Unexpected Formation of a Spiro Acridine and Fused Ring System from the Reaction between an *N*-Acridinylmethyl-Substituted Thiourea and Bromoacetonitrile under Basic Conditions

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Only a few heterocyclic compounds possessing the spiro ring structural unit actually incorporate the acridinyl moiety[1,2] despite the likely predisposition of acridine and its derivatives to form such structures. Structures incorporating the acridine moiety have shown marked mutagenic,[3] antiviral,[4] and antitumor[5−8] activities and are thus of prime interest for pharmaceutical applications. In our previous studies[9−13] a convenient synthesis of spiro acridine compounds was described. It also highlighted the particular susceptibility of the acridine C9 to nucleophilic attack and the subsequent ready formation of a five-membered ring. The spiro ring structure formed resulted from the attack of a carbanion produced from a methylene carbon α to either an ester carbonyl or a nitrile functionality. In this work, we attempted to again generate a presupposed analogous intermediate under similarly basic conditions whereby a methylene carbon was again α to a nitrile functionality (and also α to an sp^3-hybridized sulfur atom) by reacting *N*-(9-acridinylmethyl)-*N*′-(*p*-nitrophenyl)thiourea (**1**, produced from the reaction between 9-acridinylmethylamine and *p*-nitrophenyliso-thiocyanate) with bromoacetonitrile (see Scheme 1). Under these conditions, instead of the expected formation of a new six-membered ring, the spiro[dihydroacridine 9(10*H*),2′-(2′,7′-dihydro-3′*H*-imidazo[1,2-*c*]-thiazol-5′-ylidene-(*p*-nitrophenyl)amine] (**2**), incorporating once again a new five-membered ring as a part of the spiro structure, was obtained. This time, however, it was further fused to another five-membered, newly formed heterocyclic ring.

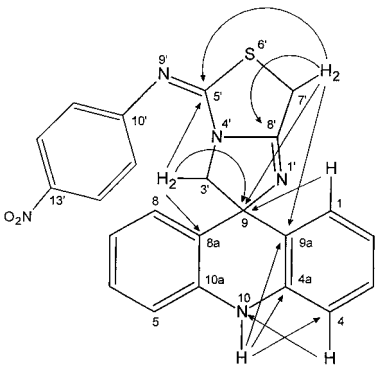

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Figure 1. The structure of the product together with the numbering system in use and pertinent HMBC correlations assisting in the structural elucidation. Note that the two longitudinal halves of the acridinyl moiety are time-averaged equivalent and for clarity degenerate correlations have been omitted.

The structural elucidation of **2** was initially based on NMR studies incorporating a suite of experiments. In addition to the 1D ^{1}H, NOE difference, ^{13}C and DEPT, and ^{15}N INEPT (based on 90 Hz) spectra, 2D DQF COSY, CHSHF, FG HMBC (^{1}H−{^{13}C} and ^{1}H−{^{15}N}), and ^{1}H-{^{15}N}-HSQC experiments were acquired. Of immediate focus from the ^{13}C NMR spectrum was the presence of an aliphatic quaternary carbon at 78.03 ppm, some several ppm downfield of that typical for the C9 of acridine, which is part of a spiro structure and bound to both a carbon and a nitrogen extraneous to the acridine moiety.[12] Furthermore, a suitable carbon resonance typical for a nitrile carbon was lacking, which was consistent with the IR spectrum, which lacked a band typical for a nitrile functionality. HMBC correlations (see Figure 1) readily confirmed that C9 carbon is the quaternary carbon at high field and that therefore it is sp^3-hybridized. Furthermore, HMBC correlations (^{1}H−{^{13}C} and ^{1}H−{^{15}N}) also identified the highfield nitrogen at −285.2 ppm bearing one proton (from ^{1}H−{^{15}N} HSQC) as N10, and therefore it too is sp^3-hybridized. The remaining exceptional HMBC correlations provided little assistance in the structural elucidation (see Figure 1), but the changes in the hybridization states of C9 and N10 clearly speak for a spiro structure or at the very least for two substituents to be attached to C9.

The ^{1}H and ^{13}C chemical shifts (4.41 and 27.51, respectively) of position 7′, however, pointedly indicated C7′ to be S-bound, as one such carbon would well be expected from the conditions of the experiment. The relatively small NOEs (1.2% enhancement) from the isochronous H7′ protons to the H1 and H8 acridine protons in comparison to the similarly isochronous me-

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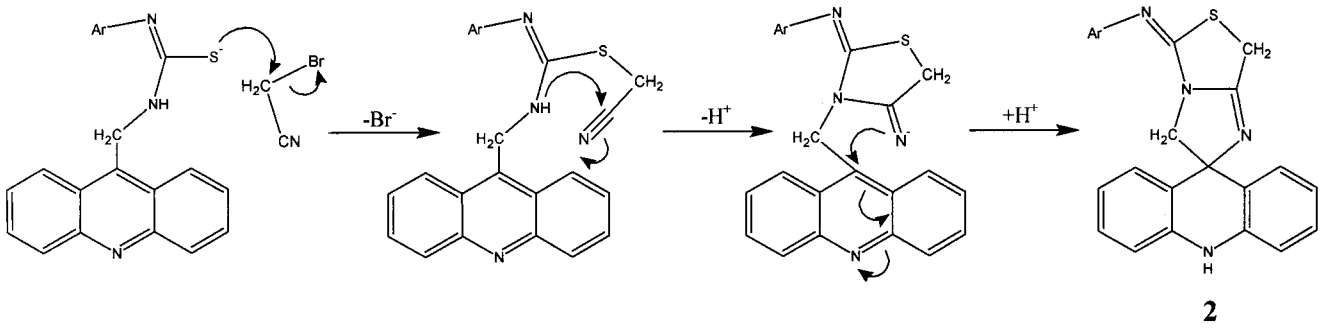
Scheme 1. Proposed Reaction Pathway[a]



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[a] An intermediate was detected by TLC, and it presumably results from displacement of the bromine and prior to the formation of the new rings. The result of the second step may not necessarily constitute a discrete intermediate, and the second and third steps could well be considered as one concerted step.

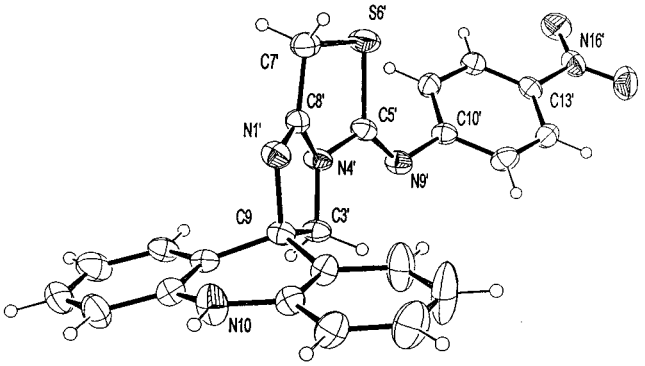

Figure 2. The X-ray crystallographic structure depicting the enantiomorph present in the particular crystal examined.

thylene H3′ protons (7.7% enhancement) are suggestive for their location being more remote from that segment. Indeed, no NOE was detected between the two sets of methylene protons. Thus, only by constructing a bond between N1 and C9 (Figure 1) can one readily account for the chemical shift of C9 and at the same time maintain some degree of separation between the two methylene pairs. The DBE constraints are satisfied by a bond between N4′ and C8′ and this inclusion accounts for the two lowfield carbon shifts that are not part of an aromatic system. Thus the structure can be formulated as depicted in Figure 1.

The structure of **2**, initially concluded from the NMR data, was confirmed by subjecting suitable crystals to X-ray crystallographic analysis, the pictorial result of which is presented in Figure 2. The X-ray structure determination itself was most illuminating. Of note is the near ideal planarity of both the acridinyl and fused five-membered ring systems, the two planes of which are essentially orthogonal to one another in accordance with expectations. Interestingly, the plane of the *p*-nitrophenyl ring is also more or less orthogonal to the fused five-membered ring segment in the solid state. From the presentation in Figure 2 it is most apparent that the structure, although not "inherently" chiral since it lacks a chiral center, is in fact enantiomeric—as can be visualized by the bending of the plane of the two fused five-membered rings to one side and the orientation of the *p*-nitrophenyl ring. The compound does indeed crystallize out in an enantiomeric space group (orthorhombic, *P*212121), but in solution rapid fluxional motion time-averages the two (or more) enantiomorphs and results in an achiral structure.

The likely reaction pathway leading to the product presumably begins with displacement of the bromine in bromoacetonitrile by the nucleophilic sulfur anion (see Scheme 1). Following the formation of this likely intermediate, an intramolecular attack by the nitrogen closest bound to the acridinyl moiety (ultimately N4′) could then lead to the formation of both the first five-membered thiazolidine ring and a highly reactive imino anion that is confined proximally to the highly susceptible C9 of acridine. The ensuing third step, which may in fact be essentially concerted with the previous step, then leads to the formation of the second five-membered imidazoline ring and the spiro ring structure **2**.

In conclusion, we have characterized and determined the structure of a highly unusual and quite unexpected product of a simple reaction that results in the formation of elaborate substructures, namely, spiro and fused ring systems. Thus, although the generation of spiro structures incorporating the acridine moiety might be well anticipated given the susceptible nature of the C9 carbon to nucleophilic attack, unexpected products can result even from seemingly simple and limited systems. The reaction may hold potential for producing analogous spiro structures, but the course of the reaction seems actually to be dependent on the nature of the phenyl substituent, the detailed elucidation of which is now the focus of present investigations.

Experimental Section

NMR spectra were acquired at 25 °C on a JEOL Alpha 500 NMR spectrometer equipped with either a 5-mm normal configuration tunable probe or a 5-mm inverse *z*-axis field-gradient probe operating at 500.16 MHz for ^{1}H (internal tetramethylsilane, TMS_{int} = 0 ppm), 125.78 MHz for ^{13}C (TMS_{int} = ppm), and 50.69 MHz for ^{15}N (external 90% nitromethane in CD_3NO_2 = 0 ppm). Spin analysis was performed using PERCH software[14] for the extraction of chemical shifts and coupling constants. Further details of NMR experiments are given in the Supporting Information.

X-ray structure of compound **2** was determined by using essentially the same methodology as prescribed in ref 15 and according to the principles outlined in the references therein (29−33).

Spiro[dihydroacridine 9(10*H*),2′-(2′,7′-dihydro-3′*H*-imidazo[1,2-*c*]thiazol-5′-ylidene-(*p*-nitrophenyl)amine] (2). 9-Acridinylmethylamine was liberated as a white precipitant

(14) See for example: Laatikainen, R.; Niemitz, M.; Weber, U.; Sundelin, J.; Hassinen, T.; Vepsäläinen, J. *J. Magn. Reson., Ser. A* **1996**, *120*, 1 or the program website at http://www.uku.fi/perch.html.

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from an aqueous solution of 9-acridinylmethylamine dihydrochloride[16] (0.562 g in 20 mL, 2 mmol) by the addition of aqueous potassium hydroxide (0.280 g in 30 mL, 5.0 mmol). The precipitate was extracted into chloroform (2 × 20 mL), which was then dried over $CaCl_2$ followed by the dropwise addition at room temperature of a chloroform solution of *p*-nitrophenylisothiocyanate (Aldrich, 0.360 g in 15 mL, 2 mmol). After stirring for 1 h, the solution was filtered to collect the adduct, *N*-(9-acridinylmethyl)-*N*′-(*p*-nitrophenyl)thiourea (**1**); a further crop of precipitant was then obtained by the addition of petroleum ether to the filtrate. The dried thiourea was suspended in methanol (50 mL) and dissolved by the portionwise addition of solid sodium methoxide at room temperature until a slightly alkaline solution was obtained. An excess of bromoacetonitrile (Aldrich, 264 mg, 2.2 mmol) was then added dropwise with stirring, affording a yellow-brownish precipitate after 10 min. After 1 h of standing, the precipitant was filtered off, washed with ether, and dried. From the combined reaction solution and ethereal washings, a further batch of crude product was obtained by the addition of water. The crude material had a melting point of 164−168 °C but could be recrystallized from dichloromethane/diethyl ether, acetonitrile, or chloroform to yield rhombic yellow, analytically pure crystals of (**2**), mp 215−217 °C, 210−214 °C, or 210−215 °C, respectively. Yield 67%. Microanalysis for $C_{23}H_{17}N_5O_2S$ calcd: C, 64.6; H, 4.0; N, 16.4; S, 7.5. Found: C 64.5; H, 3.8; N, 16.4; S, 7.3. HRMS provided a $M^{+\bullet}$ of 428.09415, which corresponds to a calculated formula weight of 428.09431 (Δ = 0.2 mDa, 0.4 ppm). ^{1}H NMR {$CDCl_3$/d_6-DMSO (1:1)} δ ppm: 9.19 (br s, H10); 8.18 (AA′ part of AA′BB′ system, $J_{A,B}$ = 9.0, $J_{A,A'}$ = 2.8, $J_{A,B'}$ = 0.2 Hz, H12′ & H14′); 7.26 (approximately ddt, $J_{1,2}$ = 7.8, $J_{1,3}$ = 1.5, $J_{1,10}$ = 0.52, $J_{1,4}$ = 0.50 Hz, H1 & H8); 7.17$_5$ (ddd, $J_{3,4}$ = 8.1, $J_{3,2}$ = 7.2, $J_{3,1}$ = 1.5 Hz, H3 & H6); 7.14 (BB′ part of AA′BB′ system, $J_{A,B}$ = 9.0, $J_{B,B'}$ = 2.5, $J_{A,B'}$ = 0.2 Hz, H11′ & H15′); 6.92 (approximately ddd, $J_{4,3}$ = 8.1, $J_{4,2}$ = 1.2, $J_{4,1}$ = 0.5 Hz, H4 & H5); 6.90 (approximately ddd, $J_{2,1}$ = 7.8, $J_{2,3}$ = 7.2, $J_{2,4}$ = 1.2 Hz, H2 & H7); 4.41 (2H s, H7′); 3.87 (2H s, H3′). ^{1}H NMR {$CDCl_3$} δ ppm: 8.20 (AA′ part of AA′BB′ system, $J_{A,B}$ = 8.8, $J_{A,A'}$ = 2.3, $J_{A,B'}$ = 0.3 Hz, H12′ & H14′); 7.29 (approximately ddt, $J_{1,2}$ = 7.8, $J_{1,3}$ = 1.4, $J_{1,10}$ = 0.6, $J_{1,4}$ = 0.4 Hz, H1 & H8); 7.24 (ddd, $J_{3,4}$ = 8.0, $J_{3,2}$ = 7.3, $J_{3,1}$ = 1.4 Hz, H3 & H6); 7.09 (BB′ part of AA′BB′ system, $J_{A,B}$ = 8.8, $J_{B,B'}$ = 2.7, $J_{A,B'}$ = 0.3 Hz, H11′ & H15′); 7.02 (ddd, $J_{2,1}$ = 7.8, $J_{2,3}$ = 7.3, $J_{2,4}$ = 1.2 Hz, H2 & H7); 6.82 (ddd, $J_{4,3}$ = 8.0, $J_{4,2}$ = 1.2, $J_{4,1}$ = 0.4 Hz, H4 & H5); 6.44 (br s, H10); 4.25 (2H s, H7′); 4.03 (2H s, H3′). ^{13}C NMR {$CDCl_3$/d_6-DMSO (1:1)} δ ppm: 161.08 (s, C5′); 155.11 (s, C10′); 151.53 (s, C8′); 143.39 (s, C13′); 136.96 (2 × s, C4a & C10a); 128.11 (2 × d, C3 & C6); 127.08 (2 × d, C1 & C8); 124.82 (2 × d, C12′ & C14′); 122.89 (2 × s, C8a & C9a); 122.10 (2 × d, C11′ & C15′); 119.82 (2 × d, C2 & C7); 113.88 (2 × d, C4 & C5); 78.03 (s, C9); 63.67 (s, C3′); 27.51 (s, C7′). ^{15}N NMR {$CDCl_3$/d_6-DMSO (1:1)} δ ppm: −285.2 (d, N10).

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Supporting Information Available: X-ray crystallographic data and details of NMR experiments for compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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