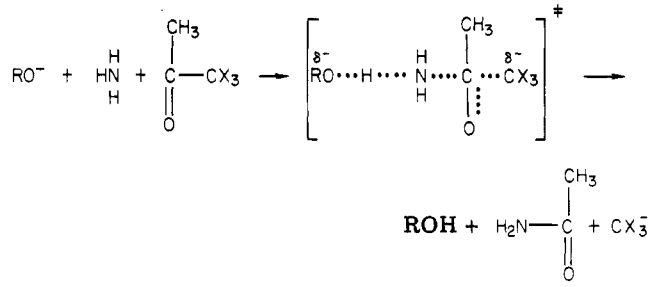
Scheme III



The kinetics of the solvolytic cleavage of the $C_{sp^2}$–$C_{sp^3}$ bond in these trihaloacetones resemble those of the cleavages of Si–$C_{sp^3}$ and Sn–$C_{sp^3}$ bonds studied in similar systems.[5,6,14] All of these reactions involve competition between direct base solvolysis and base-catalyzed ammonolysis. Similar mechanisms have been proposed for all, although the kinetic data do not distinguish among them. The general expression for the observed first-order rate constant is shown in eq 3.

$$k_I = k_1[NH_3] + k_2\frac{[NH_3]}{[NH_4Cl]} + k_3\frac{[NH_3]}{[NH_4Cl]}[NH_3] = k_1'[NH_3] + k_2'[RO^-] + k_3'[RO^-][NH_3] \quad (3)$$

Catalysis by the weak base ammonia ($k_1$) is the predominant reaction in the solvolysis of Sn–C bonds, whereas only simple base ($k_2$) and base–nucleophile ($k_3$) catalyses are observed in the solvolysis of Si–C and C–C bonds.[15] The catalytic rate constants for solvolysis of these three bond types are shown in Table II.

## Experimental Section

All solvents were carefully dried and purified by standard techniques.[16] Kinetic analyses were performed with a GCHF 18.3 Willy Giede gas chromatograph equipped with a Takeda Riken TR 2215 A integrator.

1,1,1-Trichloroacetone was prepared from acetic anhydride and sodium trichloroacetate in 1,2-dimethoxyethane;[17] NMR ($CCl_4$) $\delta$ 2.89 (s, 3 H, $CH_3$).

1,1,1-Tribromoacetone was obtained by bromination of bromoacetone[18] with *N*-bromosuccinimide in $CCl_4$. It was separated from the reaction mixture and purified by preparative GLC using a column packed with SE-30 on Chromosorb W (45/60 mesh); NMR ($CCl_4$) $\delta$ 2.77 (s, 3 H, $CH_3$) (lit.[19] NMR $\delta$ 2.73).

Kinetic measurements were carried out in thermostated flasks, sealed with silicone rubber membranes, at 25 °C. Samples (0.3 $\mu$L) were taken at predetermined intervals with a 1-$\mu$L gas-tight Hamilton syringe and analyzed by GLC (see Figure 2) using a double FID system. The haloforms were determined with the aid of internal standards: *n*-octane for $CHCl_3$ and $CH_2I_2$ for $CHBr_3$.

**Registry No.** $MeC(O)CCl_3$, 918-00-3; $MeC(O)CBr_3$, 3770-98-7.

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# Conformational Studies by Dynamic Nuclear Magnetic Resonance. 22.[1] Torsional Barriers in Some (Dimethylamino)nitrothiophens

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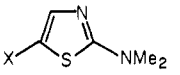
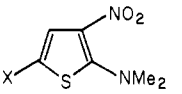
Evidence for restricted rotation about the C–N bond in a number of amino-substituted aromatic derivatives has been obtained by dynamic nuclear magnetic resonance spectroscopy.[2-9] The same effect has recently been observed in some 5-substituted 2-(dimethylamino)thiazoles (1; X = H, Br, $NO_2$).[8] We now report the results of a



**1**

similar study of some 5-substituted 2-(dimethylamino)-3-nitrothiophenes (**2a–h**).



**2a**, X = H
**b**, X = Br
**c**, X = $CONH_2$
**d**, X = $CO_2Me$
**e**, X = COMe
**f**, X = $SO_2Me$
**g**, X = CN
**h**, X = $NO_2$

The interaction of the dimethylamino group with the aromatic ring and the consequent double bond character of the C–N linkage are determined by two factors: the conjugative effect and the steric effect. The hyperortho relation[10] between substituents linked to the 2- and 3-

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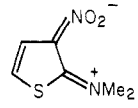
0022-3263/82/1947-3759$01.25/0 

Table I. Chemical Shift Differences ($\Delta\nu$),[a] Line-Coalescence Temperatures ($t_c$), and Free Energies of Activation ($\Delta G^{\ddagger}$) for C-N Rotation

| compd | $\Delta\nu$, Hz | $t_c$, °C | $\Delta G^{\ddagger}$,[b] kcal mol$^{-1}$ |
|---|---|---|---|
| **2a** | 67 | −143 | 6.1 |
| **2d** | 56 | −112 | 7.7 |
| $ArCO_2CH_3$ | 33 | −92 | 8.9 |
| **2e** | 50 | −100 | 8.5 |
| **2f** | 60 | −113 | 7.6 |
| **2g** | 70 | −110 | 7.75 |
| **2h**[c] | 4.2 | −106 | 8.8 |
| **4**[c] | 1.4 | −105 | 9.3 |
| **5**[c] | 38 | −129.5 | 7.0 |
| **7** | 100 | −137 | 6.3 |

[a] $^{13}C$ NMR measurements were performed at 25.16 MHz. [b] Estimated error ±0.15 kcal mol$^{-1}$. [c] $^1H$ NMR determination performed at 100 MHz.

carbon atoms of the thiophene ring, exemplified by the limiting structure **3**, enhances the mesomerism of the dimethylamino group. Moreover, the geometry of the thiophene ring lowers, compared to the benzene ring, the steric interactions between adjacent substituents such as the 2-$NMe_2$ and 3-$NO_2$ groups. The results of our NMR study of **2** and some related compounds substantiate this picture of the thiophene system.



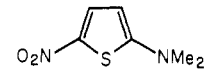
**3**

## Results and Discussion

**Thermodynamic Determinations.** Either $^1H$ or $^{13}C$ NMR gives at low temperatures two lines of equal intensity for the two diastereotopic methyl groups of **2**. The coalescence of these lines at a specific temperature permits determination of the free energy of activation ($\Delta G^{\ddagger}$) for C–N rotation.[11] Many investigations have shown that the values so obtained are equal to those obtained by lineshape analysis, within experimental error. It has also been reported that in this kind of conformational process[8,12,13] $\Delta S^{\ddagger}$ is usually negligible[8,14,15] and that $\Delta G^{\ddagger}$ can be used as a reliable measure of the barrier independent of the line-coalescence temperature at which it was determined. We were able to detect the nonequivalence of the two methyl groups more readily by $^{13}C$ than by $^1H$ NMR in **2a** and **2d–g** because of the larger chemical shift differences. In **2h**, the low solubility made $^1H$ NMR the better method. We were not able to detect the diastereotopic methyl groups in **2b** and **2c** because of their poor low-temperature solubilities. The chemical shift differences, line-coalescence temperatures, and free energies of activation for C–N rotation of **2a** and **2d–h** in $CHF_2Cl$ are shown in Table I.

The nitro group at position 3 of **2** should lead to a lower rotational barrier than that in 5-substituted (dimethylamino)thiophenes. It is well-established that ortho substituents destabilize the ground state, where the dimethylamino group is coplanar with the ring, with respect to the transition state, where it is perpendicular to the ring, thus reducing the barrier to the torsional process.[9b,12,13,16] However, in **2** this factor is offset to some extent by the through-conjugation effect between the 2-dimethylamino and 3-nitro groups (hyperortho relation), a factor that has a leveling effect on the values of $\Delta G^{\ddagger}$ (Table I). Study of some 4-substituted *N*-methylanilines showed a difference of 5.4 kcal mol$^{-1}$ between the highest and lowest values of $\Delta G^{\ddagger}$, and the trend of the $\Delta G^{\ddagger}$ values followed that of the Hammett substituent constants.[9b] On the other hand, with **2** the difference between the highest and lowest values of $\Delta G^{\ddagger}$ is only 2.7 kcal mol$^{-1}$, and because of this narrow range of values, no Hammett correlation could be made. Nevertheless, the introduction of electron-withdrawing substituents at position 5 (**2d–h**) does cause an increase in the free energy of activation over that in 2-(dimethylamino)-3-nitrothiophene (**2a**).

To investigate this point further, we determined the torsional barrier in 2-(dimethylamino)-5-nitrothiophene (**4**), which has no ortholike substituent at position 3.



**4**

A comparison of $\Delta G^{\ddagger}$ values (Table I) shows that the less crowded **4** has a significantly higher barrier than **2a**; because of the electron-withdrawing effect of the nitro group in **2h**, its torsional barrier is intermediate between those of **2a** and **4**.

The effects of the different geometries of the thiophene and benzene rings on the rotational barrier are apparent from a comparison of **2a** with the analogous 2-nitro-*N*,*N*-dimethylaniline, in which we could not detect rotational isomers even at −150 °C. This result could indicate either a large excess of the less-hindered rotamer or a lowering of $\Delta G^{\ddagger}$ caused by steric hindrance. Evidence for the latter comes from a comparison of the torsional barriers in **2h** and in 2,4-dinitro-*N*,*N*-dimethylaniline (**5**; Table I).

**Restricted Ar–CO Rotation in 2d.** In contrast to the effect of electron-releasing substituents on the Ar–N rotational barrier in aromatic amines, such substituents increase the Ar–CO rotational barrier in aldehydes and ketones.[17,18] Thus it has been possible to detect the two rotational conformers generated by slow rotation about both the Ar–N and the Ar–CO bonds in 4-acetyl-*N*-methylaniline;[9b] on the other hand, we did not observe such rotamers in **2e**. Apparently in this thiophene either the Ar–CO barrier is too low or one of the two rotamers exists in a negligible amount.

Recently Anet and Ghiaci[19] showed that in carbonyl derivatives of the type ArCOX, where X is a strong electron-attracting substituent such as F, Cl, Br, or CN, the barrier is much larger than that for ArCOMe.[18] However, they did not observe restricted Ar–CO rotation in methyl benzoate (X = OMe) and suggested that the ortho carbon atoms of the benzene ring have too small a chemical shift difference for detection since they are flanked by similar oxygen functions.[19] If this hypothesis is correct, a change

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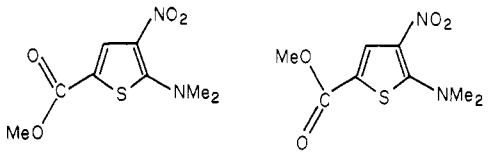
Table II. Dimethylamino Compounds[a]

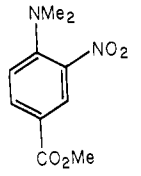
| compd | crystallization solvent | mp, °C |
|---|---|---|
| 2a | petroleum ether-benzene | 32-33 |
| 2b | ligroin-benzene | 83-84 |
| 2c | ethanol-dioxane | 212-213 |
| 2d | ethanol | 125-126 |
| 2e[b] | methanol-dioxane | 150-151 |
| 2f | ethanol-dioxane | 159-160 |
| 2g | methanol-dioxane | 149-150 |
| 2h[c] | chloroform | 153-154 |
| 4 | benzene | 138-139 |
| 5 | ligroin-benzene | 72-73 |

[a] Satisfactory analytical data (±0.3% for C, H, and N) were obtained for all new compounds listed in the table. The compounds are yellow or orange. [b] Cf.: Izmail'skii, V. A.; Polevshchikov, P. F. *Dokl. Akad. Nauk SSSR* **1964**, *159* (5), 1803. [c] Cf.: Hellerbach, J.; Szente, A. German Offen 2 342 931, 1974; *Chem. Abstr.* **1974**, *80*, 146002.

in ring shape could eliminate this degeneracy. Therefore, we searched for restricted rotation about the Ar–$CO_2$Me bond in **2d** and observed at −120 °C two well-separated $^{13}$C signals for both C-4 and $OCH_3$, corresponding to the conformers **6a** and **6b** in nearly equal amounts. Unambigous NMR evidence for rotamers in an aromatic ester has thus been obtained; the $\Delta G^{\ddagger}$ value is shown in Table I. In order to confirm this interpretation, we examined the analogous benzene derivative 4-(methoxycarbonyl)-2-nitro-*N*,*N*-dimethylaniline (**7**). The introduction of the nitro group was expected to modify the symmetry of methyl 4-(dimethylamino)benzoate and thus the degeneracy postulated in this compound,[19] and this result was found. At −140 °C all the signals for ring carbon atoms, as well as that for the carbonyl group, were split, but with very small separations (maximum $\Delta\nu$ observed 0.64 ppm, minimum 0.16 ppm). The intensity ratio within each doublet was about 2:1, and such an effect can result only from restriction of the Ar–CO rotation, giving rise to a pair of unequally populated syn–anti conformers.



**6a** **6b**



**7**

Restricted rotation about the Ar–$NMe_2$ bond was also detected in **7**; this phenomenon does not affect the aromatic carbons but only makes the two *N*-methyl groups diastereotopic, with lines having an intensity ratio of 1:1. The $\Delta G^{\ddagger}$ of 6.3 kcal mol$^{-1}$ (Table I) is lower than that for the analogous thiophene **2d**.

## Experimental Section

**Materials.** Compounds **2a–h**, **4**, and **7** were prepared by reacting the appropriate bromonitro compound (5 mmol) with dimethylamine (15–50 mmol) in benzene (20 mL) at room temperature for a few minutes or several hours, depending on the substrate. The reaction mixtures were evaporated and the residue purified by column chromatography on silica gel (eluant petroleum ether–benzene) and/or crystallization (Table II).

**NMR Measurements.** NMR spectra were recorded in the FT mode on a Varian XL-100 instrument. A few hundred transients were accumulated, and an external $^{19}$F lock system made it possible to lock at the very low temperatures employed. A thermocouple inserted in a dummy tube was used to monitor the temperature, and the $\Delta G^{\ddagger}$ values were obtained by determining the line-coalescence temperature. Samples were prepared by connecting the 10-mm sample tubes to a vacuum line and condensing the gaseous solvent ($CHF_2Cl$) in them by using liquid nitrogen. The sample tubes were then sealed under vacuum and introduced into the precooled probe of the spectrometer.

**Acknowledgment.** We are grateful to the Consiglio Nazionale delle Ricerche for financial support.

**Registry No. 2a**, 82080-40-8; **2b**, 82080-41-9; **2c**, 82080-42-0; **2d**, 82080-43-1; **2e**, 881-31-2; **2f**, 82080-44-2; **2g**, 82080-45-3; **2h**, 52431-12-6; **4**, 23631-00-7; **5**, 1670-17-3; **7**, 82080-46-4.

# A Heterocyclic Diels–Alder Approach to the Synthesis of the Pyridine C Ring of Streptonigrin[1,2]

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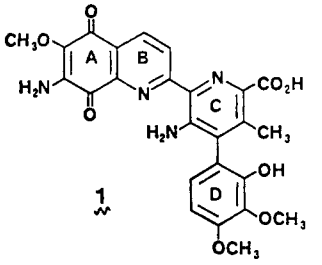
*Received February 26, 1982*

Streptonigrin 1, an antitumor antibiotic with interesting biological activities, was first isolated by Rao and Cullen from *Streptomyces flocculus*.[3] The structure was determined by spectroscopic and chemical studies[4] and later confirmed by X-ray analysis.[5] Additionally, studies of the biosynthesis[6] and mechanism of action[7] of streptonigrin have been published. Although streptonigrin has been found to be effective as an antitumor agent, it is too toxic for general clinical use.[8]



**1**

Because of its complex, unique structure and the need for less toxic analogues, streptonigrin has been the focus of considerable synthetic effort[9] including two total syntheses;[10] however, the regiospecific synthesis of its

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