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SELECTIVE SIDE-CHAIN BROMINATION OF N-ACYL-2,3-DIALKYLINDOLES: SYNTHESIS AND CHEMICAL MODIFICATION OF PYRROLO[1,2-a]INDOLES

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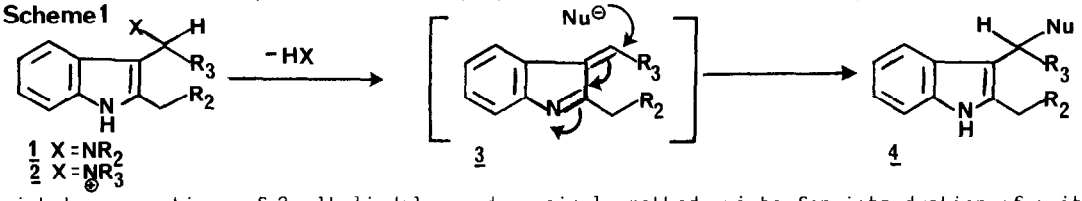
Selective side-chain modification of N-acyl-2,3-dialkylindoles at C-2, effected by bromination with NBS, and at C-3, effected via SN' type reactions of 2,3-dialkyl-2-methoxy-3-methylene indolines generated by low temperature bromination-methanolysis of N-acylindoles, can be usefully applied to the synthesis of substituted pyrrolo[1,2-a] indoles of potential value in the synthesis of mitosene analogs.

Side-chain modifications of 2,3-dialkylindoles via substitution reactions at the α-carbons at C-2 and C-3 are synthetically valuable transformations.[1] Substitutions at the C-3 α-carbon are usually performed on gramine-like compounds **1** or the corresponding quaternary ammonium salts **2** via an elimination-addition process. However, systems such as **1** are normally produced via

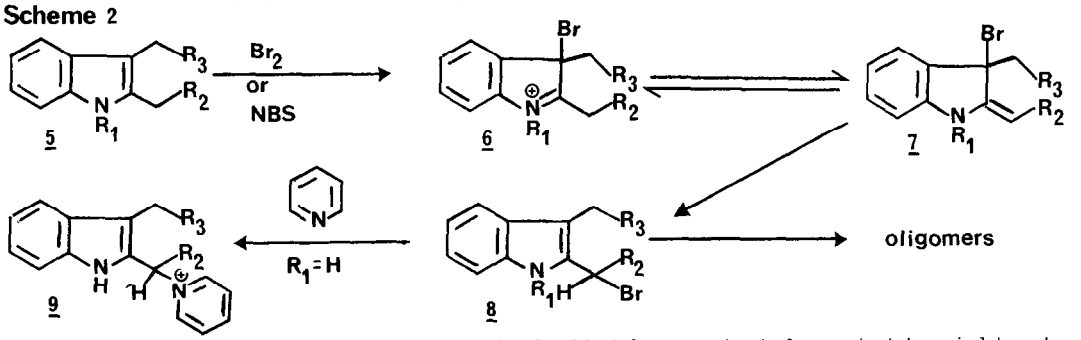
Scheme 1



Mannich-type reactions of 2-alkylindoles and no simple method exists for introduction of suitable leaving groups, X, at the C-3 α-carbon of 2,3-dialkylindoles.[2]

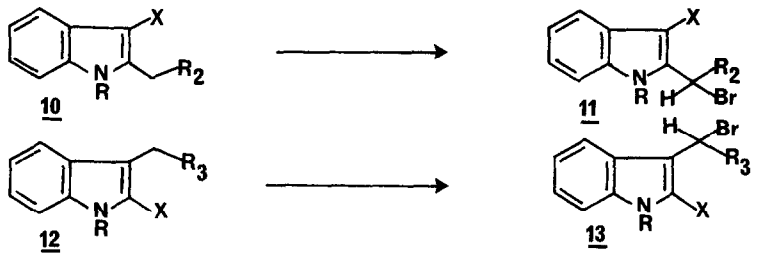
Substitution at the C-2 α-carbon of 2,3-dialkylindoles is possible via pyridinium salts such as **9** produced by reaction of 2,3-dialkylindoles with NBS in the presence of pyridine[3] but such reactions proceed in, at best, moderate yields and are quite sensitive to reaction conditions as evidenced by reports of the inability to reproduce reactions of this type.[4] C-2 Side-chain halogenated indoles **8** are very likely generated in the bromination and chlorination of N-unsubstituted indoles in the absence of nucleophiles but these compounds are not isolable and highly coloured (blue-purple) oligomeric products are usually produced in such reactions.[5,6]

Scheme 2



Since N-acyl or N-sulfonyl 2-alkyl- or 3-alkylindoles can be halogenated to yield moderately stable α-haloalkylindoles **11** or **13** [7,8] which undergo displacement reactions with various

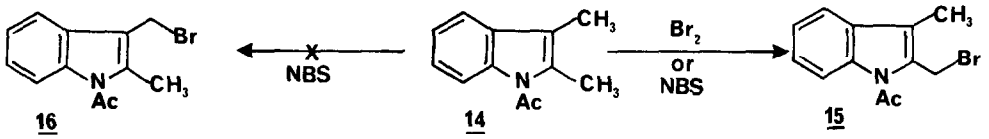
Scheme 3



nucleophiles, we have explored methods for effecting side chain modifications of N-acyl-2,3-dialkylindoles via halogenation and report our results herein.

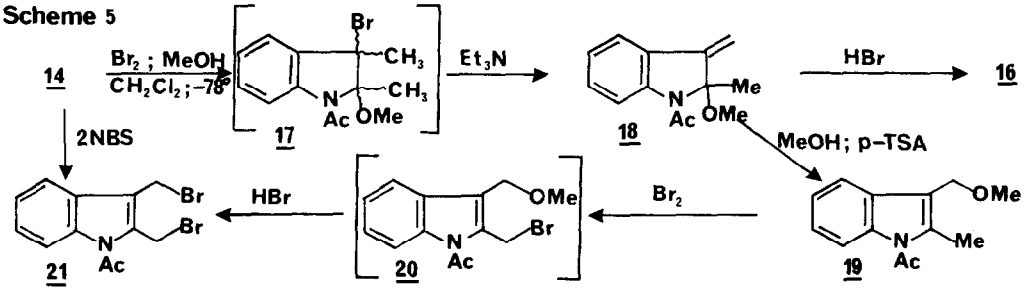
It has been known for some time that N-acetyl-2,3-dimethylindole reacts with molecular bromine to yield the moderately stable bromide **15.** [9,10] However, no methods have been reported for the generation of the isomeric C-3 side-chain brominated compound **16.** Since halogenation was potentially possible at the C-2 side-chain (eg **10** → **11**) or the C-3 side chain (eg **12** → **13**) with NBS, the selectivity of such reactions was explored with **14.** It has now been found that reaction of **14** with NBS gives the C-2 side-chain brominated product **15** exclusively and, as a result, an indirect route to **16** was sought.

Scheme 4



Since earlier work in this laboratory[10] had demonstrated that **14** reacts with molecular bromine in the presence of 1.5 equivalents of methanol at low temperature to give a solution of the unstable bromoether **17** which undergoes a facile elimination in the presence of triethylamine to yield **18,** we examined the possibility that **18** could serve as a precursor to **16** via an S_N1' process. In practice, it has been found that **18** is converted to **16** very efficiently by reaction with anhydrous HBr.[11] Further experimentation has revealed that the dibromide **21** can be generated selectively (40% overall yield from **14**) by reaction of **19,** derived from **18** by treatment with acidified methanol, with molecular bromine, likely via reaction of the intermediate **20** with the HBr byproduct. In addition, the reaction of **14** with two equivalents of NBS proceeds with high selectivity to give the crystalline dibromide **21** in 80% yield.[12,13]

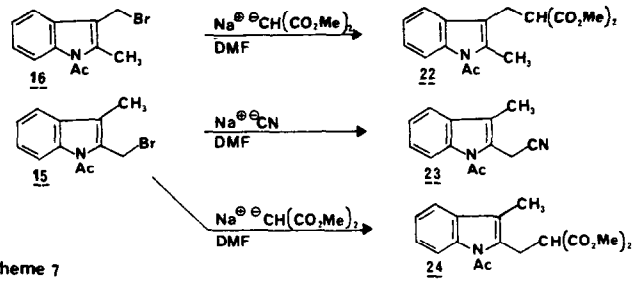
Scheme 5



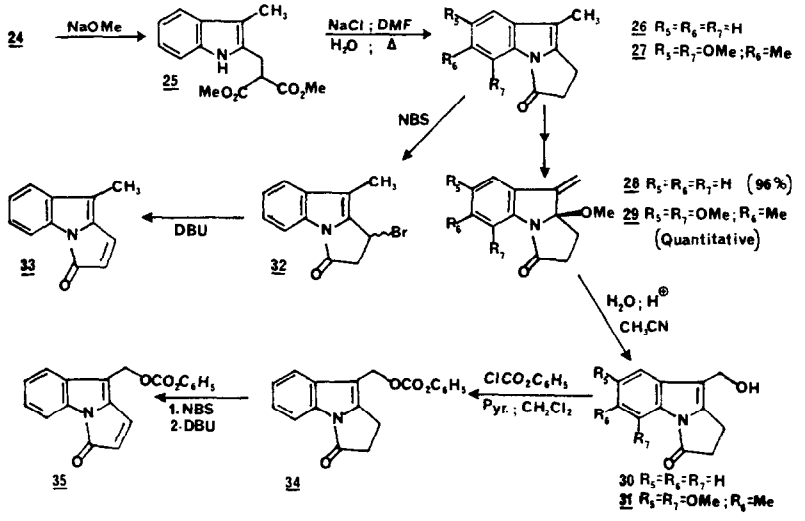
The monobromides **15** and **16** readily react with carbon nucleophiles to effect overall C-2 or C-3 side-chain alkylation as shown in Scheme **6**. The C-2 side-chain alkylated product **24** could be converted to the lactam **26** by deacylation with sodium methoxide and treatment under the conditions of the Krapcho reaction ($NaCl/H_2O/DMF/reflux$).[14] The pyrrolo[1,2-a]indole derivative **26** was of particular interest since its synthesis and chemical transformations could serve as model reactions for the synthesis of mitosene-type antibiotics and analogs.[15]

The value of selective side-chain bromination reactions is further illustrated in the efficient transformation of **26** and its substituted analog **27** to **28** and **29** respectively which may offer a route to 10-decarbamoyloxy-9,10-dehydromitomycins.[16] Reaction of **28** and **29** with water and acid gives the alcohols **30** and **31** respectively.

Scheme 6



Scheme 7



The unsaturated lactam **33** could be prepared in 98% yield from **26** by reaction with one equivalent of NBS to give **32** followed by reaction with one equivalent of DBU. In an analogous fashion, the phenyl carbonate **34** prepared from **30** was converted to **35** (90% yield) which is properly functionalized for introduction of the carbamoyloxy[17] and aziridine[18] functionalities of the mitomycins or for the preparation of mitosene analogs incorporating different electrophilic sites at C_1 and C_{10}.

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11. Some of the physical properties of compounds described herein are as follows: **15** ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3, C_3-CH_3), 2.76 (s, 3, $NCOCH_3$), 5.01 (s, 2, C_2-CH_2-Br), 7.02-7.90 (m, 4, Ar-H); **16** δ 2.57 (s, 3, C_2-CH_3), 2.70 (s, 3, $NCOCH_3$), 4.67 (s, 2, C_3-CH_2-Br), 7.1-8.2 (m, 4, Ar-H); **21** (m.p. 145-147° (decomp.)), δ 2.84 (s, 3, $NCOCH_3$), 4.70 (s, 2, -C_3-CH_2Br), 5.09 (s, 2, C_2-CH_2Br), 7.32-7.84 (m, 4, Ar-H); **22** (mp 131°) 2.57 (s, 3, C_2-CH_3), 2.71 (s, 3, $NCOCH_3$), 3.3 (d, 5Hz, 2, C_3-CH_2-CH-), 3.63-3.72 (partly obscured by singlet at 3.69, C_3-CH_2-CH-) 3.69 (s, 6, CO_2CH_3), 7.18-7.45 (m, 3, $C_{4,5,6}$-H), 7.88-8.0 (m, 1, C_7H); **23** (mp 120° (decomp)) δ 2.27 (s, 3, C_3-CH_3), 2.83 (s, 3, $NCOCH_3$), 4.16 (s, 2, CH_2CN), 7.2-7.8 (m, 4, Ar-H); 24 (mp 177-179°) δ 2.23 (s, 3, C_3-CH_3), 2.77 (s, 3, $NCOCH_3$), 3.56-4.20 (m, 3, C_2-CH_2-CH-), 3.65 (s, 6, CO_2CH_3), 7.19-7.82 (m, 4, Ar-H); **25** (mp 107°) δ 2.23 (s, 3, C_3-CH_3), 3.26-3.35 (m, 2, C_2-CH_2-CH), 3.71-3.81 (m, 1, C_2-CH_2-CH), 7.01-7.53 (m, 4, Ar-H), 8.20-8.46 (b, 1, N-H); 26 (mp 175-176°) δ 2.14 (s, 3, C_9-CH_3), 2.99 (s, b, 4, C_1H_2-C_2H_2), 7.19-7.44 (m, 3, $C_{6,7,8}$-H), 7.95-8.07 (m, 1, C_5-H); **27** (mp 194°) δ2.12 (s, 3, C_9-CH_3), 2.27 (s, 3, C_6-CH_3), 3.06 (s, 4, C_1H_2-C_2H_2), 3.85 (s, 3, C_7 or C_5-OCH_3), 3.90 (s, 3, C_5 or C_7-OCH_3), 6.60 (s, 1, C_8-H); **28** (oil) δ 2.06 (m, 4, C_1H_2-C_2H_2), 3.02 (s, 3, C_{9a}-OCH_3), 5.43 (s, 1, C_9=CH-H), 5.82 (s, 1, C_9=CH-H), 7.08-7.91 (m, 4, Ar-H); **29** (mp 138-139°) δ 2.19 (s, 3, C_6-CH_3), 2.20-2.60 (m, 4, C_1H_2-C_2H_2), 3.08 (s, 3, C_{9a}-OCH_3), 3.84 (s, 3, C_5 or C_7-OCH_3), 3.87 (s, 3, C_7 or C_5-OCH_3), 5.36 (s, 1, C_9=CH-H), 5.70 (s, 1, C_9=CH-H), 6.70 (s, 1, C_8-H); **30** (mp 150-152°) δ (acetone -d_6) 2.81-3.30 (m, 4, C_1H_2-C_2H_2), 3.96 (t, 4.8 Hz, 1, -O-H), 4.76 (d, 4.8 Hz, 2, -C_9-CH_2-OH), 7.15-7.36 (m, 2, Ar-H), 7.56-7.63 (m, 1, Ar-H), 7.89-8.01 (m, 1, ArH); **31** (mp 135-136°) δ 2.25 (s, 3, C_6-CH_3), 2.90 (s, 4, C_1H_2-C_2H_2) 3.80 (s, 3, C_5 or C_7-OCH_3), 3.89 (s, 3, C_7 or C_5-OCH_3), 4.71 (s, 2, C_9-CH_2-OH), 6.80 (s, 1, C_8-H); **33** (mp 93.5-94.5°) δ 2.04 (s, 3, C_9-CH_3), 5.79 (d, 7Hz, 1, C_2-H), 6.96-7.72 (m, s, Ar-H and C_1-H); **34** (mp 117°), δ 2.72-3.19 (m, 4, C_1H_2-C_2H_2), 5.27 (s, 2, C_9-CH_2-), 7.02-7.65 (m, 3, $C_{6,7,8}$-H), 7.87-8.06 (m, 1, C_5-H); **35** (mp 139-140° (decomp.)) δ 5.36 (s, 2, C_9-CH_2-), 6.01 (d, 5.6 Hz), 1, C_2-H), 7.11-7.43 (m, 9, ArH and C_1-H).
12. The dibromide, 21, is a useful precursor to N-acetyl-indole-2,3-quinodimethane (S.F. Vice and G.I. Dmitrienko, 65th Conference of the Chemical Institute of Canada, Toronto, 1982; Abstract #OR 18-5). For a very similar bromination of N-benzoyl-2,3-dimethylindole see: Saroja, B. and Srinivasan, D.C., Tetrahedron Lett. (1984), 5429.
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