SYNTHESIS OF BISINDOLES FROM BISIMIDAZOLINES

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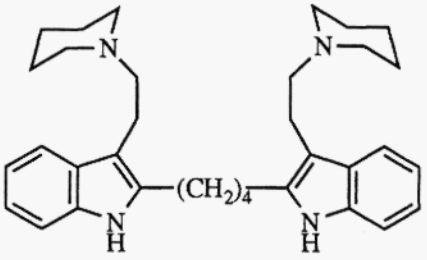
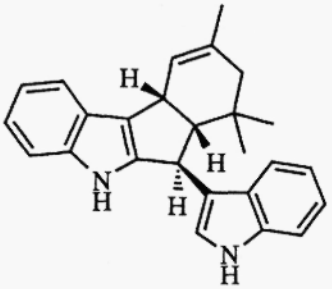
Abstract: Diacetylimidazolinium ions, generated *in situ* from imidazolines and acetic anhydride, electrophilically attack indoles in position 3. This method has now been extended to reagents obtained from α,ω-alkylene linked bisimidazolines. The adducts isolated could readily be hydrolysed to the corresponding bifunctional 3-acylindoles.

Certain bisindoles,(1) in particular biscarbazoles,(2) wherein the two heterocyclic units are separated by a linker of various length and chemical properties, are of interest as bidental intercalators with high affinity and sequence-specificity to DNA.(1,3) Furthermore, 2,2'-alkylenebisindole derivatives, such as 1, have been claimed to be potent, low-toxicity anti-ulcer agents.(4) Several natural products showing promising biological activities have two indole nuclei connected *via* a more or less rigid framework as exemplified by yuehchukene 2 (5), grossularine-1 3 (6-8) and asterriquinone 4 (9-11). Recently biindolizines with flexible spacers were synthesised in an attempt to prepare macrocyclic host compounds.(12)



1



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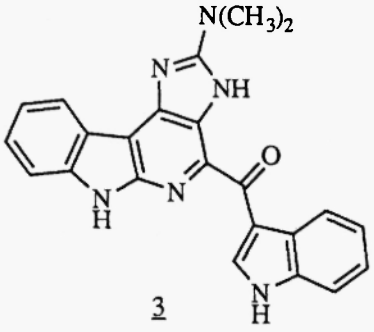

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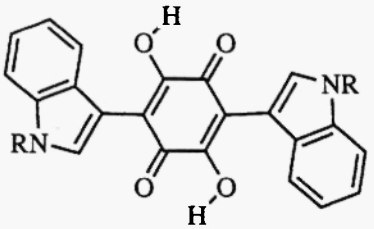
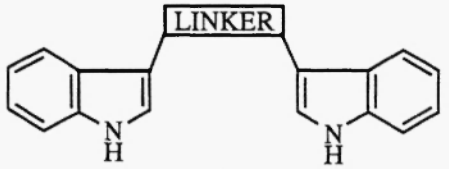


4 R = $C(CH_3)_2CH{=}CH_2$

Although bisindoles of the general structure 5 are readily available, *e.g.* by double Madelung cyclisation,(13) only the two simplest representatives 6a and 6b of the isomeric series 6 seem to have been adequatly described in the literature.(14) Potential routes to 6 include reactions of indole Grignard reagents with diacyl chlorides. Unfortunately 1,1′- and 1,3′- as well as 3,3′-coupled regioisomers are obtained in this reaction.(15) Sanna has claimed the isolation of 3,3′-(1,3-propanedioyl)bisindole and 3,3′-(1,4-butanedioyl)-bisindole from the indole Grignard reagent and malonyl chloride or succinyl chloride respectively. Unfortunately the products were poorly characterized and no yields were given.(16,17) Reactions of indole Grignard reagents with diesters predominantly yield 1,1′-coupled derivatives.(15) The Houben-Hoesch reaction offers another possibility but only minor amounts of 3,3′-(1,6-hexanedioyl)bisindole (21% after hydrolysis) have been reported.(18) A third approach makes use of an *N*-protected 3-formylindole which on treatment with a bis-Grignard reagent yielded the corresponding diol.(19) As this method involves protection and deprotection steps we considered the possibility, as an alternative, to extend a method,(20) involving electrophilic attack at the 3-position of indoles using an *N,N′*-diacetylimidazolinium ion generated *in situ* from acetic anhydride and the appropriate imidazoline, to the corresponding bifunctional reagents. In the preparation of *e.g.* 3-propionylindole simple mixing of indole, 2-ethyl-4,5-dihydroimidazole and acetic anhydride gave the adduct 7 as a precipitate, which subsequently could be hydrolysed to 3-propionylindole (19) in high yield. Extension of this method to bisimidazolines of type 8 should therefore be expected to lead to the desired bisindole derivatives 6 under mild conditions.

5



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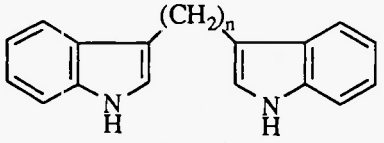
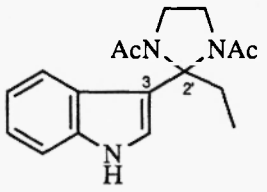
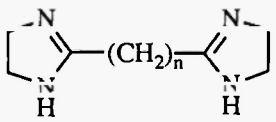


6a n=1
6b n=2

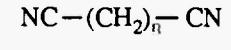


7

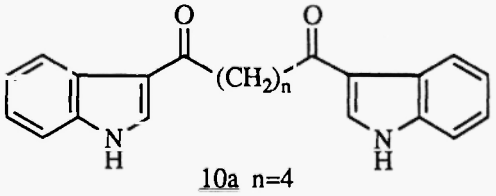
Dinitriles 9 and 1,2-diaminoethane react readily, using S_8 as the catalyst,(21) to afford bisimidazolines 8a and 8b (22-24) in 51% and 89% yields, respectively.



8a n=4
8b n=10

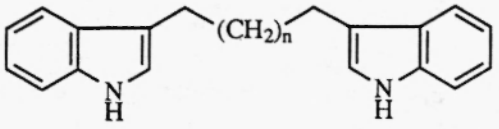


9a n=4
9b n=10

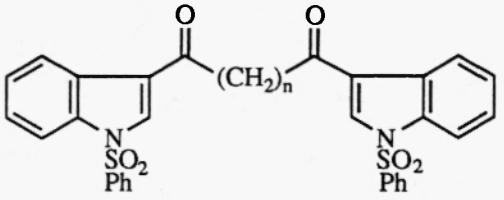


10a n=4
10b n=10

In the reactions of 8 with indole in acetic anhydride adducts, bisanalogues of 7, were obtained within 2h and were collected as white powders. The adducts were isolated as mixtures of inseparable, diastereomeric atropisomers (25,26) as could be concluded by comparison of their nmr spectra with those obtained at high temperature (110 °C). The observed atropisomerism could be due to either hindered rotation around the C3-C2′-bond as illustrated in 7, or around the amide bonds. The precipitates obtained could be used without further purification and were hydrolysed under mild acidic or basic conditions to 3,3′-(α,ω-alkanedioyl)-bisindoles 10 (27). Treatment of 10 with $LiAlH_4$ yielded, as expected,(28) the corresponding 3,3′-(α,ω-alkanediyl)bisindoles 11 (29). *N*-Protection of 10 with two phenylsulfonyl groups were achieved using NaH in DMSO and phenyl-sulfonyl chloride. The product 12b thus obtained correlated nicely with a sample, kindly supplied by Prof. Gribble, prepared by acylation of *N*-(phenylsulfonyl)indole with 1,12-dodecanediacyl chloride under Friedel-Crafts conditions.(30)



11a n=4
11b n=10



12a n=4
12b n=10

Finally we conclude that introduction of masked acyl groups into indole systems by means of *N,N′*-diacylimidazolinium ions under mild conditions constitutes a fast and useful route to 3-acylindoles and their bifunctional counterparts.

ACKNOWLEDGEMENTS

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(22) Compound 8a: Yield: 51.2%. mp: 209-210°C (lit. (23) mp: 209-210°C) . Ir (KBr): 3158 (br), 2941, 2862, 1610, 1495, 1290, 976 cm^{-1}. ^{1}H-Nmr (250 MHz, $CDCl_3$): δ 3.61 (s, 8H), 3.04 (br s, 2H), 2.33 (t, 4H), 1.69 (m, 4H). ^{13}C-Nmr (62.9 MHz, $CDCl_3$): δ 167.7 (s), 49.1 (t), 28.3 (t), 25.2 (t).

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(27) Compound 10a: Yield: 80.9%. mp: 290°C decomp. Ir (KBr): 3170 (br), 2927, 1625, 1521, 1435, 925, 746 cm^{-1}. ^{1}H-Nmr (250 MHz, DMSO-d_6): δ 11.90 (br s, 2H), 8.34 (s, 2H), 8.18 (d, 2H), 7.45 (d, 2H), 7.19-7.15 (m, 4H), 2.88 (tr, 4H), 1.71 (tr, 4H). ^{13}C-Nmr (62.9 MHz, DMSO-d_6): δ 195.3 (s), 136.5 (s), 133.7 (d), 125.3 (s), 122. 5 (d), 121.5 (d), 121.3 (d), 116.3 (s), 111.9 (d), 36.6 (t), 24.7 (t).

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(29) Compound 11b: Yield: 90.2%. mp: 122-123°C. Ir (KBr): 3416, 2915, 2848, 1455, 1091, 741 cm^{-1}. ^{1}H-Nmr (250 MHz, DMSO-d_6): δ 10.71 (s, 2H), 7.46 (d, 2H), 7.30 (d, 2H), 7.05-6.90 (m, 4H) , 2.65 (t, 4H), 1.70-1.55 (m, 4H), 1.30-1.20 (m, 16H). ^{13}C-Nmr (62.9 MHz, DMSO-d_6): δ 136.2 (s), 127.1 (s), 121.9 (d), 120.6 (d), 118.1 (d), 117.9 (d), 114.6 (s), 111.2 (d), 29.9 (t), 28.9 (t, 4C), 28.6 (t, 4C), 24.6 (t).

(30) Unpublished results, but analogous to: D. M. Ketcha, G. W. Gribble, J. Org. Chem. 50, 5451 (1985)

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