233–235 °C); $[\alpha]^{25}_D$ −51.8° (*c* = 1, MeOH; lit.[3] rotation $[\alpha]^{25}_D$ −54.8°).

By use of the same procedure, 0.23 g (0.68 mmol) of **16a** was converted to 80 mg (50%) of **17a**, the *S* enantiomer of **6**: mp 238–239.5 °C (lit.[3] mp 241–243 °C); $[\alpha]^{25}_D$ +53.1° (*c* = 1, MeOH;

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(20) A. Lawson and J. O. Stevens, *J. Chem. Soc.*, **1968**, 1514.

lit.[3] rotation $[\alpha]^{25}_D$ +54° (c = 1, MeOH).

In a similar fashion, 100 mg (0.2 mmol) of **16b** was converted to 38 mg (54%) of (*S*)-6-chloro-2,3-dihydrospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (**17b**) as the monohydrate: mp 244–246 °C; $[\alpha]^{25}_D$ +46.6° (c = 1, MeOH); ^{1}H NMR (XL-100, CD_3OD–Me_4Si) δ 2.05–2.5 (m, 2 H), 3.3 (m, CD_2HOD), 4.1–4.35 (m, 1 H), 4.22–4.8 (m, 1 H), 4.85 (s, CD_3OH), 6.85 (d, 1 H), 7.1–7.3 (m, 2 H). Anal. Calcd for $C_{11}H_9ClN_2O_3 \cdot H_2O$: C, 48.80; H, 4.09; N, 10.35. Found: C, 49.14; H, 3.69; N, 10.13.

(*R*)-6-Fluoro-2,3-dihydro-5′-imino-3′-[(*R*)-1-phenylethyl]spiro[4*H*-1-benzopyran-4,4′-imidazolidin]-2′-one (11). To a solution of 50 mg (0.17 mmol) of **3** in 2 mL of CH_2Cl_2 was added 24 mg (0.17 mmol) of chlorosulfonyl isocyanate. After the mixture was stirred at room temperature for 20 min, 1 mL of water was added and the mixture agitated at room temperature for 1 h. After extraction with CH_2Cl_2 the organic layers were dried over $MgSO_4$ and evaporated, and the residue (52 mg) was crystallized from EtOAc–hexane to give hygroscopic crystals. A slow recrystallization from EtOAc–hexane gave 12 mg of **11** as the hemisulfate hydrate: mp 224–226 °C dec; IR 1810, 1725 cm^{-1}; MS, *m/e* 339. Anal. Calcd for $C_{19}H_{18}FN_3O_2 \cdot H_2O \cdot 0.5H_2SO_4$: C, 56.15; H, 5.21; N, 10.34. Found: C, 56.08; H, 4.90; N, 10.07.

Hydrolysis of 10 mg of **11** with 2 mL of 1 N HCl for 20 min at 100 °C gave after cooling and filtering a white solid: mp 224–226 °C; MS, *m/e* 340; identical by TLC (CH_2Cl_2) with **12**.

(*S*)-1′-Chloro-6-fluoro-2,3-dihydro-5′-imino-3′-[(*S*)-1-phenylethyl]spiro[4*H*-1-benzopyran-4,4′-imidazolidin]-2′-one (23). In one experiment a solution of 1.5 g (0.005 mol) of **15a** and 0.44 mL (0.005 mol) of chlorosulfonyl isocyanate in 25 mL of CH_2Cl_2 was stirred at room temperature for 20 min, and the solvent removed in vacuo to give a pale yellow foam. To this material was added 45 mL of 1 N HCl, and the suspension was heated immediately for 1.5 h on a steam bath, cooled to room temperature, and filtered to give 1.67 g of a pale yellow solid. This inhomogeneous material was chromatographed on 60 g of 230–400-mesh silica gel, eluting with CH_2Cl_2, to give 0.4 g of **16a** (mp 226–229 °C), 0.04 g of **17a** (mp 238–239.5 °C), and 0.965 g of **23** as a white solid: mp 73–75 °C dec; IR 1725, 1650 cm^{-1}; MS, *m/e* 373/375; NMR (T-60A, CD_3OD–Me_4Si) δ 1.75 (d, 3 H), 2.0–2.9 (m, 2 H), 3.3 (m, CD_2HOD), 4.1–4.5 (m, 2 H), 4.6–4.9 (m, 3 H), 6.25 (m, 1 H), 6.9 (m, 2 H), 7.2 (s, 5 H); starch–KI test positive. The ^{13}C NMR was also consistent with this structure assignment. Anal. Calcd for $C_{19}H_{17}ClFN_3O \cdot HCl$: C, 55.62; H, 4.42; N, 10.24. Found: C, 55.65; H, 4.50; N, 9.91.

Treatment of **23** with 1 N HCl at 100 °C for 2 h gave a white solid: mp 224–226 °C dec; MS, *m/e* 340; identical by TLC with **16a**.

These experiments suggest that it is important, after the reaction of the amino nitriles **3** or **15** with chlorosulfonyl isocyanate, to stir the mixture with aqueous HCl at room temperature for 10 min prior to heating in order to obtain good yields of the hydantoins **12** or **16**.

Imidazolidine-2,4-dione (19). Treatment of 2 g (0.021 mol) of aminoacetonitrile hydrochloride in 25 mL of CH_2Cl_2 with 3 mL (0.021 mol) of triethylamine, followed by 1.88 mL (0.021 mol) of chlorosulfonyl isocyanate, stirring at room temperature for 30 min, evaporation, treatment of the residue with 30 mL of 1 N HCl at room temperature for 30 min and on a steam bath for another 30 min, gave, after evaporation and fractional crystallization of the residue, 10 mg of **19**, mp 222–224 °C dec (lit.[21] mp 221–223 °C).

5-Phenylimidazolidine-2,4-dione (22). A solution of 3.45 g (26.1 mmol) of 2-phenylglycinonitrile in 50 mL of CH_2Cl_2 was stirred with 2.27 mL (26.1 mmol) of chlorosulfonyl isocyanate for 45 min at room temperature. After evaporation, the residue (*m/e* 271.9842; $C_9H_7ClN_3S^+$) was stirred with 1 N HCl at room temperature for 30 min and on a steam bath for 1 h. After the mixture cooled, the solids were filtered to give 2.15 g (50%) of **22**: mp 171–173 °C dec; after recrystallization from aqueous EtOH, mp 177.5–179 °C (lit.[22] mp 179 °C). The aqueous filtrate gave after evaporation and crystallization from acetone 2.08 g (41%) of the ureido acid **21**; mp 191–194 °C (lit.[23] mp 197 °C); MS, *m/e* 194.

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Registry No. **1**, 66892-34-0; **2**, 82808-07-9; **3**, 82799-08-4; **6**, 69881-27-2; **11** hemisulfate, 82799-11-9; **12**, 82799-09-5; **13b**, 37674-72-9; **14a**, 79791-44-9; **14b**, 79791-45-0; **15a**, 79791-46-1; **15b**, 79791-47-2; **16a**, 79791-48-3; **16b**, 79791-49-4; **17a**, 68367-52-2; **17b**, 79791-50-7; **18**·HCl, 6011-14-9; **19**, 461-72-3; **20**, 16750-42-8; **21**, 5616-20-6; **22**, 89-24-7; **23**·HCl, 82799-12-0; HCN, 74-90-8; (*R*)-(+)-α-methylbenzylamine, 3886-69-9; (*S*)-(−)-α-methylbenzylamine, 2627-86-3; chlorosulfonyl isocyanate, 1189-71-5.

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Semiempirical Investigation of n–π–σ Excitations in Carbonyl Species

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Application of a modified INDO procedure (INDOUV) developed by Van-Catledge has been extended to carbonyl systems. Transition energies and oscillator strengths have been calculated for transitions to low-lying excited states of formaldehyde, acetaldehyde, acetone, acrolein, *trans*-crotonaldehyde (*trans*-2-butenal), methyl vinyl ketone (3-buten-2-one), 3-penten-2-one, and methyl cyclopropyl ketone (acetylcyclopropane) by using limited configuration interaction involving single excitations. The ordering of excitations to observed non-Rydberg states was reproduced. Whereas both n → π* and nσ → π* states are predicted to be too low in energy, π → π* states are within 0.5 eV of their experimental locations insofar as these are obtainable. The n → σ* transition was calculated to occur at greater energies than the π → π* transition in agreement with ab initio results. In cyclopropyl ketones, the existence of two intense bands designated as Δ_p(a) → π* and Δ_p(s) → π* was reproduced, as well as the effects of conformation on the location and intensity of the Δ_p(a) → π* band. The theory of cyclopropyl interaction with the carbonyl π system was explored.

The ground and low-lying excited states of molecules containing the carbonyl group, C=O, play a significant role in organic and biological chemistry. Its strongly dipolar character and the presence of two sets of high-energy nonbonding electrons create some important differences in electronic structure between systems containing the C=O double bond and those containing the C=C double bond. Previous work[1-3] has considered excited σ → π states

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