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REGIOSELECTIVITY IN ELECTROPHILIC SUBSTITUTION OF 5-AMINOINDOLES AND 5-AMINOINDOLINES: SYNTHESIS OF PYRROLO[3,2-e]INDOLES AND ISOMERIC PYRROLO[2,3-f]INDOLES †

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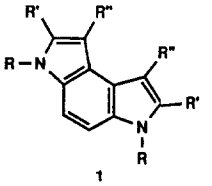
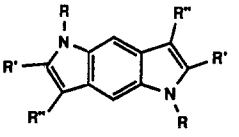
Abstract: An FMO Theory prediction that 5-aminoindoles, **5**, should react with electrophiles preferentially at C_4 rather than at C_6 whereas N_1-acyl-5-aminoindolines, **6**, should react preferentially at C_6 rather than C_4 is borne out experimentally by the synthesis of a pyrrolo[3,2-e]indole from **5** and pyrrolo[2,3-f]indoles from **6**.

Recent interest in derivatives of pyrrolo[3,2-e]indole, **1**, has been stimulated by the presence of this ring system in a dihydro form in the naturally occurring potent antitumour agent CC-1065.[1,2] The isomeric pyrrolo-[2,3-f]indole system, **2**, has been of interest as a precursor to conducting polymers produced by electropolymerization of **2**.[3] In this laboratory an interest has developed in studying the possibility of employing

Figure 1



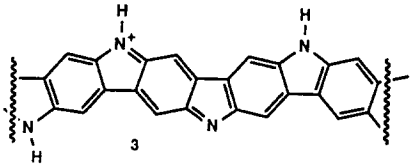
1



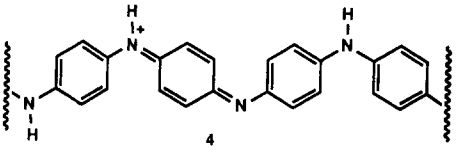
2

pyrrolo[2,3-f]indoles in the construction of bridged analogs **3** of polyaniline **4** [4,5] in order to explore the influence of such bridging on the electrical conductivity properties of this class of polymers. As indicated in

Figure 2



3



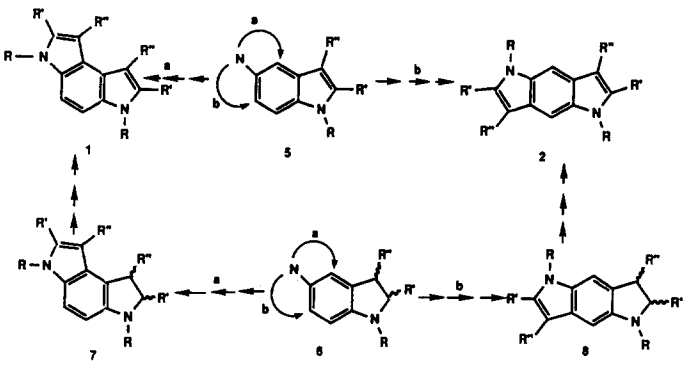
4

Scheme **1**, one potential approach to the construction of derivatives of **1** or **2** could involve electrophilic substitution of a 5-aminoindole **5** which might occur via path **a** or path **b**. On the other hand, 5-aminoindoline **6** might lead to dihydro analogs **7** or **8** which might be converted to **1** or **2** by appropriate dehydrogenation processes.

Reported herein, in preliminary form, are the results of theoretical and experimental studies which define the regioselectivity of processes designed to produce **1** or **2** through variations of the general pathways shown in Scheme 1.

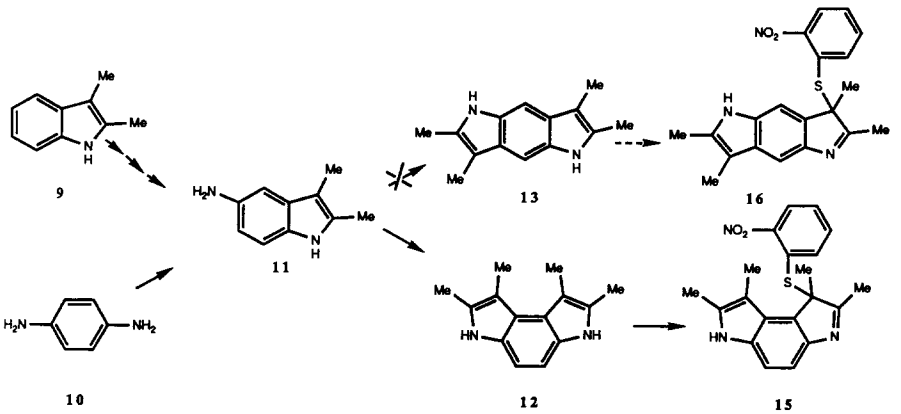
† Dedicated to the memory of David A. Holden

Scheme 1



Semi-empirical molecular orbital calculations employing the AM1 method [6,7] reveal that the HOMO coefficient at C_4 of 5-aminoindoles (0.409 for 5-aminoindole; 0.417 for 5-amino-2,3-dimethylindole) is substantially larger than that at C_6 (0.166 for 5-aminoindole; 0.115 for 5-amino-2,3-dimethylindole). Based on these coefficients, FMO arguments [8-10] would predict preferential electrophilic attack at C_4. In practice, reaction of 5-amino-2,3-dimethylindole, **11**, with 3-bromo-2-butanone under Bischler conditions [11, 12] gave a product (40% yield) with spectroscopic features compatible *a priori* with the pyrrolo[3,2-e]indole structure **12** or the isomeric pyrrolo [2,3-f]indole structure **13** (Scheme 2). The same product was obtained by reaction of

Scheme 2

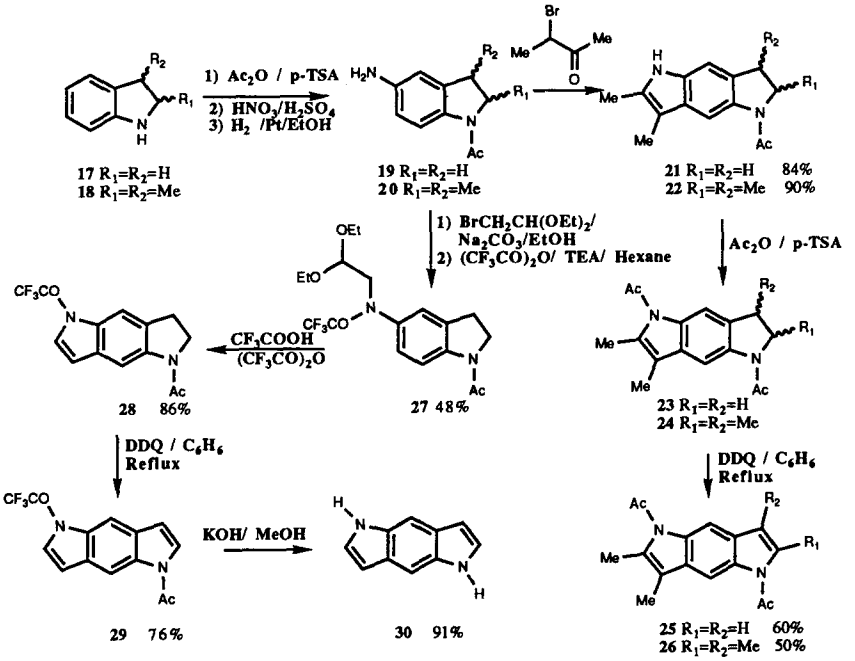


3-bromo-2-butanone with *p*-phenylenediamine (35% yield). That this product was **12** and not **13** was demonstrated by reaction with one equivalent of *o*-nitrophenylsulfenyl chloride, **14**, [13] which led to desymmetrization of the system and removal of the chemical shift equivalence of the aromatic hydrogens. The magnitude of the coupling constant (6Hz) of the aromatic AB quartet in the sulfenylated product clearly established the ortho relationship of the aromatic hydrogens thus ruling out structure **16** and indicating that the Bischler cyclization proceeded predominantly in the direction predicted by FMO analysis.

In contrast, AM1 computations on N_1-formyl-5-aminoindoline reveal that the HOMO coefficient at C_6 (0.261) exceeds that at C_4 (0.194) leading to the FMO prediction that electrophilic attack should occur preferentially at C_6. This prediction has now been borne out experimentally in that Bischler indolization of N_1-acetyl-5-aminoindoline, **19**, yields the dihydropyrrolo[2,3-f]indole **21** in which the para relationship of the aromatic hydrogens is readily established by the magnitude of the coupling constant ($J_{4,8} < 1$ Hz) between the aromatic-

hydrogens. N-Acetylation of **21** followed by dehydrogenation with DDQ yielded the pyrrolo[2,3-f]-indole **25**. An analogous sequence of reactions employing N-acetyl-5-amino-2,3-dimethylindoline, **20**, (*cis/trans* mixture) as starting material has furnished the pyrrolo[2,3-f]indole **26**.

Scheme 3

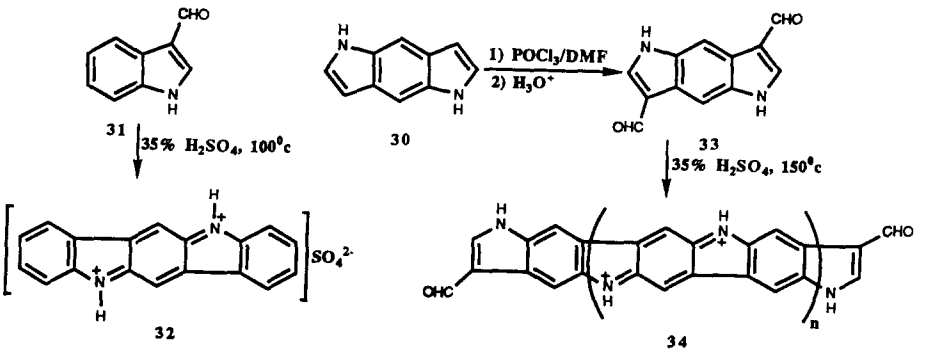


In addition, it has been possible to generate the known unsubstituted pyrrolo[3,2-e]indole **30** [3c] from **19** employing the indolization strategy developed by Norlander and coworkers.[14] Reaction of **19** with bromoacetaldehyde diethylacetal followed by trifluoroacetylation gave **27** which cyclized smoothly in the presence of trifluoroacetic acid and trifluoroacetic anhydride to yield the dihydropyrrolo[3,2-e]indole **28**. DDQ dehydrogenation followed by alkaline hydrolysis, yielded **30**.

Thus, pyrrolo[3,2-e]indoles **1** are accessible in moderate yield from 5-aminoindole and the isomeric[2,3-f]-indoles **2** are accessible from 5-aminoindolines via electrophilic cyclizations which occur in accord with predictions of FMO analysis.

Vilsmeier formylation of **30** yields the dialdehyde **32** which is a potential precursor to bridged polyanilines of the type **3** described above. Preliminary experiments indicate that **32** undergoes sulfuric acid catalyzed

Scheme 4



condensation polymerization by analogy with the known conversion of 3-formylindole **30** into urorosein **31** [15] to yield a purple polymeric material with physical properties similar to those of polyanilines. The physical and electrical properties of this material will be described in detail elsewhere.

Acknowledgements:

The authors would like to acknowledge the assistance of L.A. Burke in identifying bridged polyanilines as worthy targets for synthetic investigation and of H. Nandin de Carvalho and P. Dibble in preparing samples of authentic pyrrolo[2,3-f]indole. The contribution of the late Professor David Holden to this research project through numerous valuable discussions is gratefully acknowledged. Financial support for this study has been provided by the Natural Sciences and Engineering Research Council of Canada in the form of a Strategic Operating Grant.

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10. (a) For a discussion of FMO analysis of electrophilic aromatic substitution in general see: Reference 8, pp 47-66; (b) For a recent review of quantitative and theoretical analysis of electrophilic substitution of heterocyclic compounds see: Katritsky, R.A.; Taylor, R. "Electrophilic Substitution of Heterocycles: Quantitative Aspects; Advances in Heterocyclic Chemistry" 47, (1990), Academic Press, Inc., New York.
11. In a typical experiment the aniline (**11, 19** or **20**) and 3-bromo-2-butanone (0.5 equivalents) were dissolved in n-butanol (14 mL/mmol of aniline) containing acetic acid (58 μL/mmol of aniline) and the solution was heated at reflux in a nitrogen atmosphere for 24 hr. Aqueous workup involving extraction with evaporation of the solvent *in vacuo* and purification of crude residue by column chromatography on silica gel gave the final product.
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