by coinjection of authentic material with the crude reaction mixture.

Reduction of Ketoaldehyde 1 to Hydroxyaldehyde 2.[10] One-Step Procedure. Compound **1** (150 mg, 0.88 mmol), prepared by ozonolysis of (+)-α-pinene,[11] was dissolved in 2.5 mL of methanolic 0.4 M $ErCl_3 \cdot 6H_2O$ solution and 0.7 mL of trimethyl orthoformate. The mixture was heated to 50 °C for 2 min and then left at room temperature for 15 min. After the addition of excess $NaBH_4$ (60 mg) and workup, the crude oil was dissolved in acidified acetone. After hydrolysis of the ketal was complete (TLC), the reaction was worked up as usual to obtain 125 mg of a colorless oil which was purified on silica gel. A pure fraction (110 mg, 70% yield) of hydroxy aldehyde **2** was obtained: IR 3400, 2840, 2720, 1720 cm^{-1}; NMR 9.5 (1 H, br s), 3.9–3.1 (1 H, br m), 1.1 (3 H, s), 1.05 (3 H, d, J = 6 Hz), 1 ppm (3 H, s); $[\alpha]_D$ −13.1° (MeOH); mass spectrum, m/e 100 (ring cleavage), 85, 69.

Isolation of the Reaction Intermediates 3 and 4. Repetition of the first step of the above procedure from 150 mg of **1** yielded 180 mg of the keto ketal **3** in high purity (yield 94%): IR 1700, 1180, 1130, 1060 cm^{-1}; NMR 4.2 (1 H, t), 3.25 (6 H, s), 2.0 (3 H, s), 1.3 (3 H, s), 0.83 ppm (3 H, s); mass spectrum, m/e 214, 183, 151, 124, 84, 75, 43; $[\alpha]_D$ +35.5° (benzene). Compound **3** was not further purified, due to its instability. Reduction of **3** (40 mg) with excess $NaBH_4$ (15 mg) yielded 40 mg of an oil which was assigned structure **4** (quantitative yield): IR 3440, 1140, 1105, 1090, 1070 cm^{-1}; NMR 4.2 (1 H, t), 3.9–3.2 (1 H, m), 3.2 (6 H, s), 1.1–0.9 ppm (9 H); mass spectrum m/e 185, 166, 151, 119, 109, 91, 85, 75; $[\alpha]_D$ −3.5° (benzene).

A 20-mg sample of **4** was used in Horeau's method[12] for the determination of the absolute configuration of the secondary alcohol. The final α-phenylbutyric acid was dextrorotatory ($[\alpha]_D$ +1°), allowing the assignment of configuration **4** to the reduction product from **3**.

Reduction of Ketoaldehyde 5 to Hydroxyaldehyde 6.[13] One-Step Procedure. Compound **5**[14] (160 mg, 0.63 mmol) was dissolved in 1.6 mL of methanolic 0.4 M $CeCl_3 \cdot 6H_2O$ solution and 487 mg (4.41 mmol) of trimethyl orthoformate added. The mixture was left at room temperature for 2.5 h, and then $NaBH_4$ (70 mg, 1.89 mmol) was added with stirring. After 5 min the solution was acidified by addition of 1 N aqueous HCl and 15 mL of acetone. After 6 h and workup as usual, 150 mg of an oil was obtained and purified on a silica gel column. A pure fraction (123.5 mg, 76%) of **6** was obtained: IR 3480, 2960, 2880, 2840, 1735, 1460 cm^{-1}; NMR 9.36 (1 H, br s), 3.36 (3 H, s), 4.16 (1 H, br s), 2.5–1.16 (18 H); mass spectrum m/e 238, 204 (metastable peak), 193 (metastable peak), 177, 145, 105, 57, 44, 43.

Compound **5** (75 mg, 0.29 mmol) was ketalized as previously described. Treatment with aqueous $NaHCO_3$ and usual workup yielded 87 mg (100% yield) of an oil which was identified as the keto ketal **7** by comparison with an authentic sample.[14]

Reduction of Androstane-3,17-dione 8 to 17β-Hydroxyandrostan-3-one 9. One-Step Procedure. Androstane-3,17-dione (288 mg, 1 mmol) was dissolved in 5 mL of methanolic $ErCl_3 \cdot 6H_2O$ (0.2 M) and 750 mg (7 mmol) of trimethyl orthoformate added. The solution was left at room temperature for 15 min, and then 80 mg (2 equiv) of $NaBH_4$ was added in one portion with stirring. The mixture was left for 5 min, and then the pH was brought to ~2 with aqueous 1 N HCl. After a further 20 min period, water was added and the mixture extracted with ether. The organic phase was washed (saturated aqueous NaCl) and dried (Na_2SO_4) and the solvent evaporated, leaving an oil (300 mg) which crystallized readily; mp 176–178 °C. After recrystallization (CH_2Cl_2, hexane), 275 mg (95%) of **9**, mp 178–179 °C (lit.[15] mp 180–181 °C), was obtained with physical data identical with those of an authentic sample.

3,3-Dimethoxyandrostan-17-one.[6] Androstane-3,17-dione (**8**; 60 mg, 0.20 mmol) was dissolved in 1 mL of methanolic $ErCl_3 \cdot 6H_2O$ (0.2 M) and 100 mg of trimethyl orthoformate added. The solution was left at room temperature for 15 min and then poured into 5% aqueous $NaHCO_3$. After extraction (CH_2Cl_2), drying of the organic solution (Na_2SO_4), and evaporation, 60 mg of an oil (86%) was obtained and crystallized readily. Recrystallization from MeOH gave pure compound: mp 124–125 °C (lit.[6] mp 128 °C), $[\alpha]_D$ +85° ($CHCl_3$) [lit.[6] +85.5° ($CHCl_3$)].

17β-Hydroxyandrostan-3-one 9. Compound **11** (50 mg) in 1 mL of methanolic $ErCl_3 \cdot 6H_2O$ (0.2 M) was treated with 30 mg of $NaBH_4$ and then left for 5 min at room temperature. Water was then added and the mixture extracted with CH_2Cl_2. After the mixture was dried (Na_2SO_4) and evaporated, 56 mg of a white solid was recovered: mp 177–180 °C (lit.[16] mp 180–182 °C), $[\alpha]_D$ + 12.5° (lit.[16] +14°). Hydrolysis of the preceding compound (MeOH, aqueous 1 N HCl, 20 min, room temperature) led to 42 mg (98%) of 17β-hydroxyandrostan-3-one (**9**), identical in all respects with an authentic sample.

Reduction of Progesterone (12) to 3β-Hydroxypregnen-20-one (14). Progesterone (90 mg, 0.28 mmol) and 100 mg (1 equiv) of $CeCl_3 \cdot 6H_2O$ were dissolved in 1.5 mL of MeOH and cooled to −20 °C. $NaBH_4$ (5 mg, 0.5 equiv) was added and the mixture stirred for 10 min. Acetone (1 mL) was added, and the temperature was allowed to reach ambient temperature. After the usual workup, 87 mg of an oil was obtained, which was chromatographed (SiO_2, CH_2Cl_2–MeOH). Starting material (25 mg, 28%) was recovered in addition to 43 mg (48%) of compound **14**: mp 161–162 °C, $[\alpha]_D$ +140° (lit.[17] mp 155–161 °C, $[\alpha]_D$ +136°). A third fraction (17 mg, 20%) containing impure pregnene-3,20-diol was isolated. The diol was identified by TLC and comparison with an authentic sample.[8]

Acknowledgment. The authors wish to thank Prof. P. Crabbé and Dr. A. E. Greene for stimulating discussions. Significant improvement of the English is also due to A. E. Greene. One of us (A.L.G.) thanks the coordenaçao de Aperfeiçoamento de Pessoal de N. Superior (CAPES) (Brazil) for a fellowship.

Registry No. **1**, 71628-89-2; **2**, 71582-31-5; **3**, 71582-32-6; **4**, 71582-33-7; **5**, 61659-10-7; **6**, 58282-89-6; **7**, 71582-34-8; **8**, 5982-99-0; **9**, 29873-50-5; **11**, 71628-90-5; **12**, 57-83-0; **14**, 566-66-5; 3,3-dimethoxy-17β-hydroxyandrostane, 71582-35-9; 3β,20-dihydroxy-4-pregnene, 71628-91-6; cyclohexanecarboxaldehyde, 2043-61-0; cyclododecanone, 830-13-7; benzyl methyl ketone, 103-79-7; benzaldehyde, 100-52-7; cycloheptanone, 502-42-1; 5-nonanone, 502-56-7; 2-cyclohexenone, 930-68-7; *p*-anisaldehyde, 123-11-5; acetophenone, 98-86-2; cyclohexanemethanol, 100-49-2; cyclododecanol, 1724-39-6; α-methylbenzeneethanol, 698-87-3; benzyl alcohol, 100-51-6; cycloheptanol, 502-41-0; 5-nonanol, 623-93-8; 2-cyclohexen-1-ol, 822-67-3; 4-methoxybenzenemethanol, 105-13-5; α-methylbenzenemethanol, 98-85-1; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; 2-methylcyclohexanone, 583-60-8; 2-octanone, 111-13-7; camphor, 76-22-2; cyclohexanol, 108-93-0; cyclopentanol, 96-41-3; 2-methylcyclohexanol, 583-59-5; 2-octanol, 123-96-6; 1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, 10385-78-1.

(10) J. Kulesza and J. Kula, *Int. Congr. Essent. Oils*, [Pap], 6th, 137 (1974).
(11) J. M. Conia and C. Faget, *Bull. Soc. Chim. Fr.*, 1963 (1964).
(12) A. Horeau, *Bull. Soc. Chim. Fr.*, 2673 (1964).
(13) J. F. Bagli and T. Bogri, U.S. Patent 3907998 (1975).
(14) P. Crabbé, E. Barreiro, A. Cruz, J. P. Deprès, M. C. Meana, and A. E. Greene, *Heterocycles*, **5**, 725 (1976); J. Bagli and T. Bogri, *Tetrahedron Lett.*, 3815 (1972).
(15) C. Djerassi, *J. Org. Chem.*, **12**, 823 (1947).
(16) D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1297 (1960).
(17) M. Stefanovic and S. Lajsic, *Tetrahedron Lett.*, 1777 (1967).

Chiral (Arene)tricarbonylchromium Complexes: Resolution of Aldehydes

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Functionalized chiral metallocenes are of great potential interest for asymmetric synthesis. However, the scope of their use is at present limited because of the difficulties encountered in the resolution of racemates.

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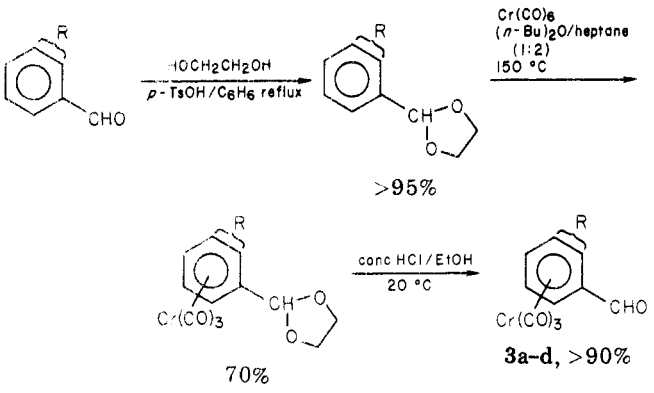
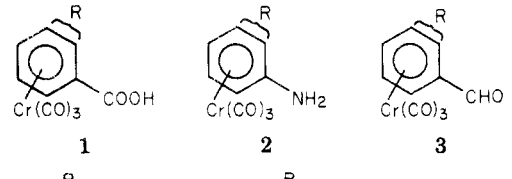
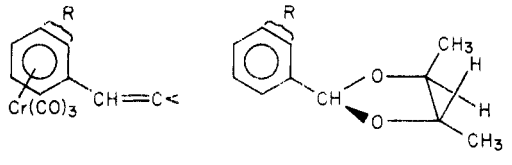
Scheme I



Of the (arene)tricarbonylchromium complexes, only the racemic acids **1** can be readily resolved.[1-4] The amines **2** are too weak as bases to give diastereomeric salts with the optically active acids commonly employed for resolution. Dabard et al.[3] failed in their attempt to resolve the aldehydes **3** because their diastereomeric (-)-menthylhydrazones could not be hydrolyzed.

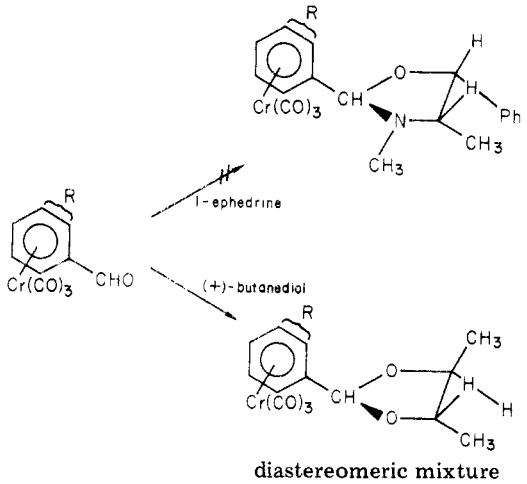


1 **2** **3**



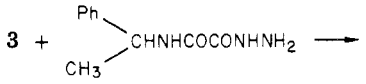
4 **5**

As part of our studies on asymmetric Diels–Alder reactions of the complexes **4** it was of crucial importance to resolve the racemic aldehydes **3**. Some of our attempts also failed: the required oxazolidine was not formed with l-ephedrine; the diastereomeric ketals with (*S*,*S*)-(+)-butanediol could not be separated either by crystallization or by column chromatography; complexation of the optically pure ketal **5** with $Cr(CO)_6$ led to 20% asymmetric induction (further improvement was not achieved).

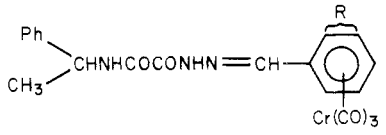


diastereomeric mixture

Resolution of the racemates of aldehydes of type **3** was finally achieved by use of the derivatives **7** prepared by reaction with (*S*)-(-)-5-(α-phenylethyl)semioxamazide (**6**).

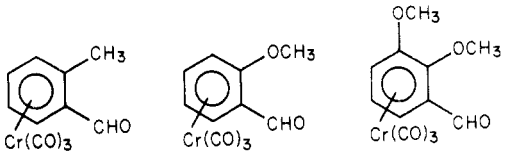


(*S*)-(-)-**6**

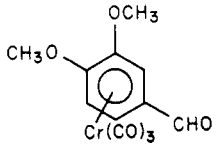


7
(I + II)

Four aldehydes have been resolved by this method (**3a–d**).



3a **3b** **3c**



3d

The derivatives **7** (semioxamazones) were obtained in 70–90% yields, depending on the starting aldehyde. Separation of the diastereomers was achieved by column chromatography.[5] Each diastereomer (whose purity was monitored by TLC) was recovered in at least 90% yield. Optically pure enantiomers of the complexed aldehydes were subsequently obtained almost quantitatively by acidic hydrolysis.

Experimental Section

Preparation of Racemates 3a–d. Complexes **3a–d** were obtained in three steps with an overall chemical yield of 62% according to Scheme I. Step 2 was preformed under argon in a Strohmeier apparatus[6] with a 300% excess of free ligand which is easily recovered by column chromatography.

Syntheses of Semioxamazones 7a–d. (*S*)-(-)-5-(α-Phenylethyl)semioxamazide. Compound **6** [mp 168–169 °C; $[\alpha]_D$ -103° (*c* 1, $CHCl_3$)] was prepared according to the procedure of Leonard et al.[7]

Semioxamazones 7a–d. A mixture of semioxamazide **6** (0.004 mol), complexed aldehyde **3** (0.004 mol), and *p*-toluenesulfonic acid (0.05 g) was refluxed in benzene until no more starting aldehyde could be detected by TLC. After being cooled, washed ($NaHCO_3$ 5%, water), and dried (Na_2SO_4), the solvent was removed under vacuum to give red-orange crystals of crude semioxamazone.

Separation of Diastereomers. Separation of the diastereomers was performed by column chromatography according to Still's technique.[5] The solvents used for elution are given in the following section. The recovery of the separated diastereomers was about 90%.

Hydrolysis of Semioxamazones 7a–d. The pure diastereoisomers **7a–d** were hydrolyzed by refluxing with 60% H_2SO_4 in benzene until no starting material could be detected by TLC. After the usual workup, the pure enantiomers were isolated by column chromatography (solvent, ether/hexane 8:2).

Semioxamazone 7a: yield, 80%; chromatography solvent, diethyl ether/petroleum ether (EE/PE) 90:10.

Diastereomer I (**7a-I**): mp 155–156 °C; R_f 0.75 (EE/PE 90:10); IR ($CHCl_3$) ν_{NH} 3360, 3290, $\nu_{C=O}$ 1975, 1900 ν_{amide} 1680 cm^{-1}; ^1H

(1) A. Mandelbaum, Z. Neuwirth, and M. Cais, *Inorg. Chem.*, **2**, 902 (1963).
(2) R. Dabard and A. Meyer, *C. R. Hebd. Seances Acad. Sci. Ser. C.*, **264**, 903 (1967).
(3) R. Dabard, A. Meyer, and G. Jaouen, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **268**, 201 (1969).
(4) H. Falk, K. Schlögl and W. Steyrer, *Monatsh. Chem.*, **97**, 1029 (1966).
(5) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
(6) W. Strohmeier, *Chem. Ber.*, **94**, 2490 (1961).
(7) N. J. Leonard and J. H. Boyer, *J. Org. Chem.*, **15**, 42 (1950).

NMR ($CDCl_3/Me_4Si$, 250 MHz) δ 1.54 (d, 3 H, J = 7 Hz), 2.26 (s, 3 H), 4.98 (d, 1 H), 5.12 (t, 1 H), 5.43 (t, 1 H), 6.17 (d, 1 H, aromatic), 5.00 (m, 1 H), 7.17 (5 H, aromatic), 7.57 (d, 1 H, NH), 8.02 (s, 1 H, imine), 10.12 (s, 1 H, NH): $[\alpha]_D$ +1013° (c 0.76, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}CrN_3O_5$: C, 56.63; H, 4.30. Found: C, 56.80; H, 4.39.

Diastereomer II (**7a-II**): mp 166–168 °C; R_f 0.46 (EE/PE 90:10); IR ($CHCl_3$) and NMR ($CDCl_3/Me_4Si$) are identical with those of diastereomer **7a-I**; $[\alpha]_D$ −1195° (c 0.69, $CHCl_3$).

Semioxamazone 7b: yield, 90%; chromatography solvent, diethyl ether.

Diastereomer I (**7b-I**): mp > 190 °C dec; R_f 0.75 (ether); IR ($CHCl_3$) ν_{NH} 3380, 3300, $\nu_{C\equiv O}$ 1975, 1905, ν_{amide} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$, 250 MHz) δ 1.60 (d, 3 H, $J \simeq 7$ Hz), 3.81 (s, 3 H), 4.98 (t, 1 H, aromatic), 5.09 (d, 1 H, aromatic), 5.12 (m, 1 H), 5.70 (t, 1 H, aromatic), 6.54 (d, 1 H, aromatic), 7.35 (s, 5 H aromatic), 7.78 (br d, 1 H, NH), 8.28 (s, 1 H), 10.4 (s, 1 H, NH); $[\alpha]_D$ +986° (c 0.07, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}CrN_3O_6$: C, 54.66; H, 4.12; N, 9.11. Found: C, 54.86; H, 4.35; N, 9.30.

Diastereomer II (**7b-II**): mp 99–101 °C; R_f 0.57 (ether); IR ($CHCl_3$) and NMR ($CDCl_3/Me_4Si$) are identical with those of diastereomer **7b-I**; $[\alpha]_D$ −959° (c 0.07, $CHCl_3$).

Semioxamazone 7c: yield, 70%; chromatography solvent, diethyl ether.

Diastereomer II (**7c-I**): mp 96–98 °C; R_f 0.72 (ether); IR ($CHCl_3$) ν_{NH} 3380, 3310, $\nu_{C\equiv O}$ 1970, 1900, ν_{amide} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$, 250 MHz) δ 1.50 (d, 3 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 5.20 (m, 1 H, also 2 H aromatic) 5.75 (d, 1 H, aromatic), 7.25 (s, 5 H, aromatic), 7.65 (d, 1 H, NH), 8.30 (s, 1 H), 10.45 (br s, 1 H, NH): $[\alpha]_D$ +556° (c 0.06, $CHCl_3$). Anal. Calcd for $C_{22}H_{21}CrN_3O_7$: C, 53.77; H, 4.28; N, 8.55. Found: C, 53.67; H, 4.31; N, 8.55.

Diastereomer II (**7c-II**): mp 118–120 °C; R_f 0.57 (ether); IR ($CHCl_3$) and ^1H NMR ($CDCl_3/Me_4Si$) are identical with those of diastereomer **7c-I**; $[\alpha]_D$ −415° (c 0.05, $CHCl_3$).

Semioxamazone 7d: yield, 70%; chromatography solvent, diethyl ether.

Diastereomer I (**7d-I**): mp 108–110 °C; R_f 0.59 (ether); IR ($CHCl_3$) ν_{NH} 3380, 3300, $\nu_{C\equiv O}$ 1970, 1895, ν_{amide} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$, 250 MHz) δ 1.60 (d, 3 H), 3.75 (s, 6 H), 5.00 (m, 1 H), 5.15 (s, 2 H, aromatic), 5.90 (s, 1 H, aromatic), 7.20 (s, 5 H, aromatic), 7.75 (br, 1 H, NH), 7.80 (s, 1 H), 10.90 (br s, 1 H NH); $[\alpha]_D$ +450 (c 0.09, $CHCl_3$). Anal. Calcd for $C_{22}H_{21}CrN_3O_7$: C, 53.77; H, 4.28; N, 8.55. Found: C, 53.85; H, 4.38; N, 8.59.

Diastereomer II (**7d-II**): mp 105–107 °C; R_f 0.39 (ether); IR ($CHCl_3$) and ^1H NMR ($CDCl_3/Me_4Si$) are identical with those of diastereomer **7d-I**; $[\alpha]_D$ −479° (c 0.10, $CHCl_3$).

Optically Active Complexes. 3a: mp 99–100 °C; R_f 0.95 (ether/hexane 9:1); IR ($CHCl_3$) ν_{CHO} 2860, 2720 (vw), $\nu_{C\equiv O}$ 1970, 1895, ν_{CO} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 2.45 (s, 3 H), 4.95 (d, 1 H, aromatic), 5.12 (t, 1 H, aromatic), 5.62 (t, 1 H, aromatic), 5.95 (d, 1 H aromatic), 9.72 (s, 1 H); from **7a-I**, $[\alpha]_D$ +665° (c 0.22, $CHCl_3$); from **7a-II**, $[\alpha]_D$ −664° (c 0.26, $CHCl_3$) (lit.[3] $[\alpha]_D$ −660°).

3b: mp 98–99 °C; R_f 0.89 (ether); IR ($CHCl_3$) ν_{OMe} and ν_{CHO} 2840, 2810 (w), $\nu_{C\equiv O}$ 1975, 1900, ν_{CO} 1675 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 3.80 (s, 3 H), 4.95 (t, 1 H, aromatic), 5.0 (d, 1 H, aromatic), 5.75 (t, 1 H, aromatic), 6.15 (d, 1 H, aromatic), 10.1 (s, 1 H); from **7b-I**, $[\alpha]_D$ +1015° (c 0.06, $CHCl_3$); from **7b-II**, $[\alpha]_D$ −1020° (c 0.09, $CHCl_3$) (lit.[8] $[\alpha]_D$ −1000°).

3c: mp 59–61 °C; R_f 0.94 (ether); IR ($CHCl_3$); ν_{OMe} ν_{CHO} 2860, 2820 (w), $\nu_{C\equiv O}$ 1975, 1900, ν_{CO} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 3.75 (s, 3 H), 3.95 (s, 3 H), 5.10 (t, 1 H, aromatic), 5.45 (d, 1 H aromatic), 5.60 (d, 1 H aromatic), 10.05 (s, 1 H); from **7c-I**, $[\alpha]_D$ +360° (c 0.12, $CHCl_3$); from **7c-II**, $[\alpha]_D$ −387° (c 0.19, $CHCl_3$).

3d: mp 83–85 °C; R_f 0.93 (ether); IR ($CHCl_3$) ν_{OMe} 2810, ν_{CHO} 2810, 2720 (vw), $\nu_{C\equiv O}$ 1970, 1885, ν_{CO} 1675 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 3.75 (s, 3 H), 3.80 (s, 3 H), 5.15 (d, 1 H, aromatic), 5.55 (d, 1 H, aromatic), 5.85 (s, 1 H, aromatic), 9.30 (s, 1 H); from **7d-I**, $[\alpha]_D$ +793° (c 0.60, $CHCl_3$); from **7d-II**, $[\alpha]_D$ −818° (c 0.77, $CHCl_3$).

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(8) R. Dabard and G. Jaouen, *Tetrahedron Lett.*, 3391 (1969).

Registry No. (±)-**3a**, 32734-21-7; (+)-**3a**, 33152-66-8; (−)-**3a**, 33152-65-7; (±)-**3b**, 12181-92-9; (+)-**3b**, 36249-94-2; (−)-**3b**, 71327-35-0; (±)-**3c**, 71243-02-2; (+)-**3c**, 71243-03-3; (−)-**3c**, 71243-04-4; (±)-**3d**, 71243-05-5; (+)-**3d**, 71243-06-6; (−)-**3d**, 71243-07-7; **6**, 6152-25-6; **7a**, 71243-08-8; **7a-I**, 71276-52-3; **7a-II**, 71276-53-4; **7b**, 71250-01-6; **7b-I**, 71300-53-3; **7b-II**, 71300-54-4; **7c**, 71250-02-7; **7c-I**, 71300-55-5; **7c-II**, 71300-56-6; **7d**, 71250-03-8; **7d-I**, 71300-57-7; **7d-II**, 71300-58-8; 2-methylbenzaldehyde, 529-20-4; 2-methoxybenzaldehyde, 135-02-4; 2,3-dimethoxybenzaldehyde, 86-51-1; 3,4-dimethoxybenzaldehyde, 120-14-9; 1,2-ethanediol, 107-21-1; 2-methylbenzaldehyde cyclic ethylene acetal, 64380-54-7; 2-methoxybenzaldehyde cyclic ethylene acetal, 4420-21-7; 2,3-dimethoxybenzaldehyde cyclic ethylene acetal, 71242-97-2; 3,4-dimethoxybenzaldehyde cyclic ethylene acetal, 71242-98-3; chromium carbonyl ($Cr(CO)_6$), 13007-92-6; 2-methylbenzaldehyde cyclic ethylene acetal chromium complex, 71250-04-9; 2-methoxybenzaldehyde cyclic ethylene acetal chromium complex, 71250-05-0; 2,3-dimethoxybenzaldehyde cyclic ethylene acetal chromium complex, 71276-89-6; 3,4-dimethoxybenzaldehyde cyclic ethylene acetal chromium complex, 71250-06-1.

Synthesis of 1,2,6-Thiadiazine 1,1-Dioxides via Isoxazolylsulfamides

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A variety of synthetic procedures have been devised for the synthesis of 1,2,6-thiadiazine 1,1-dioxides.[1] The logical extension of direct methods by which 2-pyrimidones are prepared, with the substitution of sulfamide for urea, provides the rationale for much of this work. However, although the analogy to the 2-pyrimidones has been recognized,[2] the analogues **3a** and **7a** of cytosine and thymine, respectively, in which the 2-carbonyl is replaced by the bioisosteric[3] SO_2 linkage have heretofore not been reported. The published procedures, while providing synthetic access to 1,2,6-thiadiazine 1,1-dioxides with a limited variety of substitution patterns, are not sufficiently general to be successfully adapted to the preparations of **3a** and **7a**. This paper describes the synthesis of these and related compounds by a new general method through the intermediacy of isoxazolylsulfamides.

Cytosine analogue **3a** was prepared according to Scheme I. Reaction of 3-isoxazolamine[4] (**1a**) with sulfamoyl chloride and triethylamine in benzene gave sulfamide **2a**, which was then hydrogenated in methanol, with Raney nickel catalyst, in the presence of sodium methoxide. Hydrogenolysis of the isoxazole nucleus was accompanied by spontaneous ring closure to give **3a**. Compatible spectral data are summarized in the Experimental Section; in addition, a single-crystal X-ray analysis confirmed the structure (Figure 1).

Crystals of **3a** are monoclinic, space group $P2_1/a$, with a = 15.845 (3), b = 5.313 (1), and c = 7.252 (1) Å and β =

(1) (a) Lawson, A.; Tinkler, R. B. *Chem. Rev.* **1970**, *70*, 593 and references therein. (b) Die, R.; Diez, J.; Garcia-Muñoz, G.; Madoñero, R.; Stud, M., *J. Heterocycl. Chem.* **1972**, *9*, 973. (c) Diez, J.; Garcia-Muñoz, G.; Madoñero, R.; Stud, M. *Ibid.* **1973**, *10*, 469. (d) Garcia-Muñoz, G.; Ochoa, C.; Stud, M.; Pfleiderer, W. *Ibid.* **1977**, *14*, 431. (e) Garcia-Muñoz, G.; Ochoa, C.; Stud, M. *Ibid.* **1976**, *13*, 793. (f) Ochoa, C.; Stud, M. *Ibid.* **1978**, *15*, 221. (g) Goya, P.; Stud, M. *Ibid.* **1978**, *15*, 253.

(2) Pagani, G. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2050.

(3) Burger, A. In "Medicinal Chemistry", 3rd ed; Burger, A., Ed.; Wiley-Interscience: New York, **1970**; pp 72–8.

(4) Klötzer, W.; Bretschneider, H.; Fitz, E.; Reiner, R.; Bader, B. *Monatsh. Chem.* **1970**, *101*, 1109.

0022-3263/79/1944-4191$01.00/0 © 1979 American Chemical Society