A new ring system: 3-*H*-pyrazolo[3,4-*h*]isoquinoline. An unexpected product from diazotization of an aminoisoquinoline

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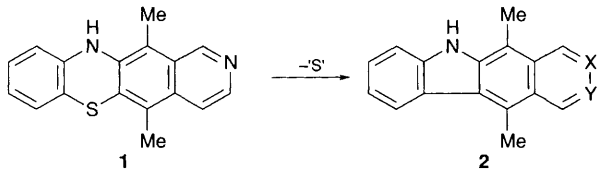
Diazotization of 7-amino-5,8-dimethyl-6-thiophenylisoquinoline with sodium nitrite in acetic acid gives a mixture of 6-thiaellipticine and 5-methyl-4-thiophenyl-3*H*-pyrazolo[3,4-*h*]isoquinoline, a new heterocyclic ring system whose crystal structure is presented.

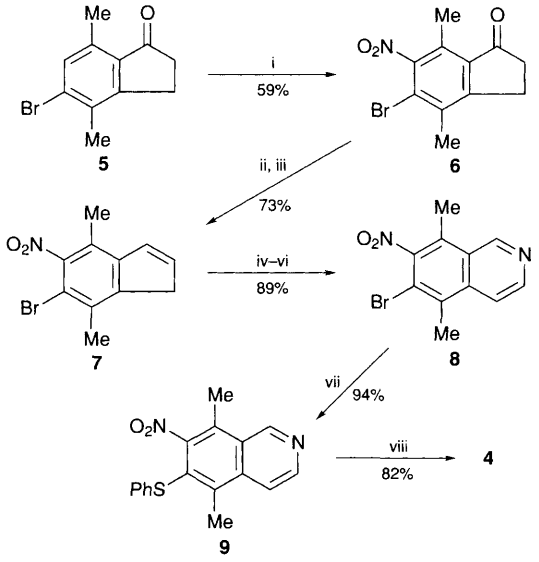
As part of a broad programme directed toward the synthesis of pyridocarbazole alkaloids such as ellipticine[1–3] **2** (X = CH, Y = N), we wished to investigate a sulfur extrusion route from a phenothiazine type molecule. Our model experiment was to be the conversion of **1** to isoellipticine[4] **2** (X = N, Y = CH)



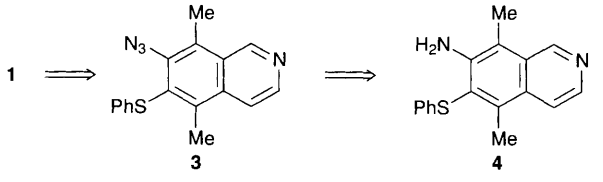
because we felt we had a ready entry into **1** based on our earlier approach to ellipticine using nitrene insertion from decomposition of an appropriate azido compound.[3c] Thus we proposed that azide **3**, which in turn would be formed from the corresponding aminoisoquinoline **4**, should lead to the desired **1** (Scheme 1). Unexpectedly, the attempted diazotization–azidification of **4** led to a mixture of compounds, the major product of which contained a new heterocyclic ring system, the 3*H*-pyrazolo[3,4-*h*]isoquinoline system, which is the topic of this communication.

The required aminoisoquinoline **4** was prepared using our isoquinoline synthesis[5] as a key step (Scheme 2). Thus, 5-bromo-4,7-dimethylindanone[3a] **5** was nitrated with fuming nitric acid to provide bromonitroindanone **6**.† Reduction of the indanone to the indanol was followed directly by dehydration without purification of the indanol to give indene **7**.† Use of acidic conditions (*p*-TsOH in refluxing benzene) for the dehydration insured the regiochemical integrity of the indene double bond. Application of our isoquinoline synthesis conditions converted **7** to isoquinoline **8**.† The bromine group was substituted by a thiophenyl group using displacement by thiophenoxide in DMF at 100 °C to give **9**.† These conditions proved to be much more efficient than refluxing isopropyl alcohol or Me_2SO at 50 °C (these latter conditions led to significant amounts of sulfoxide formation).[6] Finally, reduction of the nitro group using hydrazine and a Raney Ni catalyst gave the desired thiophenylaminoisoquinoline **4**.†

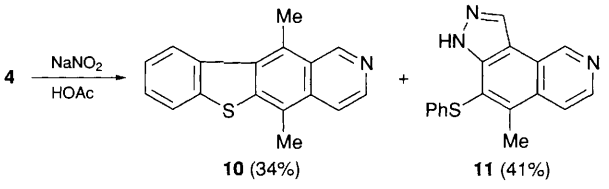
Due to the low solubility of **4** in 5% aqueous HCl, our normal experimental conditions[3c] for diazotization–azidification were altered to use glacial acetic acid as the acidic solvent along with sodium nitrite followed by treatment with sodium azide. Unexpectedly, examination of the crude reaction product indicated that very little azide was present (very small peak at 2120 cm^{-1} in the IR spectrum). Chromatography on basic alumina gave two major products: 6-thiaellipticine[7] **10** and 5-methyl-4-thiophenyl-3*H*-pyrazolo[3,4-*h*]isoquinoline **11**, which contains a new heterocyclic ring system. This reaction was repeated except that no sodium azide was added following diazotization and the same two products were formed; **10** was isolated in 34% yield and **11** in 41% (Scheme 3). The identity of **10**, presumably formed from a Pschorr reaction[8] of the intermediate diazonium salt, was confirmed from its NMR spectra (^1H and ^{13}C) and comparison of its melting point with the literature value.[7] The structure of the new heterocyclic system **11** was determined by X-ray analysis (Fig. 1).‡ We postulate that this product arises by initial formation of the



Scheme 2 *Reagents and conditions*: i, fuming HNO_3; ii, N_aBH_4, iii, *p*-TsOH, C_6H_6, reflux; iv, O_3, MeOH; v, Me_2S; vi, NH_4OH; vii, PhSNa, DMF, Δ; viii, H_2NNH_2, Ni cat.



Scheme 1



Scheme 3

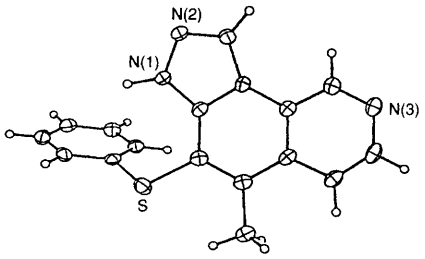
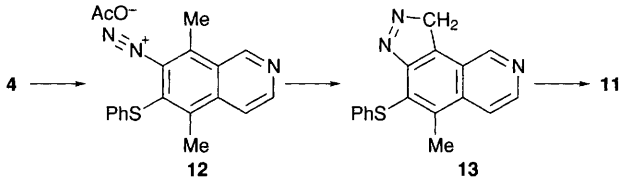


Fig. 1 A perspective view of **11**



Scheme 4

diazonium salt **12** and cyclization to **13** which tautomerizes to **11** with the driving force being aromatization of the five-membered heterocyclic ring (Scheme 4). Presumably, the presence of acetate as the counterion instead of chloride directs the course of this reaction.[9] This is supported by a recent observation that when **4** was slurried in aqueous HCl and treatment with sodium nitrite followed by sodium azide a good yield of the azidoisoquinoline **3** was formed with no observable amounts of **10** and **11**.

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Footnotes

† Satisfactory elemental combustion analysis and/or mass, IR and ^{1}H and ^{13}C NMR spectral data were obtained for all new compounds.

‡ *Crystal Data* for $C_{17}H_{13}N_3S$, **11**: M = 291.4, triclinic, a = 7.907(2), b = 8.266(2), c = 10.506(2) Å, α = 93.20(2), β = 95.90(2), γ = 92.39(2)°, U = 681.2(2) Å^3 (by least-squares refinement on diffractometer angles for 20 automatically centred reflections) at 130 K, λ = 1.54178 Å, graphite monochromator, space group $P\bar{1}$, Z = 2, D_c = 1.421 g cm^{-3}, $F(000)$ = 304. Orange blocks. Crystal dimensions 0.30 × 0.35 × 0.50 mm; μ(Cu- Kα) = 2.063 mm^{-1}. Refinement (based on F) of 1688 reflections and 190 parameters yielded R_1 = 0.0383, R_w = 0.0492 [based on observed data with $I > 2\sigma(I)$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/288.

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