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THERMAL CYCLIZATION OF N-NICOTINOYLALKYL INDOLES

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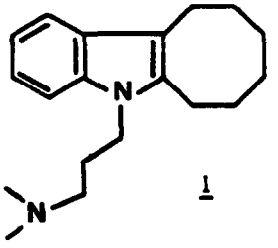
Abstract: An unusual thermal cyclization of N-nicotinoylalkylindoles using Grignard reagent is described.

As an extension of our work on conformationally restricted tricyclic anti-depressants,[1] efforts have been made to synthesize rigid analogues of the nonclassical antidepressant iprindole 1[2], such as 2a and 2b. We planned to prepare N-nicotinoylhexahydrocyclooctindole 4 to utilize as a starting material for 2a and 2b. We report here the discovery of an unusual cyclization during N-acylation of indole 3.



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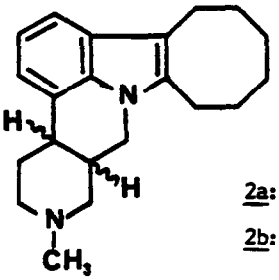
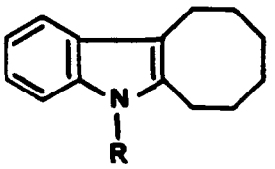


2a: cis

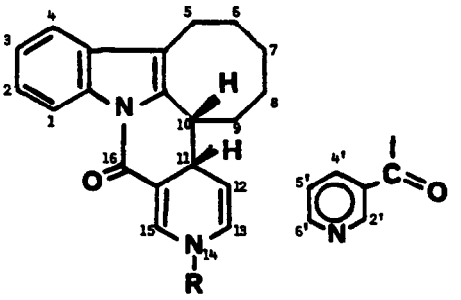
2b: trans



3 R = H

4 R = Nicotinoyl

5 R = β-picolyl



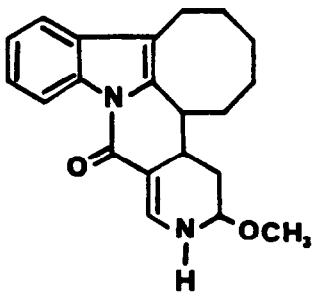
6 R = Nicotinoyl

7 R = H

Acylation of the magnesium Grignard reagent of indole 3 with an equimolar amount of nicotinoyl chloride in dry THF gave required amide 4 (20%, colorless needles from hexanes, m.p. 114°, M^+ 304, $C_{20}H_{20}N_2O$), together with considerable quantity of 6 (30%, light brown flakes from methanol, m.p. 195°, M^+ 409, $C_{26}H_{23}N_3O_2$). Elemental analysis and mass spectrum of 6 suggested the condensation of two moles of nicotinoyl chloride per mole of indole 3. Furthermore, appearance of m/e 106 as 100% and lack of other major fragments suggested that one nicotinoyl group is incorporated probably as an N-acyl group with one single bond, while the second one is involved in a cyclization. Compound 6 exhibited the following spectral data: IR (KBr), 1680, 1660, 1630 and 1610 cm^{-1}; PMR ($CDCl_3$): δ 8.78 (1H, d, 2'-H), 8.7 (1H, q, 6'-H), 8.0 (1H, broad, 15-H), 7.93 (1H, dt, J = 8 & 2 Hz, 4'-H), 7.45 (2H, m, 4- & 5'-H), 7.25 (2H, m, 2- & 3-H), 8.42 (1H, m, 1-H), 7.18 (1H, broad, 13-H), 5.2 (1H, q, J = 8 & 2 Hz, 12-H), 4.02 (1H, q, J = 5 & 2 Hz, 11-H), 3.32 (1H, m, 10-H) and 1.2-3.0 (10H, aliphatic-H_2).

When dihydropyridine 6 was heated in 5% KOH-MeOH in an attempt to deacylate it, the product obtained was 8. (Colorless prisms from methanol, m.p. 200°, M^+ 336, $C_{21}H_{24}N_2O_2$) PMR: δ 8.25, (1H, m, N-H), 7.66 (1H, d, J = 6 Hz, 15-H), 4.6 (1H, m, 13-H) and 3.25 (3H, s, $-CH_3$), wherein methanol has been incorporated into the deacylated product. Hydrolysis of 6 with con. HCl or 10% HCl in methanol led to an unstable unidentified product. Lyle and Nelson have shown that structurally similar dihydropyridine 9 under acidic hydrolysis led to an unstable solid 10.[3] N-Deacylation was successfully achieved by stirring 6 in 5% KOH-MeOH at room temperature for 30 minutes to give 7 (yellow amorphous powder, m.p. 218°, M^+ 304). PMR ($CDCl_3$): δ 8.38 (1H, q, N-H), 7.37 (1H, d, J = 7 Hz, 15-H), 6.14 (1H, q, 13-H) and 4.6 (1H, q, 12-H). Further confirmation of the structure of 6 was provided by its oxidation with $HNO_3/H_2SO_4/H_2O$[4], to the N-oxide 11 (amorphous powder, m.p. 269°, M^+ 318). Attempts to dehydrogenate 6 and 7 to the pyridine derivative with mercuric acetate, DDQ or Pd-C were unsuccessful. The PMR spectrum of 11 confirms the site of ring closure to be the 4-position of the nicotinoyl group involved in the cyclization. Thus, 15-H appears as a singlet at δ 9.3 ppm and 12-H and 13-H form two doublets (J = 8.6 Hz) at 7.2 and 8.5 ppm respectively. Decoupling experiments in the PMR spectrum of 6, 7 and 8 revealed a coupling constant of 4.5 Hz between 10-H and 11-H which strongly suggests that the ring fusion is cis as shown.

In order to confirm the site of ring closure to be the 10-position (as opposed to, for example, the 5-position) of the cyclooctindole, we investigated the analogous reaction of 2-ethyl-3-methylindole magnesium bromide with excess nicotinoyl chloride. This reaction gave as the major product, compound 12, pale brown prisms, m.p. 220°, M^+ 369, $C_{23}H_{19}N_3O_2$, PMR ($CDCl_3$): δ 1.59 (3H, d, J = 6.6 Hz, $-CH-CH_3$), 2.3 (3H, s, $-CH_3$), 3.07 (1H, qd, J = 10.5 & 1.5 Hz, 5-H) and 3.3 (1H, q, J = 10.5 & 1.5 Hz, 4a-H), wherein a



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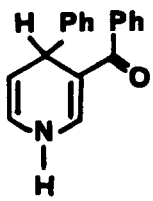

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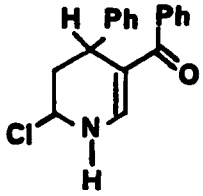

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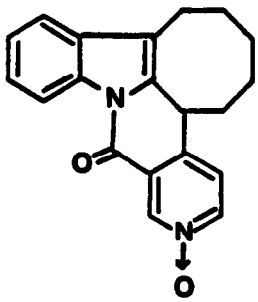
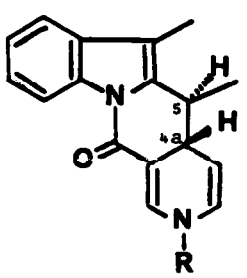


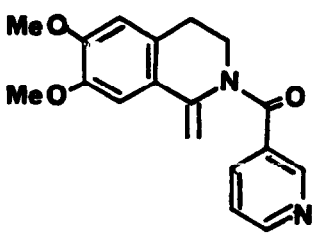
11

cyclization to the methylene of the 2-ethyl group has clearly occurred to give trans indolonaphthyridine 12 ($J_{4a,5}$ = 10.5 Hz). This result not only extends the scope of the reaction but also confirms the participation of the 2-substituent of the indoles. On the other hand, the reaction of 1,2,3,4-tetrahydro-carbazole-9-magnesium bromide with excess of nicotinoyl chloride gave a nearly quantitative yield of the corresponding N-nicotinoyl indole, with only a trace (< 1% of the cyclized product M^+ 381) being formed.

The recently described[5] thermal cyclization of enamide 13 in excess of nicotinoyl chloride to dihydropyridine 14, initially appeared to be analogous to our results. In both cases, the N-acylation of a pyridine ring forms an electron deficient pyridinium structure. The enamide 13, however, has a p-methoxyphenyl substitutuent, making the exocyclic methylene more nucleophilic for facile cyclization.[5] Treatment of amide 4 with excess of nicotinoyl chloride, with or without base (Et_3N, MeMgBr), however, failed to give product 6. N-(β-picolyl) cyclooctindole 5 also failed to give corresponding cyclic compound under these conditions. It thus appears that the Grignard complex, formed from reaction of nicotinoyl chloride with the indole Grignard reagent, must react with excess acylating agent to form 6. Furthermore, the sodium salts of 3 and 2-ethyl-3-methylindole do not form cyclic products on reaction with excess of nicotinoyl chloride, but yield the N-nicotinoylindoles quantitatively.



12 R = Nicotinoyl



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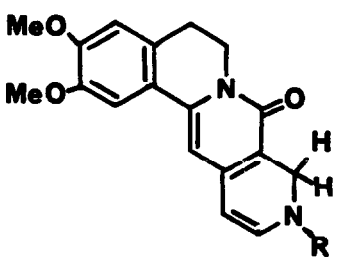
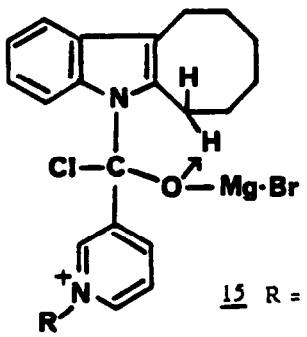
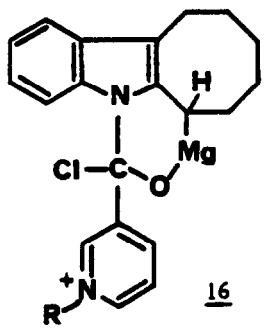


14 R = Nicotinoyl

A mechanism consistent with the above results probably involves abstraction of a proton from the 2-alkyl group by the anionic oxygen atom in the Grignard complex 15 (six-membered transition state) followed by attack of the newly generated carbanionic center on the 4-position of the pyridinium ring to form 6. The relative ease of formation of a carbanion center at the α-position of 2-alkylindoles is consistent with the facile decarboxylation of indole 2-acetic acid derivatives which has been noted previously.[6] Stabilization of the carbanion by its coordination with magnesium in the transition state, possibly as an intermediate such as 16 apparently permits the cyclization to occur. The comparative rigidity of the 6 membered ring of tetrahydrocarbazole, on the other hand, evidently either prevents partitioning of the acylated Grignard complex to 15 or 16, or their cyclization to the α-position of the 2-alkylindole.



15 R = Nicotinoyl



16

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