H_A of ABX system), 7.45 and 7.58 (2 H, thiophene H's), 8.40 (1 H, H_X of ABX system); mass spectrum (DCI, CH_4), m/e 372 $(M + H)^+$, 344, 327, 180; IR (mineral oil), 1640 (diaryl ketone).

Anal. Calcd for $C_{14}H_8F_3N_3O_4S$: C, 45.29; H, 2.17; N, 11.32. Found: C, 45.29; H, 2.08; N, 10.99.

[4-(1-Azi-2,2,2-trifluoroethyl)-2-thienyl](3-nitro-4-aminophenyl)methanone (11). A solution of 0.531 g (1.43 mmol) of **10** in 34 mL of THF was reacted in the dark with approximately an equal volume of NH_3 at room temperature for 70.5 h as described for **10**, yielding 0.496 g (97%) of product.

An analytical sample of **11** was prepared by flash chromatography, eluting with CH_2Cl_2: mp 117 °C dec; ^1H NMR ($CDCl_3$) δ 6.57 (br s, 2 H, NH_2), 6.94 and 7.94 (2 H, H_B and H_A of ABX system, J_{AB} = 8.8 Hz), 7.45 and 7.50 (2 H, thiophene H's), 8.75 (1 H, H_X of ABX system); mass spectrum (FAB), m/e 357 $(M + H)^+$; IR (mineral oil), 3450 and 3330 ($ArNH_2$), 1635 (diaryl ketone).

Anal. Calcd for $C_{13}H_7F_3N_4O_3S$: C, 43.83; H, 1.98; N, 15.73. Found: C, 43.91; H, 1.80; N, 15.78.

Methyl [5-[[4-(1-Azi-2,2,2-trifluoroethyl)-2-thienyl]-carbonyl]-1*H*-benzimidazol-2-yl]carbamate (2). A 5% solution of $NaHCO_3$ (10 mL) was added to a solution of 105 mg (0.295 mmol) of **11** in 10 mL of THF under an argon atmosphere. The mixture was stirred at room temperature while technical grade (85%) sodium hydrosulfite (211 mg, 1.03 mmol) was added in portions over a 20-min period. After stirring for an additional 10 min, the layers were separated; the organic layer was washed with saturated sodium chloride, filtered, and concentrated with mild heating to give the dark red diamine. The diamine was dissolved in 2.0 mL of MeOH, then treated with 1,3-bis(methoxycarbonyl)-*S*-methylisothiourea[12] (63.8 mg, 0.309 mmol) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was heated at reflux under argon for 5 min during which time a precipitate formed. After cooling to room temperature, the precipitate was filtered, washed with MeOH, and vacuum-dried to 40.0 mg (33%) of tan solid: mp >400 °C dec; ^1H NMR (DMSO-d_6) δ 3.79 (s, 3 H, OCH_3), 7.54 and 8.18 (2 H, thiophene H's), 7.55 and 7.66 (2 H, H_B and H_A of ABX system), 7.96 (1 H, H_X of ABX system); mass spectrum (FAB), m/e 410 $(M + H)^+$; IR (KBr), 1709 (carbamate), 1646 and 1632 (ketone and C=N).

Anal. Calcd for $C_{16}H_{10}F_3N_5O_3S$: C, 46.95; H, 2.46; N, 17.11. Found: C, 47.14; H, 2.43; N, 16.57.

Photolysis of 2. A 0.5 mM solution of **2** in MeOH (44 mL, 0.022 mmol) was irradiated for 20 min in a quartz vessel at room temperature, then concentrated to dryness, and vacuum-dried at 45 °C. HPLC analysis showed a new product with longer retention time than **2**: ^1H NMR (DMSO-d_6) δ 3.41 (s, 3 H, ether CH_3), 3.80 (s, 3 H, carbamate CH_3), 5.25 (q, 1 H, CF_3CH), 7.56 and 7.65 (2 H, H_B and H_A of ABX system), 7.71 and 8.19 (2 H, thiophene H's), 7.96 (1 H, H_X or ABX system); mass spectrum (DCl, NH_3), m/e 414 $(M + H)^+$, 398, 384.

The $t_{1/2}$ of **2** in MeOH was determined as follows: 50-μL aliquots of a 0.5 mM solution of **2** in MeOH were irradiated for 0, 20, 40 and 60 s; each aliquot was diluted with 250 μL of HPLC mobile phase [*n*-hexane–$CHCl_3$–MeOH–CH_3SO_3H (500:400:100:0.33) and 20 μL of this solution injected into the HPLC. A plot of log (area % **2**) vs time produced a slope of –0.0144; $t_{1/2}$ was calculated to be 21 s from the equation $t_{1/2}$ = 0.693/(–slope × 2.303).

Tubulin Competitive Equilibrium Binding Assay. An equilibrium binding assay was developed to determine the degree that an oncodazole analogue can compete with binding of [^{3}H]-**1** to tubulin. This assay was based on the gel partition equilibrium binding method of Hirose and Kano[13] as modified by Head et al.[1c] in their investigation of equilibrium binding of oncodazole to tubulin.

Bovine brain tubulin was utilized in these studies and was purified as described by Hamel and Lin.[14] In preparation for the binding assay 20 mg of purified tubulin was dialyzed for 2 h at 4 °C against 500 mL of 10 mM KH_2PO_4 buffer, pH 7.0 which contained 0.1 mM GTP and 12% DMSO ("PGD buffer"). After dialysis, 50-μL aliquots (containing 0.325 mg of tubulin) were added to polypropylene microfuge tubes which contained 50 mg of BioGel P-6 resin (BioRad Laboratories) previously equilibrated with 400 μL of PGD buffer. Solutions of [^{3}H]-**1** (ca. 3.66 × 10^{13} cpm/mol) and varying concentrations of oncodazole analogue were made in PGD buffer and aliquots (150 μL) were added to duplicate microtubes containing the tubulin and P-6 resin to give a final volume of 600 μL for all additions. The final concentration of [^{3}H]-**1** in the microtubes was 9.0 × 10^{-6} M and the final concentration of oncodazole analogue ranged from 10^{-8} M to 10^{-4} M. The tubes were each vortexed for 5 s and incubated at 30 °C for 20 min with 5 s of vortexing for every 5 min of incubation time. The microtubes were then placed in an Eppendorf microfuge and the resin was gently separated by a brief spin of the microfuge. A resin-free aliquot (75 μL) was removed from the supernatant of each tube and placed in a fresh microtube. Aliquots of 25 μL in duplicate were then added to minivials and counted with 5 mL of Aquasol (Dupont) in a Beckman Model 3801 scintillation counter. The binding of [^{3}H]-**1** to tubulin was determined from the radioactivity and calculated by the methods of Hirose and Kano.[13] Under these experimental conditions, [^{3}H]-**1**, in the absence of any competing analogue, will saturate ca. 50% of the tubulin. This amount of binding is taken as the maximal binding value for [^{3}H]-**1**. The concentration of the oncodazole analogue that reduces the binding of [^{3}H]-**1** to 50% of the maximal binding value is designated as the IC_{50} value for that analogue. The IC_{50} was calculated by a nonlinear least squares fit of the binding data to the equation binding/maximal binding = $1/(1 + 10^{x}/IC_{50})$ where x = log [oncodazole analogue].

Registry No. **2**, 111690-73-4; **2** (diamine precursor), 111690-68-7; **3**, 16694-18-1; **4**, 66938-33-8; **5**, 111690-61-0; **6**, 111690-62-1; **6** (ketal protected), 111690-69-8; **7**, 111690-63-2; (*E*)-**8**, 111690-64-3; (*Z*)-**8**, 111690-65-4; (*E*)-**9**, 111690-70-1; (*Z*)-**9**, 111690-71-2; **10**, 111690-66-5; **10** (diaziridine precursor), 111690-72-3; **11**, 111690-67-6; PhOMe, 100-66-3; 2,3,5-tribromothiophene, 3141-24-0; 2,4-dibromothiophene, 3140-92-9; 1,3-bis(methoxycarbonyl)-*S*-methylisothiourea, 34840-23-8; *N*-(trifluoroacetyl)-piperidine, 340-07-8.

(12) Klopping, H. L. U.S. Pat. 2 933 504, 1960.
(13) Hirose, M.; Kano, Y. *Biochem. Biophys. Acta* **1971**, *251*, 376.
(14) Hamel, E.; Lin, C. M. *Arch. Biochem. Biophys.* **1981**, *209*, 294.

Stereochemistry and Conformation of 8-Aryl-1,5-diazabicyclo[3.2.1]octanes by 2D NMR Studies

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1,4-Diazacycloheptane reacts with benzaldehyde to give 8-phenyl-1,5-diazabicyclo[3.2.1]octane (**1a**) of undetermined stereochemistry (Scheme I).[1] Nair has reported the synthesis of several compounds possessing structure **1**.[2] While their sharp melting points indicated single stereoisomers, their stereochemistry could not be established with the available data. An X-ray structure for **1e** has been published[3] but without information on its melting point or method of preparation. Thus the stereochemical outcome of the reaction of Scheme I is unknown.

We have established the stereochemistry of the products of the reaction in Scheme I through the use of 2D NMR (NOESY) at 500 MHz. In addition, we have shown that the conformation of the C8–Ar bond in **1** depends on the nature of the aryl group. A mechanism is proposed to account for the formation of only one stereoisomer.

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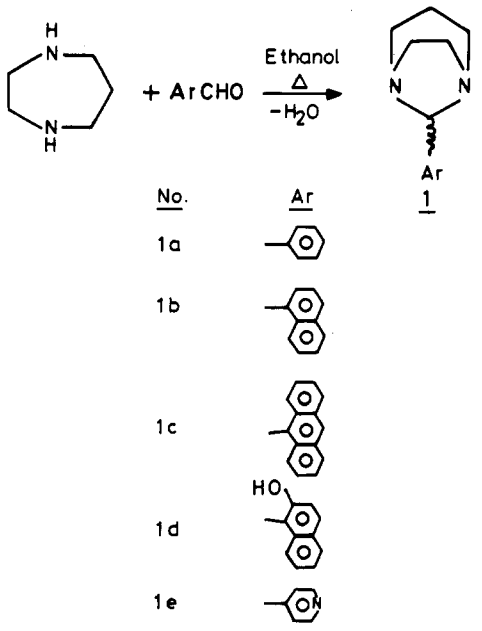
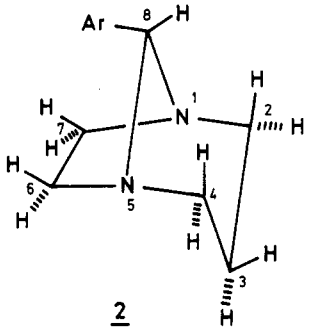
0022-3263/88/1953-0420$01.50/0

Scheme I



We have repeated the preparation of **1a** from 1,4-diazacycloheptane and benzaldehyde and found by ^1H and ^{13}C NMR that both the crude and recrystallized product are a single stereoisomer. The ^1H NMR of **1a** at 500 MHz gave well-resolved signals for all chemically different protons. Unequivocal assignments of all signals were made by the use of splitting patterns and values of coupling constants and were corroborated by decoupling experiments (Table I).

A two-dimensional NOESY experiment on **1a** established the stereochemistry at C8 (Figure 1). The strong correlation between the pairs of protons H8 and $H2(4)_{ax}$ and between $H6(7)_{exo}$ and the ortho aromatic protons unequivocally points to the stereochemistry shown in **2**.



2

The NOE correlation of $H3_{ax}$ with $H6(7)_{endo}$ indicates the boat conformation of the seven-membered ring, which was confirmed by coupling constant measurements. Thus the stereochemistry of **1a** is the same as that of **1e** as determined by X-ray analysis.[3]

As the aryl group becomes more sterically demanding (**1a–c**), the rotation of the aryl group about the aryl–C8 bond becomes increasingly restricted. The plane of the aromatic ring in **1a–c** and the plane comprising the atoms N1–C7–C6–N5 splay away from each other to relieve the interactions between $H6(7)_{exo}$ and the aromatic ring protons. This displacement leads to increased steric interactions between H8 and $H2(4)_{ax}$, resulting in the progressive deshielding of both of these hydrogens as shown by chemical shifts (Table I). Attempts to stabilize this conformation through intramolecular hydrogen bonding, for example, **1d**, were not fruitful.[4]

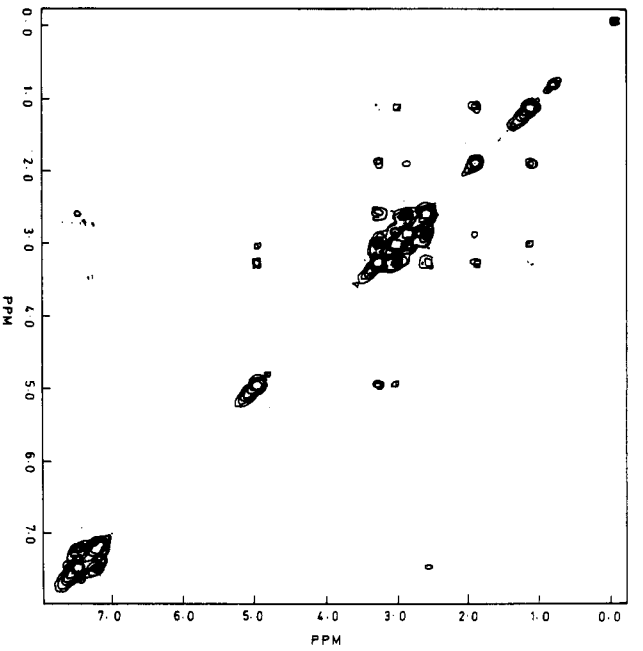
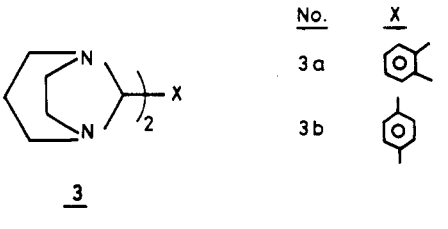
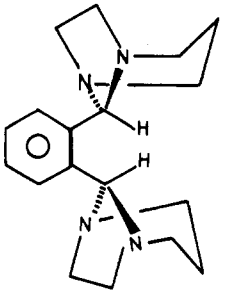


Figure 1. Proton NOESY (500 MHz) spectrum for **1a**.

Of the bis compounds **3a,b**, obtained from reaction of 1,4-diazacycloheptane with *o*-phthalaldehyde and *p*-phthalaldehyde, the ^1H NMR data on **3a** are particularly interesting. The pronounced deshielding of H8 (by approximately 0.9 ppm compared to H8 in **1a**) points to the probable conformation **4** for **3a**.



3



4

The exclusive formation of single isomers in the reaction of Scheme I can be understood by the mechanism outlined in Scheme II. Molecular models disclose that the ring closure of the iminium ion **5b** leads to unfavorable steric interactions (developing 1,3-diaxial interactions) between

(1) Poppelsdorf, F.; Myerly, R. C.; Conrow, R. G. *J. Org. Chem.* **1961**, *26*, 4138.
(2) Nair, M. D. *Indian J. Chem.* **1968**, *6*, 229.
(3) Karle, I. L.; Britts, K. *Acta Crystallogr.* **1966**, *21*, 532.

(4) The ^1H and ^{13}C NMR spectra of **1** were obtained from salicylaldehydes closely similar to the spectra of **1a**, indicating no strong intramolecular hydrogen bonding.

Table I. Physical and Spectroscopic Data on 8-Aryl-1,5-diazabicyclo[3.2.1]octanes

compd	mp, °C (solv of crystn)	^{1}H NMR data[c] (chem shift in δ, no. of protons, mult, coupling constants in Hz)	^{13}C NMR data[d]
1a	79–81[a] (ethanol)	H_{2a}, H_{4a} (3.33, 2 H, td, J_{2a-3a} = 13.3; J_{2a-3e} = 4.7); H_{2e}, H_{4e} (3.08, 2 H, q, J_{2e-2a} = 13.7; J_{2e-3a} = 6.6); H_{3a} (1.95, 1 H, nonet, J_{3a-3e} – J_{3a-2a} = 13.0; J_{3a-2e} = 6.5); H_{3e} (1.18, 1 H, dt, J_{3e-3a} = 14.0; J_{3e-2a} = 4.7); $H_{6\text{-exo}}$, $H_{7\text{-exo}}$ (2.66, 2 H, m); $H_{6\text{-endo}}$, $H_{7\text{-endo}}$ (2.93, 2 H, m); H_8 (5.03, 1 H, s); *o*-Ar H (7.54, 2 H, d, J_{o-m} = 7.5); *m*-Ar H (7.64, 2 H, t, J_{m-o} = J_{m-p} = 7.6); *p*-Ar H (7.22, 2 H, t, J_{p-m} = 7.4)	18.51 (t, C_3), 50.32 (t, C_2, C_4), 55.76 (t, C_6, C_7), 88.24 (d, C_8),126.13 (d, Ar), 127.42 (d, Ar), 128.41 (d, Ar), 139.40 (s, Ar)
1b	129–30 (ethyl acetate)	H_{2a}, H_{4a} (3.50, 2 H, td, $J_{2a-2e} \simeq J_{2a-3a}$ = 13.51 J_{2a-3e} = 5.0; H_{2e}, H_{4e}, $H_{6\text{-exo}}$, $H_{6\text{-endo}}$, $H_{7\text{-exo}}$, and $H_{7\text{-endo}}$ (2.65–3.25, 6 H, m); H_{3a} (1.95, 1 H, approx. nonet, $J_{3a-3e} \simeq J_{3a-2a}$ = 13.5; J_{3a-2e} = 6.6); H_{3e} (1.15, 1 H, dt, J_{3e-3a} = 14.0; J_{3e-2a} = 5.0); H_8 (5.45, 1 H, s); H_{Ar} (7.10–7.85, 6 H, m); $H_{Ar\text{-}8'}$ (8.45, 1 H, $J_{Ar\text{-}8'\text{-}Ar\text{-}7'}$ = 8)	
1c	198 (ethyl acetate)	H_{2a}, H_{4a} (3.70, 2 H, td, $J_{2a-2e} \simeq J_{2a-3a}$ = 13.5; J_{2a-3e} = 4.9); H_{2e}, H_{4e} (3.19, 2 H, t, J_{2e-2a} = 13.5; J_{2e-3a} = 6.5); H_{3a} (1.98, 1 H, approx. nonet, $J_{3a-3e} \simeq J_{3a-2a}$ = 14.3, J_{3a-2e} = 6.5); H_{3e} (1.30, 1 H, dt, J_{3e-3a} = 14.5, J_{3e-2a} = 4.9); $H_{6\text{-exo}}$, $H_{6\text{-endo}}$, $H_{7\text{-exo}}$, and $H_{7\text{-endo}}$ (2.56–3.04, 4 H, m); H_8 (6.20, 1 H, s); H_{Ar} (7.23–8.30, 9 H, m)	19.04 (t, C_3), 50.88 (t, C_2, C_4), 56.28 (t, C_6, C_7), 91.57 (s, C_8)[e]
1d	174–180 (ethyl acetate)	H_{2a}, H_{4a} (3.44, 2 H, td, $J_{2a-2e} \simeq J_{2a-3a}$ = 13.7; J_{2a-3e} = 4.8); H_{2e}, H_{4e}, $H_{6\text{-exo}}$, $H_{6\text{-endo}}$, $H_{7\text{-exo}}$, $H_{7\text{-endo}}$, phenolic OH (2.55–3.15, 7 H, m); H_{3a} (1.99, 1 H, approx. nonet, $J_{3a-3e} \simeq J_{3a-2a}$ = 13.7; J_{3a-2e} = 6.3); H_{3e} (1.26, 1 H, dt, J_{3e-3a} = 14.3; J_{3e-2a} = 4.8); H_8 (5.45, 1 H, s); H_{Ar} (6.90–7.70, 5 H, m); $H_{Ar\text{-}8'}$ (8.77, 1 H, dd, $J_{8'-7'} \simeq$ 8.5, $J_{8'-6'} \simeq$ 1.0)	18.59 (t, C_3), 50.37 (t, C_2, C_4), 54.46 (t, C_6, C_7), 90.01 (s, C_8), 109.83 (s, Ar), 119.97, 122.12, 124.65, 125.36, 128.16 (d, Ar), 128.81 (s, Ar), 130.11 (d, Ar), 133.16 (s, Ar), 153.63 (s, Ar)
1e	*b*	H_{2a}, H_{4a} (3.22, 2 H, td, $J_{2a-2e} \simeq J_{2a-3a}$ = 13.0, $J_{2a-3e} \simeq$ 4.8); H_{2e}, H_{4e} (3.09, 2 H, t, $J_{2e-2a} \simeq$ 13.0, J_{2e-3a} = 6.5); H_{3a} (1.96, 1 H, approx. nonet, $J_{3a-3e} \simeq J_{3a-2a}$ = 13.5, J_{3a-2e} = 6.5); H_{3e} (1.18, 1 H, dt, J_{3e-3a} = 14.0, $J_{3e-2a} \simeq$ 4.8); $H_{6\text{-exo}}$, $H_{6\text{-endo}}$, $H_{7\text{-exo}}$, $H_{7\text{-endo}}$ (2.40–3.00, 4 H, m); H_8 (4.95, 1 H, s); $H_{Ar\text{-}3',5'}$ (7.46, 2 H, dd, $J_{3'-2'}$ = 6.0; $J_{3'-6'}$ = 1.0); $H_{Ar\text{-}2',6'}$ (8.53, 2 H, dd, $J_{2'-3'}$ = 6.0; $J_{2'-5'}$ = 1.0)	18.59 (t, C_3), 49.91 (t, C_2, C_4), 55.83 (t, C_6, C_7), 87.28 (d, C_8), 121.47 (d, Ar C_3), 148.44 (s, Ar C_4), 149.61 (d, Ar C_2)
3a	134–136 (acetone)	H_{2a}, H_{4a} (3.44, 2 H, td, $J_{2a-2e} \approx J_{2a-3a}$ = 13.5, J_{2a-3e} = 4.8); H_{2e}, H_{4e} (3.09, 2 H, t, J_{2e-2a} = 13.5, J_{2e-3a} = 6.5); H_{3a} (1.96, 1 H, approx. nonet, $J_{3a-3e} \simeq J_{3a-2a}$ = 14.0; J_{3a-2e} = 6.5); H_{3e} (1.16, 1 H, dt, J_{3e-3a} = 14.0; J_{3e-2a} = 4.8); $H_{6\text{-exo}}$, $H_{6\text{-endo}}$, $H_{7\text{-exo}}$, $H_{7\text{-endo}}$ (2.34–2.90, 4 H, m); H_8 (5.92, 1 H, s); H_{Ar} (7.02, 2 H, m); H_{Ar} (7.15, 2 H, m)	19.30 (t, C_3), 50.69 (t, C_2, C_4), 56.21 (t, C_6, C_7), 88.64 (d, C_8), 126.41 (d, Ar), 126.86 (d, Ar), 137.39 (s, Ar)
3b	253–254 (ethyl acetate)	H_{2a}, H_{4a} (3.34, 2 H, td, $J_{2a-2e} \simeq J_{2a-3a}$ = 13.0; J_{2a-3e} = 4.8); H_{2e}, H_{4e} (3.08, 2 H, t, J_{2e-2a} = 13.0; J_{2e-3a} = 6.4); H_{3a} (1.93, 1 H, approx. nonet, $J_{3a-3e} \simeq J_{3a-2a}$ = 14.4; $J_{3a-2e} \simeq$ 6.4); H_{3e} (1.15, 1 H, dt, J_{3e-3a} = 14.4; J_{3e-2a} = 4.8); $H_{6\text{-exo}}$, $H_{6\text{-endo}}$, $H_{7\text{-exo}}$, $H_{7\text{-endo}}$ (2.51–3.00, 4 H, m); H_8 (5.00, 1 H, s); H_{Ar} (7.46, 4 H, s)	18.91 (t, C_3), 50.17 (t, C_2, C_4), 56.02 (t, C_6, C_7), 88.58 (d, C_8), 125.95 (d, Ar), 138.49 (s, Ar)

[a] Reported mp 82–84 °C; reference 1. [b] In spite of several attempts, crystalline **1e** could not be obtained; reference 3 however reports a crystal structure for **1e**. [c] ^{1}H NMR data (solvent $CDCl_3$) were obtained on Varian A-60 and Bruker WH-90 instruments. For **1a**, the data reported in the table were obtained on a Bruker AM-500 spectrometer. Digital resolution was 1.0 Hz/point; $J_{H_{2e}-H_{3e}}$ = 0 for all compounds in the series. [d] ^{13}C NMR data were obtained on a Bruker WH-90 instrument. [e] This compound appeared to decompose in solution during prolonged accumulation of ^{13}C NMR spectra. Hence, aromatic carbon signals could not be assigned with confidence due to the appearance of impurity signals.

the aryl ring and $H2(4)_{ax}$ so that it probably reverts back to the carbinolamine precursor, whereas **5a** ring closes to give the products **1** or **3** (Scheme II).

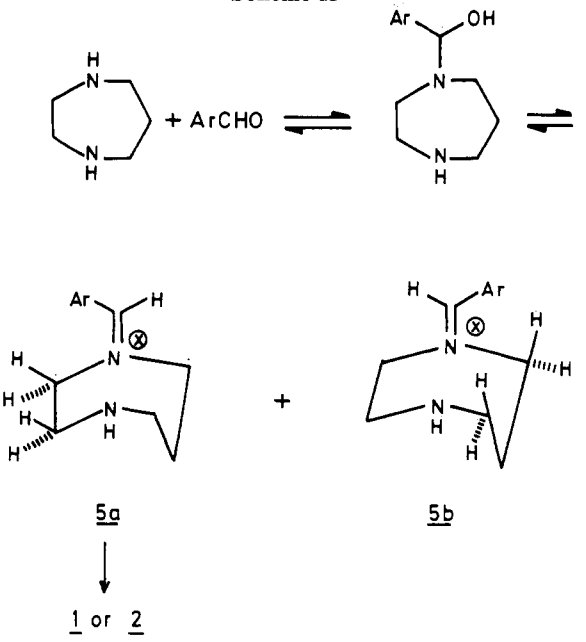
Experimental Section

Melting points are uncorrected. 2-Hydroxynaphthaldehyde and anthracen-9-aldehyde were prepared according to published procedures.

8-Aryl-1,5-diazabicyclo[3.2.1]octanes. To a solution of 1,4-diazacycloheptane (0.01 mol) in ethanol (15 mL) was added a solution of the aldehyde (0.01 mol of monoaldehyde or 0.005 mol of dialdehyde) in ethanol (15–20 mL). The resulting mixture was agitated for 15–20 min during which time the solution became warm. The mixture was left undisturbed at room temperature overnight. (In the case of **1e** the reaction mixture had to be refluxed in order to complete the reaction.) After removal of the solvent, the crude product, pure by ^{1}H NMR, precipitated in nearly quantitative yield. One recrystallization yielded analytically pure material.

2D NMR of 1a. The ^{1}H NMR spectrum of **1a** was recorded on a Bruker AM-500 spectrometer operating in the Fourier transform mode under ASPECT 2000 control. Chemical shifts are expressed in ppm from the internal standard Me_4Si. Homonuclear proton NOESY spectra were carried out with the usual pulse sequence RD – $\pi/2$ – t_1 – $\pi/2$ – t_m – $\pi/2$ – t_2, where RD is the relaxation delay (1.5 s) and t_m is the mixing time (500 ms). The t_1 value of 10 μs was used with 256 equidistant increments (Δt_1 = 600 μs), and zero filling was used. The digital resolution along both axes was 16.0 Hz/point and 32 scans were taken.

Scheme II



Satisfactory elemental analyses were obtained for new compounds **1b,c** and **2a,b**.

Acknowledgment. We gratefully acknowledge Prof. G. Govil, TIFR National NMR facility, Bombay, for 2D NOESY spectra on compound **1a**; we thank Dr. M. D. Nair and Dr. S. Selvavinayakam for helpful discussions.

Registry No. **1a**, 111159-67-2; **1b**, 111159-68-3; **1c**, 111159-69-4; **1d**, 111159-70-7; **1e**, 111159-71-8; **3a**, 111159-72-9; **3b**, 111159-73-0; *o*-phthalaldehyde, 643-79-8; *p*-phthalaldehyde, 623-27-8; 1,4-diazacycloheptane, 505-66-8; benzaldehyde, 100-52-7; 1-naphthalenecarboxaldehyde, 66-77-3; 9-anthracenecarboxaldehyde, 642-31-9; 2-hydroxy-1-naphthalenecarboxaldehyde, 708-06-5; 4-pyridinecarboxaldehyde, 872-85-5.

Improved Synthesis of 3-Substituted 7-Methoxybenzofurans, Useful Intermediates for Preparation of Morphine Analogues

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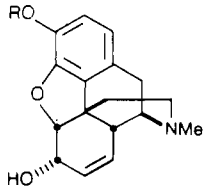
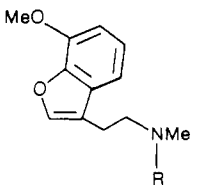
Interest in the synthesis of morphine (**1**), codeine (**2**), and their analogues and their pharmacologic properties as useful analgesics continues unabated. Several syntheses and synthetic approaches have been described recently.[3]

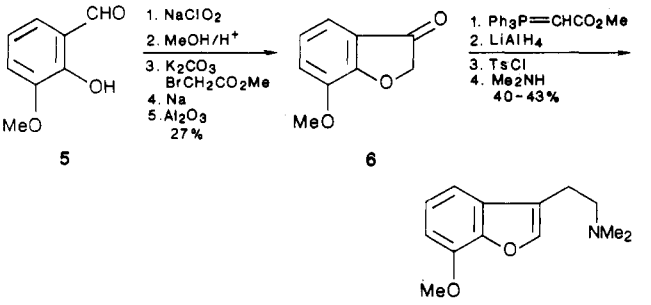


1, R=H
2, R=Me

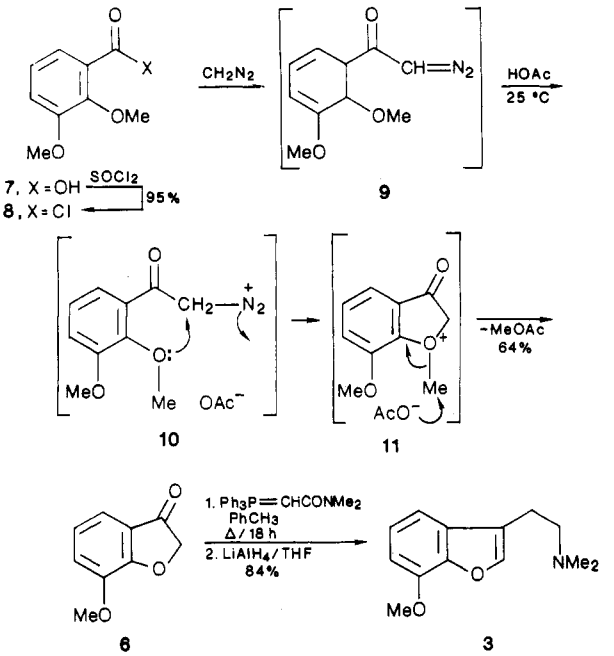


3, R=Me
4, R=H

For a proposed route to analgesics of the morphine class, we required a good supply of 3-[2-(dimethylamino)-ethyl]-7-methoxybenzofuran (**3**). Although this was an unknown compound, the analogous monomethyl amine **4** had been prepared by Ciganek and used in his synthesis of a morphine fragment.[4] However, this preparation requires nine steps from commercially available *o*-vanillin (**5**), affords **3** via the ketone **6** in reproducible yields of only



10–12% in our hands, and was therefore for us not applicable to the large-scale laboratory preparation of **3**. For this reason we have developed a rapid and efficient synthesis of **3** requiring only three operations from commercially available material.



2,3-Dimethoxybenzoic acid (**7**) was converted into the known acid chloride **8** in 95% yield by the standard method. Treatment of **8** with ethereal diazomethane followed by stirring the solution with glacial acetic acid at 25 °C afforded the ketone **6** in 64% yield. This reaction was described in 1956 by Richtzenhain and Alfredsson,[5] but their somewhat vague experimental description gives no

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