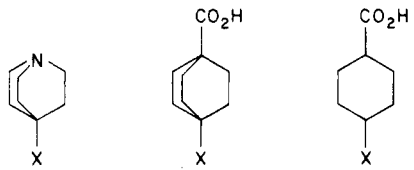
method A, the ΔE values fall off with distance approximately as $1/r^2$ ($1/r^{1.87}$), as anticipated from eq 4. With dipolar substituents polarizing a bond, as in method B, the effect falls off with distance approximately as $1/r^3$ ($1/r^{2.8}$), as expected from eq 6. The ΔE and Δq_α values for the dipolar substituents are used to obtain the β and C values for eq 9 for each series, and the correlation coefficients are also reported in Table I.

The values of σ_F derived for the monopoles (Table II) are seen to alter with distance as anticipated in the introduction. As expected, the values increase approximately linearly with distance. Further, the values obtained by method A are approximately twice the magnitude of those by method B, as anticipated above from a comparison of eq 2-6. It would thus seem well proven that general σ_F values cannot be derived for monopolar substituents by using data scaled to dipolar substituents.

This is further illustrated by pK_a values for seven series of compounds (see Table III). All are chosen as examples of systems where only field effects should be present. They are data for 2-substituted acetic acids,[16] 4-substituted quinuclidines 1,[17] 4-substituted bicyclooctanecarboxylic



1 2 3

acids 2,[10] 4-substituted cyclohexanecarboxylic acids 3,[18] and ortho,[19] meta,[20] and para,[21] XCH_2-substituted pyridines. The Cl, Br, and CN substituents are chosen as typical dipolar substituents with all pK_a values scaled to give $\sigma_F = 0.45$ for Cl. While σ_F values for the other two dipolar substituents remain essentially constant, the values for NR_3^+ change dramatically in the direction one would predict from the geometrical considerations; that is, they increase with increasing distance. The actual values here cannot be compared with those calculated above, since the electronic effect of a charged substituent is particularly sensitive to changes in solvent and counterion.[22] Experimental data do not appear to be available to check the second problem discussed above, relating to the factor of 2 between equation 5 and 6. The data required would be, for example, both NMR and pK_a results for systems of corresponding geometry under identical solvent conditions.

Conclusion

Overall then it is clearly not reasonable to quote σ_F values for polar substituents. Such values would only be valid for the particular geometry and method of measurement employed. It is also clearly unreasonable to base a scale of substituent values for mainly dipolar substituents on the value for the charged NMe_3^+ groups as has been done for the $\mathcal{F}$ values of Swain.[10]

Acknowledgment. We are grateful to the Australian Research Grants Scheme and to the Potter Foundation for financial assistance. We thank Professor B. M. Wepster for helpful comments.

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Synthesis and Oxidative Coupling of (±)-3-Oxoreticuline

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The synthesis and oxidative coupling of 3-oxoreticuline (**8**) are described. Reaction of **8** with iodosobenzene diacetate in the presence of trifluoroacetic acid gave 16-oxosalutaridine (**12**), 16-oxopallidine (**13**), 5-oxoisoboldine (**14**), and 13-oxothalidine (**15**) in yields of 27%, 8%, 6%, and 10%, respectively. Oxidation of **8** with vanadium oxytrichloride gave **13**, **14**, and **15** in yields of 26%, 11%, and 9%, respectively.

The key step in the biosynthetic pathway to codeine (**1**) and morphine (**2**) is the intramolecular oxidative coupling of a 1-benzyltetrahydroisoquinoline, reticuline (**3**), to give salutaridine (**4**).[1] Efforts to carry out the in vitro oxidative coupling of reticuline or *N*-acyl-*N*-norreticuline derivatives using a range of oxidants have given a variety of yields of the four possible products of a direct coupling between the two phenol rings, namely, salutaridine (**4**),[2] pallidine (**5**),[3] corytuberine (**6**),[4] and isoboldine (**7**),[5] or their respective *N*-acyl-*N*-nor derivatives. A major problem in synthetic application of this method has been the inability to direct the regiochemical outcome of the coupling step. McDo-

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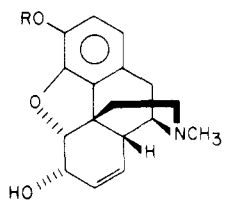
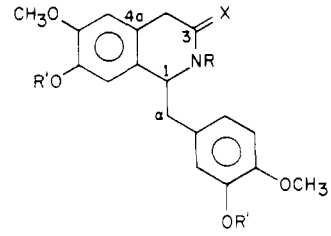
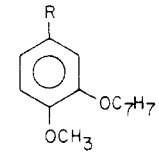
Chart I



1 R = CH_3
2 R = H



3 X = H_2, R = CH_3, R' = H
8 X = O, R = CH_3, R' = H
16 X = O, R = R' = CH_3
17 X = H_2, R = $COOCH_2CH_3$, R' = H



9 R = CH=NCH_3
10 R = CH_2Cl

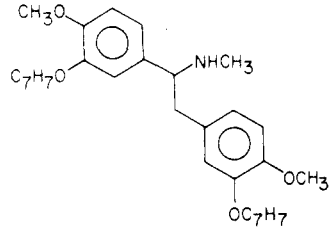


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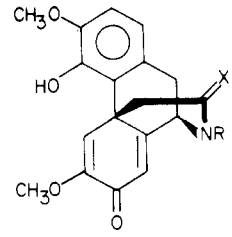
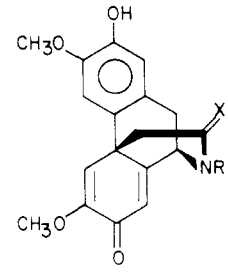
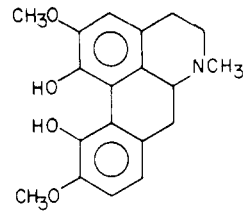
Chart II



4 X = H_2, R = CH_3
12 X = O, R = CH_3
18 X = H_2, R = $COOCH_2CH_3$



5 X = H_2, R = CH_3
13 X = O, R = CH_3



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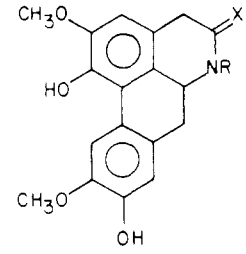

7 X = H_2, R = CH_3
14 X = O, R = CH_3
19 X = H_2, R = $COOCH_2CH_3$

nald[6] has discussed the possible effects of steric interactions on intramolecular oxidative coupling reactions. Here we report an investigation of the applicability of this concept to the oxidation of reticuline. Specifically, we report the synthesis and oxidative coupling of 3-oxoreticuline (**8**), a compound which we expected to give higher yields of dienone products derived from coupling of the 1-benzyl aromatic ring to C-4a of the tetrahydroisoquinoline nucleus, due to the elimination of a 1,3-diaxial interaction between the C-3 axial proton and the C-1 benzyl group (Chart I).

The synthesis of 3-oxoreticuline proceeded as follows. The *N*-methylbenzaldimine **9** was prepared from *O*-benzylisovanillin[7] and methylamine in 89% yield. 3-(Benzyloxy)-4-methoxybenzyl chloride (**10**)[8] was converted to a Grignard reagent which was allowed to react[9] with imine **9** to give the (methylamino)bibenzyl **11** in 84% yield (based on **9**). Conversion of **11** to 3-oxoreticuline was carried out by using a procedure recently reported by Tamura et al.[10] Amine **11** was acylated with α-chloro-α-(methylthio)acetyl chloride and then was cyclized under Friedel–Crafts conditions using stannic chloride as catalyst.[10] The crude product was subjected to zinc/acetic acid reduction to remove the methylthio group, and subsequent hydrolytic cleavage of the benzyl ethers gave crystalline 3-oxoreticuline (**8**) in 27% yield from **11**.

Oxidation of 3-oxoreticuline with iodosobenzene diacetate in the presence of trifluoroacetic acid[2b] gave 16-oxosalutaridine (**12**) in 27% yield (Chart II). Also obtained from the oxidation were 16-oxopallidine (**13**), 5-oxoisoboldine (**14**), and 13-oxothalidine (**15**) in yields of 8%, 6%, and 10%, respectively (products **14** and **15** were isolated as tertiary amines after reduction with BH_3/THF). When oxidative coupling of 3-oxoreticuline was carried out with vanadium oxytrichloride[5] as oxidant, products **13**, **14**, and **15** were obtained in yields of 26%, 11%, and 9%, respectively, but none of the salutaridine derivative **12** was isolable. 16-Oxosalutaridine, 16-oxopallidine, and 5-oxoisoboldine were all identified by comparison of their NMR spectra with those of the parent compounds or those of the respective *N*-acyl-*N*-nor derivatives. The structure of 13-oxothalidine (**15**) was confirmed by its conversion to *O*-methyl-13-oxothalisopavine, a coupling product isolated by Elliot[11] from the oxidation of the nonphenolic 3-oxo-1-benzyltetrahydroisoquinoline **16** with vanadium oxytrifluoride.

In contrast to these results with 3-oxoreticuline, oxidation of *N*-(ethoxycarbonyl)-*N*-norreticuline (**17**) with iodosobenzene diacetate in the presence of trifluoroacetic acid gave *N*-(ethoxycarbonyl)-*N*-norsalutaridine (**18**) and *N*-(ethoxycarbonyl)-*N*-norisoboldine (**19**) in 22% and 18% yields, respectively. Similarly, oxidation of reticuline or *N*-acyl-*N*-norreticuline with vanadium oxytrichloride[5,12] has been demonstrated to give only isoboldine or its *N*-acyl-*N*-nor derivative. Since pallidine and thalidine derivatives are not generated from coupling of reticuline or *N*-acyl-*N*-norreticuline with these oxidants, their formation from 3-oxoreticuline must reflect the effects of substitution of a carbonyl group for the methylene group at C-3.

It seemed possible that both the thalidine- and pallidine-type products might have been formed by cyclization of the quinone methide intermediate **20** (Chart III). In order to test this hypothesis, an alternative route to the quinone methide via 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation[13,14] was investigated. Treatment of 3-oxoreticuline with a slight excess of DDQ in methylene chlo-

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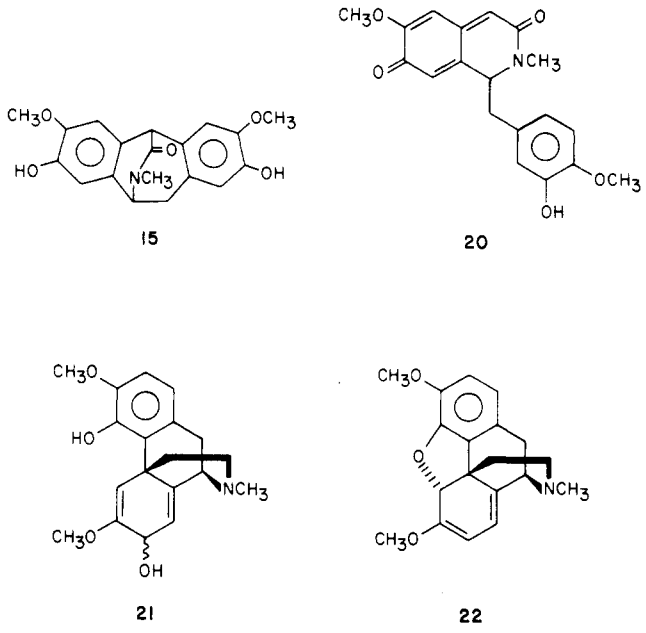
Chart III



ride gave 13-oxothalidine (**15**) as the only product, isolated in 85% yield. Addition of trifluoroacetic acid to the reaction mixture had no effect on the products formed.

Formation of the para–para coupled pallidine derivative at the apparent expense of the ortho–para coupled isoboldine derivative in the oxo series is thus likely the result of a steric effect. In order for para–para coupling of reticuline to occur, the 1-benzyl group must be in an axial conformation and must have accessible a C-1–C-α rotamer in which the 1-benzyl aromatic ring is endo to the tetrahydroisoquinoline moiety. Substitution of a carbonyl group at C-3 should favor this rotamer in 3-oxoreticuline as compared to reticuline or *N*-acyl-*N*-norreticulines.

In order to confirm the structure of 16-oxosalutaridine (**12**), it was reduced with an excess of $LiAlH_4$ in refluxing THF to give (±)-salutaridinol (**21**). The dienol was cyclized by treatment with dimethylformamide dineopentyl acetal[15] to give (±)-thebaine (**22**) in 26% overall yield from **12**. Since thebaine has been converted in two steps to codeine (**1**),[16] which has been demethylated to morphine (**2**),[17] this work constitutes a formal total synthesis of those natural products.

Experimental Section

Melting points were measured on a Kofler hot stage and are uncorrected. Infrared spectra were obtained on a Beckman Acculab 8 spectrometer. Nuclear magnetic resonance spectra were recorded on Bruker HX-270, Bruker/IBM WP200 SY, or Bruker/IBM WP270 SY spectrometers; chemical shifts are reported in parts per million downfield from tetramethylsilane, and coupling constants are reported in hertz. Preparative TLC plates were prepared at a thickness of 1 mm from Merck PF 254 silica gel. Flash chromatography was performed according to the procedure given by W. Clark Still.[18] Microanalyses were carried out by Galbraith Laboratories, Knoxville, TN.

***N*-Methyl-3-(benzyloxy)-4-methoxybenzaldimine (9).** A solution of 10.0 g (323 mmol) of methylamine in 50 mL of benzene was prepared by bubbling the gaseous amine into cooled benzene. A portion of this solution (1.5 mL, containing 0.25 g or 8.1 mmol of methylamine) was added to a solution of 1.0 g (4.1 mmol) of *O*-benzylisovanillin[7] in approximately 20 mL of benzene. The resulting solution was stirred overnight. Anhydrous Na_2SO_4 was then added to remove the water droplets which had formed. The mixture was filtered and the solvent was evaporated to give 0.94 g (3.7 mmol, 89%) of the imine **9** as slightly yellow crystals: mp 67.5–68.5 °C; IR ($CHCl_3$) 3040, 2950, 2868, 1651, 1605, 1586, 1512, 1430, 1262, 1016 cm^{-1}; NMR ($CDCl_3$) δ 8.12 (1, s), 7.20–7.50 (6, m), 7.14 (1, dd, J = 9, 2), 6.85 (1, d, J = 9), 5.14 (2, s), 3.84 (3, s), 3.44 (3, d, J = 1); mass spectrum (low resolution, 70 eV), m/e (relative intensity) 256 (11), 255 (26), 164 (18), 92 (12), 91 (100).

***N*-[1,2-Bis[3-(benzyloxy)-4-methoxyphenyl]ethyl]-*N*-methylamine (11).** Magnesium turnings (10.0 g, 412 mmol) were covered with approximately 40 mL of anhydrous THF in a round-bottomed flask which had been flushed with N_2. Several drops of methyl iodide were added, and the resulting mixture was refluxed for 10 min in order to activate the magnesium. 3-(Benzyloxy)-4-methoxybenzyl chloride (**10**)[8] (5.45 g, 20.8 mmol) in 15 mL of THF was then added dropwise via an addition funnel to the refluxing solution over a period of 1.5 h. The resulting mixture was refluxed an additional 45 min and then was cooled, and the solution was transferred under nitrogen to a dry flask equipped with a condenser and an addition funnel. A solution of 1.36 g (5.33 mmol) of imine **9** in 15 mL of anhydrous THF was added over a period of 15 min. The resulting solution was refluxed for 15 min. It was then cooled in an ice–water bath and saturated aqueous ammonium chloride was added dropwise. The mixture was poured into a separatory funnel, and approximately 200 mL of diethyl ether and 200 mL of 1.2 N hydrochloric acid were added, the layers were separated, and the aqueous layer was washed with another portion of diethyl ether. The aqueous layer was neutralized with NH_4OH and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ layer gave very little residue. Hexane was added to the combined diethyl ether layers, and the product crystallized as its hydrochloride salt. The mixture was filtered and the crystalline product was dissolved in $CHCl_3$ and NH_4OH was added. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give 2.16 g (4.47 mmol, 84%) of free amine **11**: mp 124.5–126 °C (ether); IR ($CHCl_3$) 3020, 1600, 1515, 1445, 1258, 1215, 1025 cm^{-1}; NMR ($CDCl_3$) δ 7.23–7.50 (10, m), 6.58–6.50 (6, m), 5.13 (2, s), 5.05 (2, s), 3.86 (3, s), 3.85 (3, s), 3.48 (1, t, J = 7), 2.72 (2, m), 2.12 (3, s), 1.53 (1, br s); mass spectrum (low resolution, 70 eV), m/e (relative intensity) 483 (0.3), 257 (19), 256 (100), 165 (13), 91 (20). Anal. Calcd for $C_{31}H_{33}NO_4$: C, 76.99; H, 6.88; N, 2.90. Found: C, 76.85; H, 6.93; N, 2.88.

7-Hydroxy-1-(3-hydroxy-4-methoxybenzyl)-6-methoxy-*N*-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline [3-Oxoreticuline] (8). 2-Chloro-2-(methylthio)acetyl chloride (442 μL, 658 mg, 4.14 mmol) was added by syringe to a solution of 2.00 g (4.14 mmol) of amine **11** and 577 μL (419 mg, 4.14 mmol) of triethylamine in 30 mL of methylene chloride at room temperature. The resulting solution was stirred under N_2 for 15 min. Tin(IV) chloride (581 μL, 1290 mg, 4.97 mmol) was then added, and the resulting mixture was stirred for 45 min at room temperature. It was then washed twice with ice-cold water, dried over anhydrous Na_2SO_4, and evaporated to a viscous oil. The residue was dissolved in approximately 40 mL of glacial acetic acid, a large excess of zinc dist was added, and the resulting mixture was refluxed for 1 h. The mixture was cooled and filtered, and the acetic acid was evaporated. The resulting oil was dissolved in 10 mL of 95% ethanol. Concentrated hydrochloric acid (10 mL) was added, and the solution was refluxed for 1 h. After cooling, 50 mL of water was added and the solution was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with concentrated aqueous NH_4OH, dried over Na_2SO_4, and evaporated. The product was subjected to flash chromatography, eluting with 5% methanol in $CHCl_3$, and the resulting partially purified product was dissolved in a few milliliters of $CHCl_3$ from which 426 mg (1.11 mmol, 27% from **11**) of 3-oxoreticuline (**8**) crystallized: mp 330 °C dec; IR ($CHCl_3$) 3540, 2940, 1659, 1511, 1440, 1330, 1265, 1242, 1020 cm^{-1}; NMR ($CDCl_3$) δ 6.67 (1, d, J = 8), 6.63 (1, s), 6.43 (1, s), 6.33 (1, dd, J = 8, 2), 6.28 (1, d, J = 2), 5.54 (1, s), 5.47 (1, s), 4.51 (1, t, J = 4), 3.86 (3, s), 3.84 (3, s), 3.15 (1, d, J = 20), 3.08 (3, s), 3.04 (1, dd, J = 13, 5), 2.85 (1, dd, J = 13, 4) 2.52 (1, d, J = 20); mass

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(18) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

spectrum (low resolution, 70 eV), m/e (relative intensity) 207 (26), 206 (100), 178 (32), 163 (17), 137 (11). An analytical sample was prepared by recrystallization from $CHCl_3$, followed by drying of the sample overnight at 60 °C under vacuum. Anal. Calcd. for $C_{19}H_{21}NO_5 \cdot {}^1/_3CHCl_3$: C, 62.20; H, 5.76; N, 3.75. Found (1st anal.): C, 62.57; H, 5.88; N, 3.70; (2nd anal.): C, 62.52; H, 5.89; N, 3.78.

Vanadium Oxytrichloride Oxidation of 3-Oxoreticuline (8). Vanadium oxytrichloride (82 μL, 150 mg, 0.87 mmol) was added to a solution of 100 mg (0.26 mmol) of crystalline 3-oxoreticuline (8) (containing $^1/_3$ equiv of $CHCl_3$) in 150 mL of anhydrous, degassed methylene chloride stirred at −78 °C under N_2. After 2 h at −78 °C, the solution was stirred for 1.5 h at room temperature and for 1 h at reflux. The resulting deep blue solution was washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and evaporated to give a deep red oil. The crude product mixture was subjected to preparative TLC on a 20 × 20 cm plate, eluting with 15% methanol in diethyl ether. The most polar fraction gave 23 mg (0.067 mmol, 26%) of 16-oxopallidine (13): mp 293–296 °C dec; IR ($CHCl_3$) 3530, 2913, 1640, 1512, 1462, 1401, 1284, 915, 906 cm^{-1}; NMR ($CDCl_3$) δ 6.87 (1, s), 6.67 (1, s), 6.45 (1, s), 6.31 (1, s), 5.78 (1, br s, OH), 4.43 (1, t, J = 2), 3.94 (3, s), 3.80 (3, s), 3.29 (1, dd, J = 16, 2), 3.11 (1, dd, J = 16, 3), 3.02 (1, d, J = 16), 3.01 (3, s), 2.51 (1, d, J = 16); mass spectrum (low resolution, 70 eV), m/e (relative intensity) 341 (100), 326 (26), 310 (21), 298 (24), 282 (37), 270 (29). Anal. Calcd for $C_{19}H_{19}NO_5 \cdot {}^1/_2H_2O$: C, 65.13; H, 5.75; N, 4.00. Found: C, 64.92; H, 5.69; N, 3.83.

The least polar fraction was again subjected to preparative TLC, eluting with 10% methanol in $CHCl_3$, to give 10 mg (0.029 mmol, 11%) of 5-oxoisoboldine (14) as an oil: IR ($CHCl_3$) 3530, 3000, 2930, 1638, 1510, 1462, 1321, 1220, 905 cm^{-1}; NMR ($CDCl_3$) δ 8.04 (1, s), 6.85 (1, s), 6.50 (1, s), 6.17 (1, br s), 5.74 (1, br s), 4.37 (1, dd, J = 14, 4), 3.95 (3, s), 3.94 (3, s), 3.66 (2, m), 3.20 (3, s), 2.66 (1, d, J = 12); mass spectrum (low resolution, 70 eV), m/e (relative intensity) 341 (100), 340 (51), 326 (13), 324 (15), 309 (6), 284 (12), 283 (8), 206 (37).

Further preparative TLC of an intermediate fraction, eluting with 10% methanol in $CHCl_3$, gave 5 mg (0.015 mmol) of starting material, identified by its proton NMR spectrum.

Analogous purification of another intermediate fraction gave 8 mg (0.023 mmol, 9%) of a compound identified as 13-oxothalidine (15): mp 324 °C dec; IR ($CHCl_3$) 3530, 3000, 2920, 1640, 1510, 1250, 1014, 925 cm^{-1}; NMR ($CDCl_3$) δ 6.84 (1, s), 6.76 (1, s), 6.72 (1, s), 6.56 (1, s), 5.60 (2, br s), 4.41 (1, dd, J = 4, 2), 4.26 (1, s), 3.88 (3, s), 3.87 (3, s), 3.32 (1, dd, J = 17, 4), 3.10 (3, s), 2.95 (1, dd, J = 17, 2); mass spectrum (low resolution, 70 eV), m/e (relative intensity) 341 (38), 326 (19), 285 (20), 284 (100), 241 (31), 142 (24), 83 (22). Anal. Calcd for $C_{19}H_{19}NO_5 \cdot {}^1/_2H_2O$: C, 65.13; H, 5.75; N, 4.00. Found (1st anal.): C, 65.01; H, 5.73; N, 3.93; (2nd anal.): C, 64.89; H, 5.71; N, 3.83.

To a solution of 50 mg of 13-oxothalidine (15) in 25 mL of 95% ethanol was added 300 mg of NaOH. The mixture was heated to dissolve the NaOH, and approximately 1 mL of dimethyl sulfate was added. The solution was refluxed for 1 h, the solvent was evaporated, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water and then was dried over Na_2SO_4, and the solvent was removed to give 41 mg of O-methyl-13-oxothalisopavine; mp 231–232 °C (lit.[11] mp 231–233 °C).

Iodosobenzene Diacetate Oxidation of 3-Oxoreticuline (8). Iodosobenzene diacetate (275 mg, 0.854 mmol) was added to a solution of 293 mg (0.765 mmol) of crystalline 3-oxoreticuline (8) (containing $^1/_3$ equiv of $CHCl_3$) and 66 μL (98 mg, 0.85 mmol) of trifluoroacetic acid in 300 mL of anhydrous methylene chloride, stirred under N_2 at room temperature. After being stirred for 1 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and evaporated to give a deep red oil. Flash chromatography, eluting with 15% methanol in diethyl ether, gave three fractions. The intermediate fraction was subjected to preparative TLC on a 20 × 20 cm silica gel plate to give 70 mg (0.21 mmol, 27%) of 16-oxosalutaridine (12): mp 265–266.5 °C (EtOAc); IR ($CHCl_3$) 3525, 2940, 1681, 1643, 1522, 1491, 1443, 1422, 1284, 1080, 1031, 1010, 929, 909 cm^{-1}; NMR ($CDCl_3$) δ 7.42 (1, s), 6.78 (1, d, J = 8), 6.63 (1, d, J = 8), 6.40 (1, s), 6.39 (1, br s, OH), 4.39 (1, t, J = 2), 3.89 (3, s), 3.73 (3, s), 3.56 (1, d, J = 17), 3.31 (1, dd, J = 17, 2), 3.09 (1, d, J = 17), 2.94 (3, s), 2.32 (1, d, J = 17); mass spectrum (low resolution, 70 eV), m/e (relative intensity) 342 (29), 241 (100), 340 (19), 312 (20), 310 (28), 298 (32), 283 (31), 282 (43), 270 (33), 256 (18), 239 (18), 206 (31). Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.70; H, 5.69; N, 3.96.

The most polar fraction from the flash chromatography column gave 20 mg (0.059 mmol, 8%) of 16-oxopallidine (13).

The third fraction from the flash chromatography column contained 172 mg of an alkaloid mixture, which NMR indicated to consist of 5-oxoisoboldine (14), 3-oxoreticuline (8), and 13-oxothalidine (15). Several milliliters of 1.0 M BH_3/THF were added to this mixture and the resulting solution was stirred for 2 h, after which the excess BH_3 was decomposed by dropwise addition of methanol. The solvent was removed and the residue was warmed in 5 mL of concentrated HCl and 5 mL of methanol for 0.5 h to decompose the amine–borane complexes. The solvent was evaporated and the residue was dissolved in water, neutralized with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4, the solvent was evaporated, and the products were separated by using a 20 × 20 cm preparative TLC plate, eluting with 10% methanol/$CHCl_3$ with several drops of NH_4OH added, to give 15 mg (0.046 mmol, 6% from 8) of isoboldine, identical with authentic[5] isoboldine by TLC and NMR analysis. Also isolated were 5 mg (0.015 mmol, 2% from 8) of reticuline (3), identified by TLC and NMR, and 25 mg (0.076 mmol, 10% from 8) of thalidine; mp 236–239 °C (lit.[14] mp 237.5–239 °C); IR ($CHCl_3$) 3555, 3010, 2840, 1510, 1453, 1271, 1030, 875, 847, 800 cm^{-1}; NMR ($CDCl_3$) δ 6.73 (1, s), 6.70 (1, s), 6.60 (1, s), 6.52 (1, s), 3.86 (6, s), 3.40–3.64 (4, m), 2.80–2.94 (2, m), 2.47 (3, s); mass spectrum (low resolution, 70 eV), m/e (relative intensity) 327 (28), 326 (25), 311 (8), 285 (10), 284 (51), 241 (11), 191 (14), 190 (100).

Iodosobenzene Diacetate Oxidation of *N*-(Ethoxycarbonyl)-*N*-norreticuline (17). Iodosobenzene diacetate (42 mg, 0.13 mmol) was added to a solution of 50 mg (0.13 mmol) of *N*-(ethoxycarbonyl)-*N*-norreticuline[2] (17) and 10 μL (0.13 mmol) of trifluoroacetic acid in 150 mL of anhydrous methylene chloride at room temperature. The solution was stirred for 2 h under N_2 and then was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed and the product mixture was subjected to preparative TLC, eluting with 5% methanol in $CHCl_3$. The major fraction was further separated on another preparative TLC plate, eluting with diethyl ether, to give 9.0 mg (0.023 mmol, 18%) of *N*-(ethoxycarbonyl)-*N*-norisoboldine (19), identical with an authentic sample[12] by TLC and NMR comparison [NMR ($CDCl_3$) δ 8.08 (1, s), 6.82 (1, s), 6.58 (1, s), 6.13 (2, br s, OH), 4.61–4.88 (1, m), 4.21 (2, q, J = 7), 3.94 (3, s), 3.92 (3, s), 2.42–3.04 (6, m), 1.28 (3, t, J = 7)] and 11 mg (0.029 mmol, 22%) of *N*-(ethoxycarbonyl)-*N*-norsalutaridine (18), also identical with an authentic sample[2a] by TLC and NMR comparison [NMR ($CDCl_3$) δ 7.53 (1, s), 6.79 (1, d, J = 8), 6.63 (1, d, J = 8), 6.34 (1, s) 5.10 (1, m), 3.90 (3, s), 3.75 (3, s), 3.17 (2, m)].

DDQ Oxidation of 3-Oxoreticuline (8). 2,3-Dichloro-5,6-dicyanobenzoquinone (33 mg, 0.15 mmol) was added to a solution of 50 mg (0.13 mmol) of crystalline 3-oxoreticuline (8) (containing $^1/_3$ equiv of $CHCl_3$) in 40 mL of anhydrous methylene chloride at room temperature. The solution was stirred for 1 h and then was evaporated to give 82 mg of crude product. Recrystallization of the solid from $CHCl_3$ gave 38 mg (0.11 mmol, 85%) of 13-oxothalidine (15).

When the same reaction was carried out in the presence of 1 equiv of trifluoroacetic acid, the only product observed by NMR was again 13-oxothalidine (15).

(±)-Thebaine (22). A solution of 17 mg (0.050 mmol) of 16-oxosalutaridine (12) in 2 mL of anhydrous THF was added to a solution of excess $LiAlH_4$ in 30 mL of anhydrous THF. The resulting mixture was refluxed under N_2 for 48 h. It was then cooled to room temperature and water was added dropwise to destroy the excess hydride. The solvent was evaporated and the resulting residue was dissolved in water. This solution was carefully acidified to approximately pH 3 and then was neutralized with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and evaporated to give 16 mg of crude (±)-salutaridinol (21).

The crude product was dissolved in 2 mL of $CHCl_3$ and to it was added 41 μL (31 mg, 0.15 mmol) of dimethylformamide dineopentyl acetal.[15] The resulting solution was allowed to stand at room temperature for 2 h. The volatile components were then

evaporated, and the residue was subjected to preparative TLC, eluting with 15% methanol/$CHCl_3$ with several drops of NH_4OH added, to give 4 mg (0.013 mmol, 26%) of (±)-thebaine (**22**): mp 184–187 °C (lit.[19] mp 184–186 °C); NMR ($CDCl_3$) δ 6.66 (1, d, J = 8), 6.59 (1, d, J = 8), 5.55 (1, d, J = 7), 5.29 (1, s), 5.04 (1, d, J = 7), 3.85 (3, s), 3.60 (3, s), 2.46 (3, s).

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Registry No. **8**, 94707-55-8; **9**, 94707-56-9; **10**, 1699-38-3; **11**, 94707-57-0; **12**, 94707-61-6; **13**, 94707-58-1; **14**, 94707-59-2; **15**, 94707-60-5; **17**, 55869-76-6; **18**, 55729-21-0; **19**, 87332-78-3; **21**, 72402-41-6; **22**, 23979-19-3; 2-chloro-2-(methylthio)acetyl chloride, 79388-13-9; *O*-methyl-13-oxothalisopavine, 68890-17-5; isoboldine, 3019-51-0; reticuline, 485-19-8; thalidine, 63110-83-8.

Nucleosides from Carbohydrate Adducts of Diaminomaleonitrile. A Novel Synthesis of 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide and 5-Amino-1-(β-D-ribopyranosyl)imidazole-4-carboxamide

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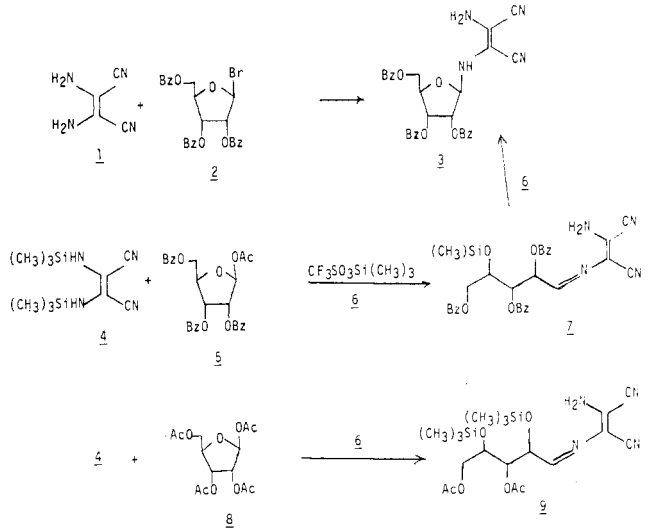
The stereospecific and regiospecific synthesis of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**16**) was achieved in six steps. A key intermediate in the synthesis, *N*-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)diaminomaleonitrile (**3**), was prepared by two routes: the reaction of diaminomaleonitrile (**1**) with 1-bromo-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) and the reaction of the bis(trimethylsilyl) derivative of diaminomaleonitrile (**4**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**). Reaction of **3** with triethyl orthoformate yielded 4,5-dicyano-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**10**). Alternatively **10** was synthesized by the acid-catalyzed cyclization of the *N*-formyl derivative **12** which was prepared by the reaction of the trimethylsilyl derivative of *N*-formyldiaminomaleonitrile **11** with **5**. Deblocking **10** with 1 equiv of sodium methoxide at room temperature resulted in the regiospecific formation of the 5-imidate **14**. Reaction of **14** with alkaline hypochlorite yielded 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonitrile (**15**) by a Hofmann rearrangement. Alkaline hydrolysis of the nitrile function yielded the corresponding amide **16**. 5-Amino-1-(β-D-ribopyranosyl)imidazole-4-carboxamide (**28**) was prepared by a similar synthetic sequence. Reaction of diaminomaleonitrile (**1**) with ribose gave a mixture of the α- and β-anomers of D-ribopyranosyldiaminomaleonitrile (**17**). Compound **17** was converted to a mixture of the anomeric tri-*O*-acetates which on heating with triethyl orthoformate gave a separable mixture of the α- and β-anomers of 4,5-dicyano-1-(2′,3′,4′-tri-*O*-acetyl-D-ribopyranosyl)imidazole (**19** and **20**, respectively). Reaction of **19** with NH_3/CH_3OH at room temperature cleaved the three acetyl groups and regiospecifically converted the 5-cyano to the 5-imidate (**26**). The regiospecificity is due to the attack of the 2′-oxy anion on the 5-cyano group as shown by the isolation of the cyclic imidate **25** when the reaction is carried out at 0 °C. The Hofmann rearrangement of imidate **26** followed by alkaline hydrolysis gave 5-amino-1-(β-D-ribopyranosyl)imidazole-4-carbonitrile **27** and **28**, respectively. The ^1H and ^{13}C NMR spectra of imidates **14** and **26** have multiple peaks for the protons and carbons, respectively. Restricted rotation of the 5-imidate (energy of activation 18 kcal) results in isomers of **14** and **26** with different NMR spectra. The C-2, H-1′ coupling constants of 2.5–3.1 Hz of the isomeric species comprising imidates **14** and **26** are consistent with a H-2, H-1′ dihedral angle of 135° and an anti orientation of the imidazole with respect to the ribose ring; a conclusion confirmed by NOE measurements.

Enamino nitriles are versatile starting materials for the synthesis of heterocyclic compounds[1] and carbohydrate adducts of enaminonitriles have been utilized in this laboratory for the thermal[2] and photochemical[3] synthesis of novel nucleosides. Diaminomaleonitrile (DAMN) (**1**), a "double" enaminonitrile, has rich and varied chemistry, both in the areas of organic synthesis[4] and prebiotic synthesis.[5] The use of ribopyranosylDAMN as the starting material for the synthesis of the ribopyranosides of 4,5-dicyanoimidazole and 4,5-dicyanotriazole was outlined in a preliminary communication.[6]



The synthesis of a corresponding β-D-ribofuranoside and β-D-ribopyranoside adducts of DAMN is reported herein along with their conversion to the corresponding ribo-

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