Novel Ring–Chain Tautomers Derived from (*o*-Formylphenyl)ethylamines[1]

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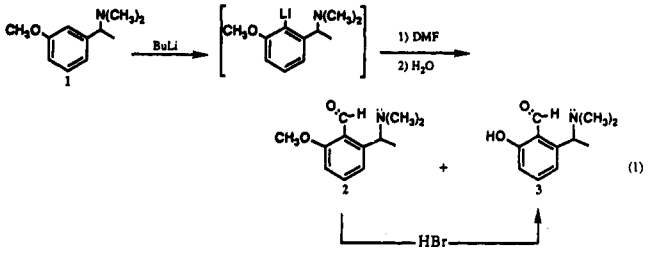
The synthesis and characterization of some (*o*-formylphenyl)ethylamines are described. Formylation with DMF of regioselectively lithiated *N,N*-dimethyl-α-(*m*-methoxyphenyl)ethylamine (1) has provided a route to an unusual ring–chain tautomeric system in which the ring has the dihydroisoindolium structure. The ring tautomers, with two chiral centers, consist of unequal amounts of two racemates, which undergo rapid, base-catalyzed interconversion at ambient temperature on the 360-MHz NMR time scale. The geometry and relative energies of the diastereomeric ring structures were estimated from MMP2 calculations. The trans dihydroisoindolium 3,5-dinitrobenzoate (**4d**) was characterized by X-ray diffraction, and its geometry was compared with that predicted by calculation. From NMR experiments with the simpler amino aldehyde **6**, it has been concluded that, although a methoxy or hydroxy substituent ortho to the formyl group is not a structural requirement for ring tautomerism, it serves to favor the ring over the chain tautomer. The (*o*-formylphenyl)ethyl sulfides **8** and **9**, obtained by nucleophilic displacement of the methiodides, show no propensity for ring formation.

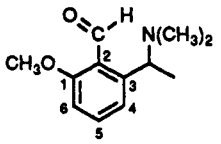
Synthesis. In the course of designing salicyl aldehydes containing a resolvable functional group, we chose the phenylethylamine series, because optically active *N*-methyl(*m*-hydroxyphenyl)ethylamine had already been reported.[2] Introduction of a formyl group between the two substituents in **1** by way of a directed metalation seemed a promising route. We eventually worked out conditions for efficient, regioselective lithiation of **1** and its in situ formylation with DMF. The aldehyde **2** was isolated in 85% yield under optimum conditions (see the Experimental Section). Although the salicyl aldehyde **3** could not be obtained efficiently by a similar metalation–formylation of the aminophenol, we synthesized it by two different routes. Cleavage of the methoxy group in **2** (albeit by way of the ring tautomeric salt) by HBr afforded **3** in 83% yield. This product was identical with a second



(1)

material isolated from the metalation–formylation of **1** with excess butyllithium. Isolation of **2** and **3** separately from the metalation reaction depends on the amphoteric nature of **3**. The initial reaction mixture, decomposed with water, was made even more strongly alkaline by the addition of NaOH. Extraction at this high pH removed **2** into the organic phase. Readjustment of the pH to about 8 and a second extraction removed the phenolic aldehyde **3**. It was crucial that the amount of water be minimized because of the high solubility of both **2** and **3** in water. The use of increasing amounts of butyllithium enhanced the formation of **3** at the expense of **2**. Presumably the intermediate A, formed initially from reaction of DMF with the metalated compound, can coordinate with another lithium atom through the ether oxygen and thus nucleophilic attack by butyllithium at the methyl in B is facilitated.[3]

Table I. ^{13}C Correlation Values for Compound 2



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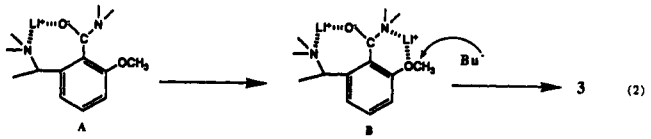
C	calcd (ppm)	actual ($CDCl_3$)	C	calcd (ppm)	actual ($CDCl_3$)
1	161.0	159.9	4	122.2	118.7
2	123.5	125.4	5	134.8	132.5
3	141.9	147.8	6	113.2	109.7



(2)

Ring–Chain Tautomeric Structures. The structure of **2** in chloroform was confirmed by its ^1H and ^{13}C NMR spectra. The aldehyde proton is at 10.14 and the aldehydic carbon at 187.7 ppm. The chemical shifts and couplings of the three adjacent aromatic protons are consistent with predictions,[4] as is the correlation of carbon shifts with calculated values[5,6] (see Table I). The carbonyl stretching in the IR spectrum (KBr) is strong at 1680 cm^{-1}, and a 2,4-dinitrophenylhydrazone sulfate derivative made from the hydrochloride salt was fully characterized. The structure of the phenolic aldehyde **3** was confirmed in much the same way (see the Experimental Section).

The situation changes drastically, however, when **2** and **3** are examined in the presence of water or as their salts. All characteristics of an aldehyde disappear, and the NMR spectra take on new features that are consistent with the ring tautomeric structure **4**. This can be illustrated by contrasting the NMR spectra of the methoxy compound

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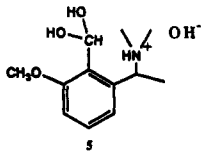
in chloroform, described above, with those in D_2O. In the ^1H NMR spectrum a new peak at 6.45 ppm is assigned to the hemiaminal methinyl (formerly aldehydic) proton; the quartet at 4.55 ppm (also one H), downfield from that in **2**, is assigned to the methinyl adjacent to the quaternary nitrogen; finally, the *N*-methyls (6 H's) have changed from a sharp singlet to a broad doublet shifted somewhat downfield. The ^{13}C NMR spectrum has changed in a consistent manner: the aldehyde carbon at 187.7 has disappeared and been replaced by a resonance at 117.8; the *N*-methyl carbons have changed from a sharp singlet at 41.7 to two broad peaks centered at 43.5. The spectra of salts **4b–d**, also devoid of any aldehyde characteristics, exhibit very similar patterns (see the Experimental Section). An alternative structural assignment for **4a** (but not the salts **4b–d**) would be the hydrate of the ammonium hydroxide **5**, which should also contain the downfield



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methines and diastereotopic *N*-methyls, consistent with the NMR spectra. We feel the hydrate is unlikely after an analysis of the direction of ^{13}C NMR shifts from the "ring" **2** to the "chain" **4a**. It is known that alkylation of an amine to give the quaternary salt causes a significant downfield shift (~10 ppm) of the carbons α to the nitrogen because of the β-effect of the added carbon.[7,8] Protonation of the amine, on the other hand, is associated with a smaller shift which can be upfield or downfield.[9] The ^{13}C NMR spectra of both **2** and **3** in D_2O show the downfield shift (9.6 and 10.2, respectively) expected for a quaternary nitrogen. As a point of reference, the model compound **1**, protonated as the picrate, shows a downfield shift in the benzylic carbon of only 1.1 ppm.

Isolation and Characterization of the Ring Tautomers. Conversion of **2** to its hydrochloride **4b** and picrate **4c** led to a mixture of diastereomers, as evidenced by a doubling of all the resonances in the ^1H and ^{13}C NMR spectra, but the peaks remained sharp. Although we were not able to assign each set of resonances to the cis and trans diastereomeric structures **4b,c**, we prepared the corresponding 3,5-dinitrobenzoate **4d**, which crystallized as the trans isomer. X-ray crystal diffraction analysis of **4d** confirms the ring tautomeric structure and the configuration, as depicted in Figure 1. The C–N bond of the hemiaminal is unusually long [1.581 (4) Å], and the C8–O2 bond is unusually short [1.366 (3) Å], characteristics that have been reported in fused hemiaminals such as the cation of retusamine.[10] Of particular note is the unsymmetrical hydrogen bonding between the carboxylate and the hemiaminal OH, which is in the pseudoaxial conformation.

From MMP2 calculations[11] carried out with a carbon in place of the quaternary nitrogen, we were able to assemble a structure for the trans pseudoaxial tautomer whose dihedral angles for the most part are in good agreement with those from the X-ray structure (Table II). The only anomaly is the hemiaminal OH, which from the MMP2 calculations is consistently oriented toward a lone pair of the methoxy group.

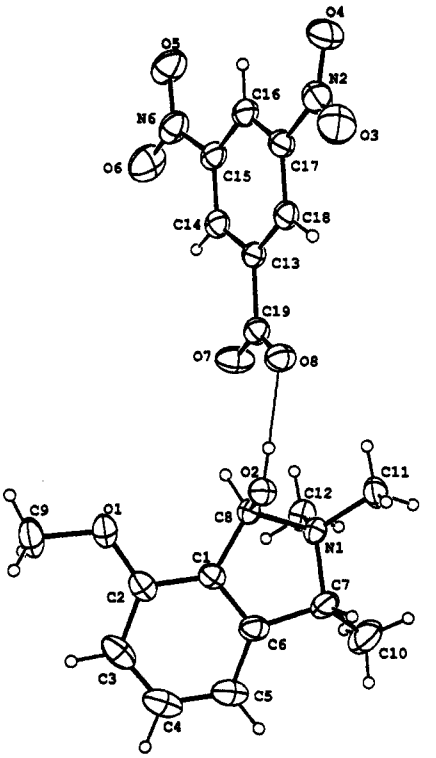
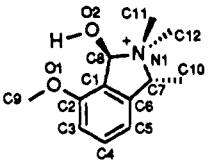


Figure 1. X-ray structure of *trans*-**4d**.

Table II. Dihedral Angles in *trans*-4d



atoms	ϕ^a	ϕ^b	atoms	ϕ^a	ϕ^b
N1–C7–C6–C1	-19.3	-18.3	O2–C8–C1–C6	-99.9	-100.2
C1–C8–N1–C11	-149.9	-150.3	C1–C8–O2–HO2	~170	-60.7
C1–C8–N1–C12	90.5	90.3	C9–O1–C2–C3	-9.4	-1.8
C1–C6–C7–C10	-144.4	-145.0			

[a] From X-ray data. [b] Calculated by the MMP2 program for the energy minimized trans isomer with the hydroxyl group in the *pseudoaxial* conformation (C substituted for N1).

Both the hydrochloride **4b** and the picrate **4c** exist as unequal amounts of the cis and trans diastereomers in CD_3CN–D_2O solution, as evidenced by the doubling of the NMR resonances. The ratio of diastereomers is 1.5–1.6, as determined by integration. From the energy differences obtained from MMP2 calculations, one can estimate a diastereomeric bias of 1.1–1.2. The cis isomer with pseudoaxial OH actually has the lowest energy of the four possibilities, but because the differences are unusually small (0.5 kcal at the extreme),[11] there is no basis on which to make a configurational assignment for the favored diastereomer in solution. By contrast the 3,5-dinitrobenzoate in the same solvent shows only a single set of resonances, which appear at about the weighted average of those in **4b** and **4c**. Addition of a trace of NaOD to **4b** caused its ^1H NMR spectrum to simplify to a single set of peaks, and addition of 0.9 equiv of triethylamine to **4c** had the same effect. A plausible pathway for the interconversion of

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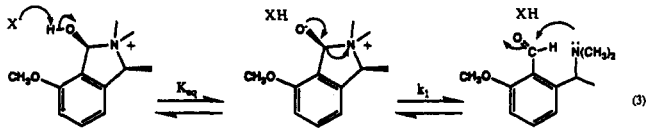
Table III. UV Spectral Study

compound	solvent	λ (nm)	log ε
o-methoxybenzaldehyde	CH_3CN	252	4.0
		320	3.73
2 methiodide	CH_3CN	248	4.11
		325	3.61
2	CH_3CN	253	3.57
		322	3.45
2	$CHCl_3$	257	3.70
		324	3.40
2	H_2O	278	3.37
		375	2.77
4b	CH_3CN/H_2O	278	3.30
		373	2.92

diastereomers by way of the aldehyde is represented in eq 3. From this it can be shown that the rate of ring opening

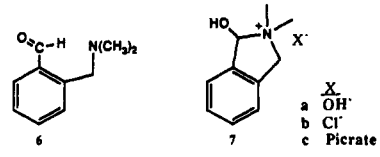


(3)

to 2 is inversely proportional to acid concentration; thus the addition of base would be expected to increase the rate of interconversion of diastereomers through ring opening. Apparently in the case of the 3,5-dinitrobenzoate 4d the aqueous acetonitrile solution represents a rapidly interconverting diastereomeric pair. Evidence in support of this assumption came from an experiment in which 0.75 equiv of trifluoroacetic acid was added to the sample, whereupon all of the resonances doubled, the ratio of diastereomers again being 1.6. It seems that substitution of the weaker base trifluoroacetate for the stronger base 3,5-dinitrobenzoate slows the rate of interconversion to the point that both diastereomers are observed.

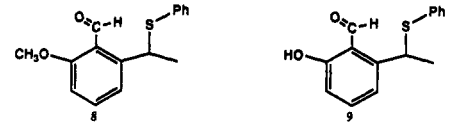
Any aldehyde present in the equilibrating mixture of diastereomers must be very low, for it is undetectable by UV. In fact the UV spectral study summarized in Table III further supports the ring structures 4. While the spectra of o-methoxybenzaldehyde, the methiodide of 2, and of 2 in nonaqueous solvents are all quite similar, those of 2 in water and of the HCl salt (4b) show weaker maxima shifted to lower energy. This change is consistent with a disappearance of the benzaldehyde chromophore, which would come about through interaction of the nitrogen lone pair with the carbonyl carbon.

Even though the methoxy series has been discussed in more detail, we propose that the hydroxy compounds derived from 3, whose spectral properties parallel those in the methoxy series, exhibit a similar tautomeric behavior (see the Experimental Section). We have reexamined the spectral behavior of the known amino aldehyde 6[12] to determine whether the substituent ortho to the aldehyde is a structural requirement for ring tautomer formation. Its behavior is qualitatively similar to that for 2 and 3; that is, it fits the aldehyde structure in a nonaqueous solvent but gives evidence of the ring tautomeric, ammonium structure 7 in the presence of water. The striking difference, however, is that salts of 6 are mixtures of the ring (7) and its tautomer, the N-protonated aldehyde. The hydrochloride and picrate, for example, exist as mixtures of N-protonated aldehyde (chain) and quaternary hemiaminal (ring, 7b,c) in aqueous acetonitrile, with a ring/chain ratio of 2.5–3. This ratio is based upon relative integrations of either methine:aldehyde or benzylic protons. We do not feel the integration values for the N-methyls are as reliable, because the upper singlet for the ring tautomer overlaps with the singlet for the chain tautomer and thus the integrations are not internally consistent. The ^1H NMR spectrum of the hydrochloride of 6 in water is very broad, suggesting relatively fast ring/chain interconversion. This was confirmed by adding to the solution a trace of TFA, which slowed the exchange, as expected, and produced a spectrum showing both tautomers in a ring/chain ratio of about 1.5. In another experiment, TFA was added gradually to 6 in D_2O. No change was observed in the broad ^1H NMR spectrum until a slight excess of TFA was present. At this point the spectrum shows both ring and chain tautomers, in a ratio of about 1.5, and is virtually identical with that of the HCl salt with a trace of TFA. These NMR experiments involving 2, 3, 6, and their ring tautomers demonstrate that the o-methoxy and hydroxy groups, while not essential, serve to favor the ring tautomer. A plausible explanation is a stabilization of the ring tautomer through hydrogen bonding of the hemiaminal OH with the ether or phenolic oxygen in solution.[13]



6 7 a OH⁻ b Cl⁻ c Picrate

By means of a nucleophilic displacement with benzenethiolate on the methiodides of 2 and 3 we were able to prepare the benzaldehydes 8 and 9. In neither case was there any indication from the spectra that the sulfur function showed any tendency to participate in a similar ring tautomer formation.



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Conclusion

To our knowledge the (o-formylphenyl)ethylamines represent the first examples of ring–chain tautomerism in which the ring is a monocyclic aminal derivative containing a quaternary nitrogen and the chain tautomer is an N-protonated amino aldehyde. A reexamination of the structures of similarly constituted amines may reveal this to be a general phenomenon. This type of behavior is reminiscent of the transannular interaction first reported by Leonard and co-workers in amino ketones leading to bicyclic structures, exemplified by medium-ring aza acyloins and aza cyclanones[14-17] where the structural assignments were based on IR analysis. Evidence from ^{13}C NMR spectroscopy in a similar aza cyclanone depends on the marked shift in the carbonyl carbon with a change in solvent.[18]

Our model compounds resemble several alkaloids with the aza cyclanone backbone which have been studied by

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a variety of methods. The X-ray structure of clivorine[19] shows that the nitrogen–carbonyl carbon distance is unusually short; that of the bromocamphorsulfonate of retusamine[20] indicates it to be the O-protonated tautomer. According to NMR studies,[21] the alkaloids themselves appear to exist as one diastereomer in solution, in contrast to our observations for the (*o*-formylphenyl)ethylamines.

Experimental Section

All elemental analyses were performed by Ms. Deanna Cardin at the University of New Hampshire with a Perkin-Elmer 240B elemental analyzer.

Infrared spectra were recorded with a Nicolet MX-1 Fourier transform spectrophotometer or a Perkin-Elmer Model 283B grating spectrophotometer. The ^1H and ^{13}C NMR spectra were determined with a Bruker AM 360 Fourier transform spectrometer operating at 360 MHz relative to TMS unless otherwise indicated. The UV/vis spectra were recorded with a Varian/Cary 219 spectrophotometer interfaced with an Apple IIe computer. The mass spectra were determined with a Hewlett-Packard 5890 instrument by Mr. William Dotchin at the University of New Hampshire. Flash chromatography was accomplished with Merck Kieselgel 60, 230–400-mesh ASTM.

(±)-*N,N*-Dimethyl-α-(2-formyl-3-methoxyphenyl)ethylamine (2). The amine 1 was prepared by methylating (±)-*N*-methyl-α-(3-methoxyphenyl)ethylamine with formaldehyde and formic acid.[22] To a solution of the amine 1 (2.01 g, 11.2 mmol) in anhydrous ether was added 1.1 equiv of *n*-butyllithium (2.5 M in hexane) with stirring at ambient temperature in a stream of N_2. Stirring was maintained for 2.5 h and then DMF was added from a syringe until the solution no longer refluxed spontaneously (total of 1.1 equiv). The resulting clear yellow solution was stirred for 15 min and then decomposed with H_2O. When the mixture had cooled to room temperature, 10 mL of 33% NaOH was added, the organic phase was separated from the aqueous phase, and the latter was extracted with 4 × 100 mL of ether. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to leave 1.98 g of an orange oil (85%). This was converted to the HCl salt, which was recrystallized once from methanol/ether. The salt was then taken up in 20% NaOH, and the free amine was recovered by ether extraction, drying ($MgSO_4$), removal of solvent, and Kugelrohr distillation (99–108 °C (1.2 mmHg)). For example, 1.52 g of salt afforded 1.086 g (84%) of a pale green solid: mp 57–58 °C; IR (KBr) 1049 (sym COC stretch), 1180 (CN stretch), 1262 (asym COC stretch), 1677 cm^{-1} (C=O stretch); ^1H NMR ($CDCl_3$) δ 1.32 (d, 3 H, CH_3CH, ^3J = 7 Hz), 2.18 (s, 6 H, $(CH_3)_2N$), 3.86 (s, 3 H, CH_3O), 4.00 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 6.84 (d, 3 H, ArH_c, $^3J_{bc}$ = 8 Hz), 7.08 (d, 1 H, ArH_a, $^3J_{ab}$ = 8 Hz), 7.38 (m, 1 H, ArH_b), 10.14 (s, 1 H, CHO); ^1H NMR (D_2O, CH_3CN reference) δ 1.58 (d, 3 H, CH_3CH, ^3J = 7 Hz), 2.54, 2.80 (2 br s, 6 H, $(CH_3)_2N$), 3.86 (s, 3 H, CH_3O), 4.55 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 6.45 (s, 1 H, CHOD), 6.88–7.44 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$) 187.70, 159.95, 147.91, 132.50, 125.44, 118.70, 109.68, 59.77, 55.74, 41.66, 17.03; ^{13}C NMR (D_2O, CH_3CN reference) 158.46, 142.47, 133.95, 129.98, 118.02, 117.75, 114.48, 69.42, 58.20, 45.37 (br), 41.55 (br), 14.28; MS 207 (10), 192 (61), 162 (100), 149 (34), 133 (31), 91 (32), 72 (22). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.76; H, 8.42; N, 6.80. When the butyllithium was added in excess (3–5 equiv), cleavage of the methoxy group was extensive. Extraction with chloroform of the reaction mixture adjusted to pH ~8 afforded the salicyl aldehyde 3, which was identical with the product of HBr cleavage of 4b. **Methiodide of 2.** Methyl iodide (2 mL, 0.032 mol) was added with stirring under N_2 to a solution of the amino aldehyde 2 (3.33 g, 0.016 mol) in acetonitrile (20 mL) cooled in an ice water bath. After addition of 20 mL of ether in 10 min and refrigeration overnight, the solvents were removed under reduced pressure to leave a solid residue (4.72 g). This was crystallized from methanol/ether and then recrystallized once each from 1-propanol and ethanol/ether and twice from ethyl acetate/ethanol to yield 2.09 g (37%) of a pale yellow solid: mp 164–166 °C dec; IR (KBr) 1051 (sym COC stretch), 1267 (asym COC stretch), 1679 cm^{-1} (C=O stretch); ^1H NMR (D_2O, CH_3CN reference) δ 1.72 (d, 3 H, CH_3CH), 3.06 (s, 9 H, $(CH_3)_3N$), 3.96 (s, 3 H, CH_3O), 5.99 (q, 1 H, $CHCH_3$), 7.36–7.80 (m, 3 H, ArH), 10.49 (s, 1 H, CHO); ^{13}C NMR (D_2O, CH_3CN reference) 198.30, 166.89, 139.41, 137.01, 125.80, 124.37, 117.61, 68.68, 59.22, 53.83 (br d), 17.66. Anal. Calcd for $C_{13}H_{20}INO_2$: C, 44.71; H, 5.77; N, 4.01. Found: C, 44.54; H, 6.04; N, 4.04.

(±)-1*H*-1-Hydroxy-2,3-dihydro-2,2,3-trimethyl-7-methoxyisoindolium Chloride (4b). A solution of the amine 2 (3.00 g, 0.0145 mol) in 10 mL of H_2O and 3 mL of concd HCl was concentrated by chasing with methanol under reduced pressure. The residue was taken up in methanol, and ether was added until cloudiness persisted. After the contents had been refrigerated for 4 days, the crystals were collected and recrystallized once from 1-propanol and twice from methanol/ether to yield 1.891 g (54%) of white solid: mp 210–211 °C dec; IR (KBr) 1271 cm^{-1} (asym COC stretch); ^1H NMR (CD_3CN with D_2O) δ 1.59 (d), 1.61 (d, 3 H, CH_3CH), 2.76 (s), 2.88 (s), 3.06 (s), 3.10 (s, 6 H, $(CH_3)_2N$), 3.85 (s), 3.86 (s, 3 H, CH_3O), 4.69 (q, 0.4 H, $CHCH_3$), 4.94 (q, 0.6 H, $CHCH_3$), 6.10 (s, 0.6 H, CHOH), 6.18 (s, 0.4 H, CHOH), 6.86–7.52 (m, 3 H, ArH); ^{13}C NMR (CD_3CN with D_2O) 157.52, 157.11, 141.68, 140.66, 134.19, 133.86, 122.50, 121.47, 116.03, 115.83, 112.91, 112.75, 100.49, 100.05, 73.49, 71.41, 56.60, 55.90, 50.85, 44.19, 43.84, 40.27, 17.80, 11.50. Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.14; H, 7.44; N, 5.75. Found: C, 59.20; H, 7.65; N, 5.73.

2,4-Dinitrophenylhydrazone from 4b. A solution of 4b (0.138 g, 6.7 × 10^{-4} mol) in 5 mL of 95% ethanol was combined with 4 mL of a solution of 0.4 g of 2,4-dinitrophenylhydrazine, 10 mL of 95% ethanol, 3 mL of H_2O, and 2 mL of concd H_2SO_4. After 4 h the solid was collected and washed with ethanol. It was recrystallized twice from 1:1:1 methanol/ethyl acetate/hexanes to give 0.057 g (18%) of an orange powder: mp 212–220 °C dec; IR (KBr) 1336 (sym NO_2 stretch), 1588 (asym NO_2 stretch), 1618 (C=N stretch), 2600–3200 cm^{-1}, broad absorption; ^1H NMR (CD_3OD/TMS) δ 1.80 (d, 3 H, CH_3CH, ^3J = 7 Hz), 2.78 (s, 3 H, $(CH_3)_2N$), 2.96 (s, 3 H, $(CH_3)_2N$), 3.97 (s, 3 H, CH_3O), 5.41 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 7.24–7.65 (m, 3 H, ArH), 8.44 (s, 1 H, CHN), 7.88 (d, 1 H, ^3J = 10 Hz), 8.44 (dd, 1 H, ^3J = 10 Hz, ^4J = 3 Hz), 9.07 (d, 1 H, ^4J = 3 Hz, ArH of 2,4-DNP); ^{13}C NMR (CD_3OD/TMS) 161.35, 147.39, 145.81, 139.66, 136.87, 133.56, 131.46, 131.09, 124.17, 122.93, 120.23, 117.38, 113.43, 63.49, 56.80, 42.91, 40.73, 16.57. Anal. Calcd for 2,4-DNP·H_2SO_4, $C_{18}H_{23}N_5O_9S$: C, 44.53; H, 4.56; N, 14.42. Found: C, 44.93; H, 4.74; N, 14.60.

(±)-1*H*-1-Hydroxy-2,3-dihydro-2,2,3-trimethyl-7-methoxyisoindolium Picrate (4c). A solution of the HCl salt 4b (0.099 g, 4.07 × 10^{-4} mol) in 5 mL of 95% ethanol was combined with an equimolar amount of picric acid in 95% ethanol. Crystals formed after the solution had been cooled overnight at −20 °C. Three recrystallizations from 95% ethanol afforded 0.042 g (24%) of feathery yellow crystals: mp 167–168 °C; R_f 0.23 (2:1:1 methanol/hexanes/ethyl acetate); IR (KBr) 1280 (asym COC stretch), 1321 (sym NO_2 stretch), 1568 (asym NO_2 stretch), 3424 cm^{-1} (OH stretch); ^1H NMR (acetone-d_6) δ 1.78 (d), 1.81 (d, 3 H, CH_3CH), 3.04 (s), 3.16 (s), 3.33 (s), 3.34 (s, 6 H, $(CH_3)_2N$), 3.88 (s), 3.89 (s, 3 H, CH_3O), 5.04 (q, 0.4 H, $CHCH_3$), 5.21 (q, 0.6 H, $CHCH_3$), 6.32 (s, 0.6 H, CHOH), 6.42 (s, 0.4 H, CHOH), 6.92–7.55 (m, 3 H, ArH, isoindolium), 8.65 (s, 2 H, ArH, picrate); ^1H NMR (CD_3CN with D_2O) δ 1.583 (d), 1.575 (d, 3 H, CH_3CH), 2.71 (s), 2.78 (s), 3.00 (s), 3.01 (s, 6 H, $(CH_3)_2N$), 3.82 (s), 3.83 (s, 3 H, CH_3O), 5.04 (q, 0.4 H, $CHCH_3$), 4.66 (q, 0.4 H, $CHCH_3$), 4.88 (q, 0.6 H, $CHCH_3$), 5.97 (s, 0.6 H, CHOH), 6.06 (s, 0.4 H, CHOH), 6.84–7.51 (m, 3 H, ArH, isoindolium), 8.67 (s, 2 H, ArH, picrate). Anal. Calcd for $C_{18}H_{20}N_4O_9$: C, 49.55; H, 4.62; N, 12.84. Found: C, 49.16; H, 4.59; N, 12.82.

(±)-1*H*-1-Hydroxy-2,3-dihydro-2,2,3-trimethyl-7-methoxyisoindolium 3,5-Dinitrobenzoate (4d). Solutions of the amine 2 (0.758 g, 0.0037 mol) in 5 mL of 95% ethanol and of 3,5-dinitrobenzoic acid (0.784 g, 0.0037 mol) in 10 mL of 95% ethanol were combined and diluted with 40 mL of ether. Crystals, which began appearing at room temperature after 3 h, were collected after 3 days and recrystallized once from 95% ethanol

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and twice from 95% ethanol/ether to yield 0.422 g (29%) of pale green crystals: mp 180–184 °C dec; IR (KBr) 1079 (sym COC stretch), 1275 (asym COC stretch), 1343 (sym NO_2 stretch), 1545 (asym NO_2 stretch), 1618 (asym CO_2 stretch), 3443 cm^{-1} (OH stretch); ^1H NMR (CD_3CN and D_2O) δ 1.59 (d, 3 H, CH_3CH), 2.78, 3.01 (br, 6 H, $(CH_3)_2N$, O*H*), 3.81 (s, 3 H, CH_3O), 4.47 (q, br, 1 H, $CHCH_3$), 6.07 (s, 1 H, C*H*OH), 6.85–7.47 (m, 3 H, Ar*H*, isoindolium), 8.88–8.93 (m, 3 H, Ar*H*, benzoate); ^{13}C NMR (CD_3CN) 168.40, 157.28, 149.30, 143.15, 140.96 (br), 134.21, 130.30, 122.07 (br), 120.70, 116.06, 112.96, 100.48, 72.19 (br), 56.66, 42.86 (br), 13.59 (br). Anal. Calcd for $C_{19}H_{21}N_3O_6$: C, 54.41; H, 5.05; N, 10.02. Found: C, 54.34; H, 5.29; N, 9.92.

(±)-*N,N*-Dimethyl-α-(2-formyl-3-hydroxyphenyl)ethylamine (3) from 4b. A solution of the hydrochloride salt **4b** (0.976 g, 4.0×10^{-3} mol) in 8 mL of 48% aqueous HBr was heated at reflux for 4.5 h under N_2 with stirring. After cooling to room temperature, the reaction mixture was diluted with 10 mL of H_2O and saturated with NaCl, and then solid Na_2CO_3 was added until the pH of the solution was ~8 by test paper. The aqueous solution was extracted with 3×20 mL of $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 0.472 g of a yellow solid. A second crop (0.167 g) was obtained by $CHCl_3$ extraction of the remaining aqueous solution, to which more NaCl had been added, yield 83%. A portion of this solid (0.562 g) was sublimed (85 °C (1.2 mmHg)) to yield 0.456 g (81%) of a yellow solid: mp 87–88 °C; IR ($CHCl_3$) 1640 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.41 (d, 3 H, CH_3CH, ^3J = 7 Hz), 2.21 (s, 6 H, $(CH_3)_2N$), 3.77 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 6.84–7.41 (m, 3 H, Ar*H*), 10.71 (s, 1 H, C*H*O); ^1H NMR (D_2O, CH_3CN reference) δ 1.60 (d, 3 H, CH_3CH, ^3J = 7 Hz), 2.88 (s, br, 6 H, $(CH_3)_2N$), 4.72 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 6.20 (s, br, 1 H, C*H*OH), 6.53–7.30 (m, 3 H, Ar*H*); ^{13}C NMR ($CDCl_3$) 196.93, 163.41, 136.24, 118.63, 118.05, 117.05, 62.69, 42.31, 16.84; ^{13}C NMR (D_2O, CH_3CN reference) 164.69, 142.40, 135.40, 125.01, 122.56, 112.48, 108.05, 72.80, 45.32, 14.88. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.26; H, 7.75; N, 7.50. **Methiodide of 3.** The reaction mixture obtained by stirring under N_2 the amino salicyl aldehyde **3** (0.080 g, 4.1×10^{-4} mol) and methyl iodide (0.1 mL, 1.6×10^{-3} mol) was concentrated under reduced pressure, and the residue was taken up in 5 mL of hot absolute ethanol. The cooled solution was diluted with 5 mL of ether and placed in the freezer for 5 days. The solid was collected by gravity filtration and washed with $CHCl_3$ to yield 0.046 g (33%) of a light yellow powder: mp 169–173 °C dec; IR (KBr) 1631 cm^{-1} (C=O stretch); ^1H NMR (D_2O, acetone reference) δ 1.80 (d, 3 H, CH_3CH, ^3J = 7 Hz), 3.09 (s, 9 H, $(CH_3)_3N$), 5.85 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 7.16–7.72 (m, 3 H, Ar*H*), 10.54 (s, 1 H, C*H*O); ^{13}C NMR (D_2O, acetone reference) 196.34, 163.81, 138.07, 136.04, 122.29, 121.12, 120.84, 66.81, 52.12, 15.92. Anal. Calcd for $C_{12}H_{18}INO_2$: C, 43.00; H, 5.41, N, 4.18. Found: C, 42.55; H, 5.61; N, 4.08.

2-((Dimethylamino)methyl)benzaldehyde (6). The aldehyde was prepared in 42% yield by metalation of *N,N*-dimethylbenzylamine[23] with *n*-butyllithium and formylation of the aryllithium intermediate with DMF:[12] bp 76 °C (1.8 mmHg) [lit.[12] bp 122–123 °C (14 mmHg)]; IR (neat) 1693 cm^{-1} (C=O stretch) (lit.[12] IR (CCl_4) 1695 cm^{-1}; C=O stretch); ^1H NMR ($CDCl_3$) δ 2.24 (s, 6 H, $(CH_3)_2N$), 3.73 (s, 2 H, CH_2Ar), 7.36–7.89 (m, 4 H, Ar*H*), 10.41 (s, 1 H, C*H*O) [lit.[12] ^1H NMR (CCl_4) δ 2.17 (s, 6 H, $(CH_3)_2N$), 3.67 (s, 2 H, CH_2Ar), 7.3–7.9 (m, 4 H, Ar*H*), 10.30 (s, 1 H, C*H*O)]; ^{13}C NMR ($CDCl_3$) 192.14, 141.70, 135.03, 133.21, 130.49, 129.47, 127.77, 60.96, 45.14; ^1H NMR (D_2O, CH_3CN reference) δ 2.77 (s, 6 H, $(CH_3)_2N$), 4.40 (s, 2 H, CH_2Ar), 6.68 (s, 1 H, C*H*OH), 7.32–7.47 (m, 4 H, Ar*H*); ^{13}C NMR (D_2O, CH_3CN reference) 142.65, 135.60, 132.29, 131.71, 127.01, 126.95, 121.26, 65.21, 46.69; ^1H NMR (D_2O/TFA (1 equiv), CH_3CN reference) δ 2.94 (s, 3.5 H, $(CH_3)_2N$), 3.26 (s, 2.5 H, $(CH_3)_2N$), 4.51 (s, 0.8 H, CH_2Ar), 4.77 (s, 1.2 H, CH_2Ar), 6.32 (s, 0.6 H, C*H*OH), 7.44–8.10 (m, 4 H, Ar*H*), 10.02 (s, 0.4 H, C*H*O); ^{13}C NMR (D_2O/TFA (1 equiv), CH_3CN reference) 200.51, 140.22, 138.05, 137.27, 136.88, 136.38, 135.45, 134.17, 133.96, 132.42, 132.19, 127.23, 126.76, 103.43, 68.80, 62.75, 51.75, 46.72, 45.58.

***N,N*-Dimethyl(2-formylphenyl)methylamine Hydrochloride (7b).** HCl gas was passed through a solution of the tertiary amine **6** (0.27 g, 1.7×10^{-3} mol) in 15 mL of ether. Solvent was removed from the sticky white mass under reduced pressure, and the residue was taken up in 2 mL of methanol. The solution was diluted with ether and placed in the freezer. The crystals were collected by suction and washed with ether to yield 0.311 g (94%) of transparent granular crystals: mp 159–161 °C; IR (KBr) 2400–3100 cm^{-1}, broad absorption (no carbonyl band); ^1H NMR (D_2O, CH_3CN reference) δ 3.05 (s, br, 6 H, $(CH_3)_2N$), 4.69 (s, br, 2 H, CH_2Ar), 5.50–7.00 (br, C*H*OH), 7.3–8.0 (m, br, 4 H, Ar*H*); ^{13}C NMR (D_2O, CH_3CN reference) 136.68, 136–120 (br), 132.98 (br), ~76 (br), 47.5 (br); ^1H NMR (CD_3CN with D_2O) δ 2.83 (s, 3.7 H, $(CH_3)_2N$), 3.18 (s, 2.3 H, $(CH_3)_2N^+$), 4.45 (s, 0.5 H, CH_2Ar), 4.66 (s, 1.5 H, CH_2Ar), 6.25 (s, 0.7 H, C*H*OH), 7.32–7.47 (m, 4 H, Ar*H*), 10.00 (s, 0.3 H, C*H*O); ^{13}C NMR (CD_3CN with D_2O) 197.39, 137.93, 135.93, 135.33, 135.10, 133.81, 132.30, 131.84, 130.44, 125.52, 125.00, 119.07, 101.78, 66.84, 60.32, 49.89, 44.80, 43.82. A sample was sublimed at 125 °C (1.2 mm). Anal. Calcd for $C_{10}H_{14}NOCl$: C, 60.45; H, 7.10; N, 7.05. Found: C, 60.37; H, 7.18; N, 7.07.

***N,N*-Dimethyl(2-formylphenyl)methylamine Picrate (7c).** The picrate, formed in 95% yield in 95% ethanol, was recrystallized twice from 95% ethanol: bright yellow needles; mp 145–147 °C (lit.[24] mp 148–149 °C); IR (KBr) 1332, 1346 (sym NO_2 stretch), 2600–3200 cm^{-1}, broad absorption (no carbonyl band); ^1H NMR (CD_3CN with D_2O) δ 2.82 (s, 3.84 H, $(CH_3)_2N$), 3.16 (s, 2.16 H, $(CH_3)_2N^+$), 4.42 (s, 0.56 H, CH_2Ar), 4.63 (s), 4.64 (s, 1.44 H, CH_2Ar), 6.22 (s, 0.71 H, C*H*OH), 7.33–8.01 (m, 4 H, Ar*H*), 8.63 (s, 2 H, Ar*H* of picrate), 9.97 (s, 0.29 H, C*H*O); ^{13}C NMR (CD_3CN with D_2O) 197.30, 162.88, 142.93, 137.91, 135.86, 135.27, 135.03, 133.72, 132.28, 131.82, 130.43, 127.53, 127.03, 125.47, 124.94, 101.92, 66.81, 60.50, 49.79, 44.76, 43.86. Anal. Calcd for $C_{16}H_{16}N_4O_8$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.88; H, 4.17; N, 14.23.

(±)-Phenyl α-(2-Formyl-3-methoxyphenyl)ethyl Sulfide (8). Freshly distilled benzenethiol (1.9 g, 0.017 mol) and 5.9 mL of 10% aqueous NaOH were combined in a round-bottomed flask, and after 5 min the methiodide of **2** (1.51 g, 4.3×10^{-3} mol) was added. The flask was heated in an oil bath at 128 °C under N_2 with stirring for 9 h. After the mixture was cooled to room temperature, 4 mL of 10% aqueous NaOH was added. The aqueous phase was extracted with 10 mL of ether and 4×10 mL of $CHCl_3$. The combined organic extracts were washed with 10 mL of H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to leave an oil (0.915 g). This oil was then flash chromatographed through a 2 cm × 27 cm column. After elution of the first component with hexanes, the product was eluted with ethyl acetate. This was then purified by Kugelrohr distillation to yield 0.563 g (48%) of a pale yellow viscous oil: bp 153–160 °C (0.9 mm); IR (neat) 1040 (sym COC stretch), 1263 (asym COC stretch), 1684 cm^{-1} (C=O stretch); ^1H NMR ($CDCl_3$) δ 1.57 (d, 3 H, CH_3CH, ^3J = 7 Hz), 3.88 (s, 3 H, CH_3O), 5.73 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 6.84–7.48 (m, 8 H, Ar*H*), 10.57 (s, 1 H, C*H*O); ^1H NMR (CD_3OD) δ 1.51 (d, 3 H, CH_3CH, ^3J = 7 Hz), 3.88 (s, 3 H, CH_3O), 5.67 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 6.98–7.51 (m, 8 H, Ar*H*), 10.47 (s, 1 H, C*H*O); ^1H NMR (CD_3OD with 1.4 equiv of CF_3CO_2H) δ 1.45 (d, 3 H, CH_3CH, ^3J = 7 Hz), 3.79 (s, 3 H, CH_3O), 5.39 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 5.83 (s, 1 H), 6.81–7.39 (m, 8 H, Ar*H*); ^{13}C NMR ($CDCl_3$) 192.80, 162.70, 146.74, 135.19, 134.85, 131.65, 128.66, 126.78, 122.42, 120.21, 109.92, 55.90, 41.30, 22.35; ^{13}C NMR (CD_3OD) 194.14, 164.27, 147.76, 136.48, 136.28, 132.91, 129.73, 128.03, 123.73, 121.21, 111.42, 56.59, 42.31, 22.51; ^{13}C NMR (CD_3OD with 1.4 equiv of CF_3CO_2H) 158.80, 146.36, 137.60, 132.94, 130.86, 129.51, 127.62, 125.30, 121.93, 110.24, 102.51, 56.41, 44.40, 24.26; MS 272 (15), 163 (100), 162 (52), 148 (35), 133 (9), 105 (17), 91 (17), 77 (15), 65 (12). Anal. Calcd for $C_{16}H_{16}O_2S$ (272): C, 70.55; H, 5.92. Found: C, 70.70; H, 6.17.

(±)-Phenyl α-(2-Formyl-3-hydroxyphenyl)ethyl Sulfide (9). The reaction mixture obtained by heating, with stirring in a stream of N_2, benzenethiol (0.24 g, 2.1×10^{-3} mol), 0.75 mL of 10% aqueous NaOH, and the methiodide of **3** (0.18 g, 5.4×10^{-4} mol) at 130 °C for 12 h was neutralized with 6 mL of 0.24 M HCl and extracted with 2×10 mL of $CHCl_3$. The combined extracts were washed with 10 mL of H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was flash chromatographed

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through a 2 cm × 22 cm column. After removal of the less polar components with hexanes, the product was washed from the column with ethyl acetate. The residue (0.051 g) was purified by sublimation (90 °C (1.5 mmHg)) to yield 0.032 g (23%) of clear, pale yellow crystals: mp 83.5–84.5 °C; IR (KBr) 1638 cm^{-1} (C=O stretch); ^1H NMR ($CDCl_3$) δ 1.71 (d, 3 H, CH_3CH, ^3J = 7 Hz), 4.89 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 6.85–7.44 (m, 8 H, ArH), 10.42 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) 194.25, 165.32, 146.48, 137.12, 133.77, 133.38, 129.03, 128.37, 118.23, 117.28, 116.98, 42.04, 21.67; MS 258 (21), 149 (100), 148 (61), 131 (16), 103 (31), 91 (25), 77 (26). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.61; H, 5.59.

X-ray Crystallography. A colorless, prismatic crystal of (±)-1*H*-1-hydroxy-2,3-dihydro-2,2,3-trimethyl-7-methoxyisoindolium 3,5-dinitrobenzoate (**4d**) ($C_{19}H_{21}N_3O_8$), grown from ethanol, having approximate dimensions of 0.23 × 0.20 × 0.31 mm, was determined to be monoclinic with space group $P2_1/n$ and cell constants of a = 12.826 (2) Å, b = 7.170 (1) Å, c = 21.606 (5) Å, β = 91.66 (2), Z = 4, D_c = 1.402 g cm^{-3}, and μ = 8.97 cm^{-1}. It was mounted on an Enraf-Nonius CAD4 automated diffractometer, and all intensity measurements were performed at 23 °C with Cu Kα (λ = 1.541 84 Å) radiation with a graphite crystal, incident beam monochromator, scan type ω. Of the 4229 unique reflections, 2795 having $I > 3\sigma(I)$ were used in the structure solution and refinement. The structure was solved with the direct methods program SHELXS-86,[25] and refinement was carried out by using full-matrix least-squares techniques. All H atoms attached to C were included at their calculated positions by assuming C–H = 0.95 Å. These atoms were then included in the calculations with fixed, isotropic thermal parameters 1.2 times that of the attached atom and constrained to "ride" with this atom. The H atom on the hydroxyl was located in a difference Fourier map and included in the calculations with its positional and isotropic thermal parameters refined. The final agreement factors were R_1 = 0.065, and GOF = 5.18. Figure 1 is a computer-generated perspective drawing of **4d** from the final X-ray coordinates.

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Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles (5 pages). Ordering information is given on any current masthead page.

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Nucleosides. 3. Reactions of AICA-Riboside with Isothiocyanates. A Convenient Synthesis of Isoguanosine and Xanthosine Derivatives[1]

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Cyclodesulfurative annulations of 5-[1-(3-substituted-thioureido)]-1-(β-D-ribofuranosyl)imidazole-4-carboxamides (**3a–h**) with *N,N'*-dicyclohexylcarbodiimide are described. Isoguanosine (**4**) and several 1-substituted isoguanosines **6a–f,h** are readily prepared by a ring closure of the appropriate resulting 5-(3-substituted-1-ureido)-1-(β-D-ribofuranosyl)imidazole-4-carbonitriles **5a–h**. Treatment of the appropriate 1-substituted isoguanosines under basic conditions has furnished the corresponding 1-substituted xanthosine **12**.

Introduction

Isoguanosine (**4**), one of the unusual naturally occurring nucleosides, was first synthesized by Fischer[2] and was subsequently isolated from plant[3] and animal sources,[4,5] for example, *Croton tiglium* and *Diaulula sandiegensis*, respectively. Later on, doridosine (**6a**), an isoguanosine derivative possessing a methyl group on the N-1 position of the purine ring, was isolated from a marine animal by three independent research groups as well.[6,7] The chemical properties of isoguanosine derivatives, such as poor solubility, are similar to those of guanosine. However, biologically and physiologically, doridosine-like adenosine analogues promote the accumulation of cyclic AMP in the brain,[8] inducing a more profound lowering of blood pressure, decreasing heart rate, and smooth muscle relaxation than that observed for isoguanosine per se.[9] Recently, several analogues of doridosine were synthesized[10] due to an appreciation of the important effect of the purine receptor on the cardiovascular system and the discovery of the mechanism of action of doridosine related to the A_2 agonists.[11]

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