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SYNTHETIC APPLICATIONS OF 2-(1,3-DITHIAN-2-YL)INDOLES. SYNTHESIS OF 1-METHYL-15-HYDROXY-20-DEETHYLDASYCARPIDONE

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The first synthesis of 1-methyl-15-hydroxy-20-deethyldasycarpidone has been achieved via acid-induced cyclization of the 4-hydroxy-4-indolylcarbonyl-2-piperidinecarbonitrile which in turn are obtained by a modified Polonovski reaction. The formation of lactams **6** and **7** in the acid cyclization conditions are reported for the first time.

In recent publications[1] concerning the reactivity of the anions of 2-(1,3-dithian-2-yl)indoles with electrophiles it was shown that the dianion of **1a** and the anion of **1b** react with 1-methyl-4-piperidone to give the addition products **2a** and **2b** in high yields. Conditions for the subsequent liberation of the keto function were also developed involving sequential treatment with *m*-chloroperbenzoic acid and aqueous acetic acid.

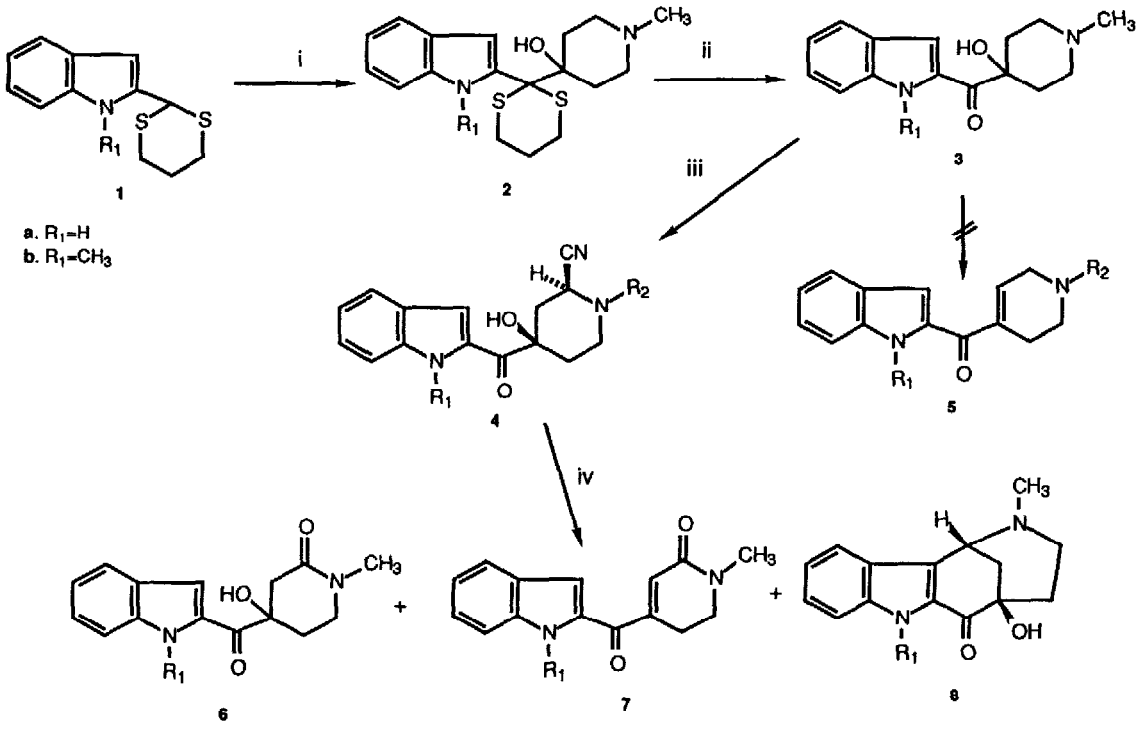
As part of a project on the total synthesis of *Strychnos* alkaloids[2] we required means for creating a bond between the C-2 position of the piperidine ring in **3a,b** and the C-3 center of the indole nucleus. One approach that appeared attractive was to convert **3a,b** to the α,β-unsaturated ketone **5**[3,4] and attempt to isomerize the double bond thereby creating an iminium ion that would cyclize giving **8**.[5] However, all attemps to dehydrate **3**[6,7] failed to give either product **4** or **8**.

Conversion of 4-piperidinols **3** to the corresponding α-aminonitriles **4** were therefore studied employing the now established modified-Polonovski-cyanide trapping protocol.[8] In fact reaction of the *N*-oxides of **3** with trifluoroacetate anhydride followed by reaction of the resultant iminium ion with sodium cyanide led to compounds **4a** and **4b** in ~55 % yield. This result is quite remarkable in that it is known that the modified Polonovski reaction of piperidine *N*-oxides bearing NR_2, OR, and SR substituents at C-4 gives 2-cyano-Δ^3-piperideines in a considerable extent.[8,9]

Subsequent reaction of aminonitrile **4a** under standard acid conditions (80% AcOH, reflux, 16 h) proved to be equally remarkable as the major component was the lactam **6a**[10,11] (yield

28%) and its dehydration product **7a**[12] (yield 17%). The expected product **8a** was formed in only minor amounts (yield ~5%), and was assigned by the presence of a characteristic triplet (J=3 Hz) at δ 4.52 for the methine proton on C-1 (C-21 in the biogenetic numbering)[2] in its ^{1}H-nmr spectrum.

Anticipating that molecular oxygen may play a role in this transformation it was found that in the reaction of α-aminonitrile **4b** the yield of compounds **6b**[13] and **7b**[14] decreased, and the yield of product **8b** increased (yield ~25%) when strict precaution was taken to employ degassed solvents. To our knowledge this is the first example of the conversion of an α-aminonitrile to an amide with oxygen in acidic media. The exact mechanism of this novel reaction and the possible role of the C-4 hydroxyl group in amide function is presently under investigation.



Reagents and conditions. i) (1) n-BuLi, THF, -20ºC, 15 min; (2) 1-methyl-4-piperidone, THF, -20ºC . ii) (1) 85% MCPBA, CH_2Cl_2, -20ºC; (2) 1:10 HCl-THF, r.t., 5 h. iii) (1) 85% MCPBA, 0ºC; (2) TFAA; (3) KCN-H_2O. iv) 80% AcOH , reflux, 16 h.

Scheme 1

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4. A sample of **5** provided by Besselièvre, R. shown the following nmr data: ^{1}H-nmr (200 MHz, $CDCl_3$, δ) 2.33 (s, 3H, NCH_3), 2.70 (s, 4H, NCH_2CH_2), 3.19 and 3.39 (2d, J_{AB}=12 Hz, 2H, $=CCH_2N$), 6.92 (t, J=2 Hz, 1H, In-3H), 7.19 (t, J=7 Hz, 1H, In-5H), 7.39 (t, J=7 Hz, 1H, In-6H), 7.51 (d, J=7 Hz, 1H, In-4H), 7.74 (d, J=7 Hz, 1H, In-7H), 10.1 (br s, 1H, NH); ^{13}C-nmr 25.4 (NCH_2CH_2), 45.6 (NCH_3), 51.7 (NCH_2), 54.7 ($=CCH_2N$), 111.1 (In-C3), 112.3 (In-C7), 120.8 (In-C6), 123.0 (In-C5), 126.1 (In-C4), 127.6 (In-C3a), 134.2 (In-C2), 136.3 (In-C7a), 136.8 (HC=), 137.7 (COC=), 187.3 (C=O).
5. Martínez, S. J. ; Dalton, L. ; Joule, J. A. *Tetrahedron* , **1984**, *40* , 3339, and references cited therein.
6. Treatment of **3a** with *p* -toluenesulfonic acid in benzene or toluene, sulfuric acid or trifluoroacetic acid-tetrahydrofurane, 20% hydrochloric acid at reflux temperature, and *p* -toluenesulfonic acid at 150 ºC and 1 mmHg, did not afford the expected product. When the reaction was carried out upon the dithiane **2a** and *p* -toluenesulfonic acid at 150ºC and 1 mmHg the only product obtained was the dithiane **1a** formed by a fragmentation process.
7. Attempts to obtain tetrahydropiridine **5** by treatment with ethyl chloroformiate, Et_3N, CH_3CN or $SOCl_2$-pyridine, gave only the indole 3-ethoxycarbonyl or the 3-chloro derivatives of **3a**.
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9. Essawi, M. Y. H.; Portoghese, P. S. *J. Org. Chem.* , **1983**, *48* , 2138.
10. All new compounds gave elemental analysis consistent with the proposed structures.
11. **6a**: m.p. 171-172 °C (acetone-hexane); ir (KBr, cm^{-1}) 3100-3500, 3310, 1640, 1615; ^{1}H-nmr ($CDCl_3$+CD_3COCD_3, δ) 1.9-2.3 (m, 2H, 5-H), 2.65 (d, J=7 Hz, 1H, 3-H), 2.96 (s, 3H, NCH_3), 3.03 (br d, J=7 Hz, 1H, 3-H), 3.30-3.60 (m, 1H, 6-H), 3.60-3.95 (m, 1H, 6-H), 7.11 (ddd, J=7.5, 7, and 1 Hz, 1H, In-5H), 7.31 (ddd, J=7.5, 7 and 1 H, 1H, In-6H), 7.38 (dd, J=3 and 1 Hz, 1H, In-3H), 7.54 (dq, J=7.5 and 1Hz, 1H, In-4H), 7.69 (d q, J=7 and 1 Hz, 1H, In-7H),10.8 (br s, 1H, NH); ^{13}C-nmr (δ) 26.2 (C-5), 33.9 (NCH_3), 40.3 (C-3), 47.7 (C-6), 73.0 (C-4), 109.3 (In-C3), 112.3 (In-C7), 120.3 (In-C4), 122.4 (In-C5), 125.9 (In-C3a), 126.8 (In-C6), 133.2 (In-C2), 137.9 (In-C7a), 168.5 (NC=O), 192.6 (C=O).

12. **7a**: m.p. 145-150 °C (ether); ir (KBr, cm^{-1}) 3150, 1640, 1610; ^{1}H-nmr ($CDCl_3$, δ) 2.80 (td, *J* =7 and 1 Hz, 2H, 5-H), 3.09 (s, 3N, NCH_3), 3.54 (t, *J* =7 Hz, 2H, 6-H), 6.73 (t, *J* =1.5 Hz, 1H, 4-H), 7.20 (t, *J* =7 Hz, 1H, In-5H), 7.40 (t, *J* =7 Hz, 1H, In-6H), 7.55 (s, 1H, In-3H), 7.70 (d, *J* =7 Hz, 1H, In-7H), 8.70 (br s, 1H, NH); ^{13}C-nmr (δ) 24.3 (C-5), 35.2 (NCH_3), 48.0 (C-6), 112.4 (In-C3), 113.5 (In-C7), 121.8 (In-C4), 124.0 (In-C5), 127.9 (In-C3a), 127.4 (In-C6), 129.8 (=CH), 133.7 (In-C2), 138.8 (In-C7a), 146.0 (=C), 164.8 (NC=O), 186.5 (In-C=O).
13. **6b:** m.p. 114-115 °C (ether); ir (KBr, cm^{-1}) 3500 , 1650, 1610; ^{1}H-nmr ($CDCl_3$, δ) 2.0-2.2 (m, 2H, 5-H) , 2.67 (d, *J* =8 Hz, 1H, 3-Hax), 3.00 (s, 3H, NCH_3), 3.38 (d, *J* =8 Hz, 1H, 3-Heq), 3.30-3.52 (m, 1H, 6-Hax),3.68-3.84 (m, 1H, 6-Heq), 4.07 (s, 3H, NCH_3), 7.16 (t, *J* =8 Hz, 1H, In-5H), 7.32 (s, 1H, In-3H), 7.40 (dd, *J* =8 and 1 Hz , 1H, In-4H), 7.42 (br t, *J* =8 Hz, 1H, In-6H), 7.71 (dt, *J* =8 and 1 Hz, 1H, In-7H); ^{13}C-nmr (δ) 26.8 (C-5), 32.3 (N-CH_3), 34.6 (NCH_3), 42.1 (C-3), 48.4 (C-6), 77.2 (C-4), 110.4 (In-C3), 111.6 (In-C7), 121.0 (In-C4), 123.0 (In-C5), 126.4 (In-C6), 127.3 (In-C3a), 133.2 (In-C2), 140.5 (In-C7a), 168.7 (NC=O), 193.7 (C=O).
14. **7b:** ir ($CHCl_3$, cm^{-1}) 1610, 1630, 1645; ^{1}H-nmr ($CDCl_3$, δ) 2.79 (td, *J* =7 and 1.5 Hz, 2H, 5-H), 3.09 (s, 3H, NCH_3), 3.57 (t, *J* =7 Hz, 2H, 6-H), 4.03 (s, 3H, NCH_3), 6.57 (t, *J* =1.5 Hz, 1H, 3-H), 7.16 (t, *J* =7 Hz, 1H, In-5H), 7.20 (s, 1H, In-3H), 7.40 (m, 2H, In-6H and In-4H), 7.66 (dd, *J* =7 and 1.5 Hz, 1H, In-7H); ^{13}C-nmr (δ) 23.7 (C-5), 31.9 (NCH_3), 34.6 (NCH_3), 47.5 (C6), 110.3 (In-C3), 114.9 (In-C7), 121.0 (In-C4), 123.3 (In-C5), 125.7 (In-C3a), 126.6 (In-C6), 129.7 (C-3), 133.8 (In-C7a), 140.8 (In-C7a), 147.4 (C-4), 164.3 (NC=O), 187.5 (C=O).
15. **8b:** m.p. 154-155 °C (ether-acetone); ir ($CHCl_3$, cm^{-1}): 3400-3550, 1650. ^{1}H-nmr ($CDCl_3$, δ): 1.81 (br d, *J* =10 Hz, 1H, 4-Heq), 2.06 (dt, *J* =9 and 2 Hz, 1H, 4-Hax), 2.31 (s, 3H, 3H, NCH_3), 2.44 (dd, *J* =12 and 3 Hz, 1H, 12-Hax), 2.55 (dd, *J* =12 and 3 Hz, 1H, 12-Heq), 2.70 (m, 2H, 3-H), 4.13 (s, 3H, In-NCH_3), 4.55 (t, *J* =3 Hz, 1H, 1-H), 4.95 (br s, 1H, OH), 7.20 (td, *J* =8 and 1 Hz, 1H, In-10H), 7.42 (dd, *J* =8 and 1Hz, 1H, In-11-H), 7.44 (td, *J* =8 and 1 Hz, 1H, In-9H), 7.69 (dt, *J* =8 and 1 Hz, 1H, In-8H); ^{13}C-nmr 31.6 (NCH_3), 37.6 (C-4), 43.5 (NCH_3), 43.9 (C-12), 47.2 (C-3), 53.8 (C-1), 73.7 (C-5), 110.5 (C-8), 121.1 (C-9), 122.1 (C-10), 123,5 (C-11b), 125.5 (C-11a), 127.2 (C-11), 130.2 (C-6a), 140.7 (C-7a), 194.2 (C=O).

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