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An Unexpected Transformation by Reaction of Congested α-(*o*-Nitrophenyl)ketones with Tris(dimethylamino)methane. A New Heterocyclic System: 6,11b-Methanopyrrolo[2,3-*e*][1]benzazocine

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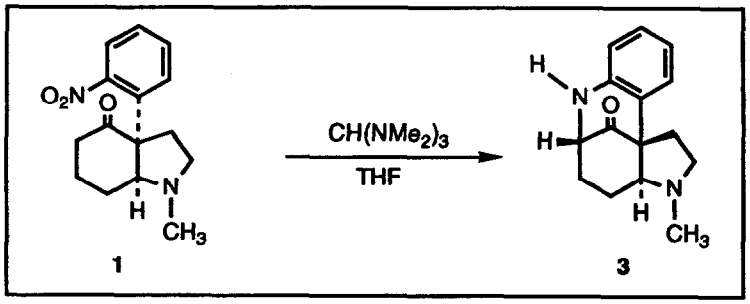
Abstract:: The crowded α-(*o*-nitrophenyl) ketone **1** reacts with tris(dimethylamino)methane to give an unexpected tetrahydroquinoline derivative **3** by means of a reductive process hitherto not described. Related compounds **8** and **9** undergo the same transformation.

In the course of our studies about the synthesis of *Strychnos* indole alkaloids of the curan type,[1,2] α-formylation of the ketone function in octahydroindolone **1** was a point of interest. The formation of α-(dimethylamino)methylene derivatives of ketones using the highly reactive tris(dimethylamino)methane[3] followed by acid hydrolysis to give the corresponding α-formyl ketones is a well established procedure.[4]

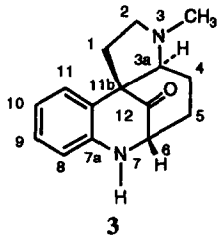
When ketone **1**[5] was treated with $CH(NMe_2)_3$, an unexpected product **3** was isolated in good yield, the expected enamine **2** being a minor product in some runs. Compound **3** showed a molecular formula of $C_{15}H_{18}N_2O$ as determined by HRMS. The presence of a carbonyl group was evident from a strong IR band at 1732 cm^{-1}, and the disappearance of nitro group was also deduced from the IR spectrum. Its tetrahydroquinoline structure was inferred from the ^1H and ^{13}C NMR spectra (see Table 1), which contained characteristic signals for the aromatic region.[6] The ^{13}C NMR spectrum exhibited signals in the aliphatic region for a quaternary carbon, two methines, four methylenes, and a methyl group. 2D NMR experiments (COSY, HMQC, and HMBC) allowed for the total elucidation of the structure of **3**. Correlation of the H-6



1 3 2

Table 1. ^1H and ^{13}C NMR Data of Compound 3 in $CDCl_3$ [a]

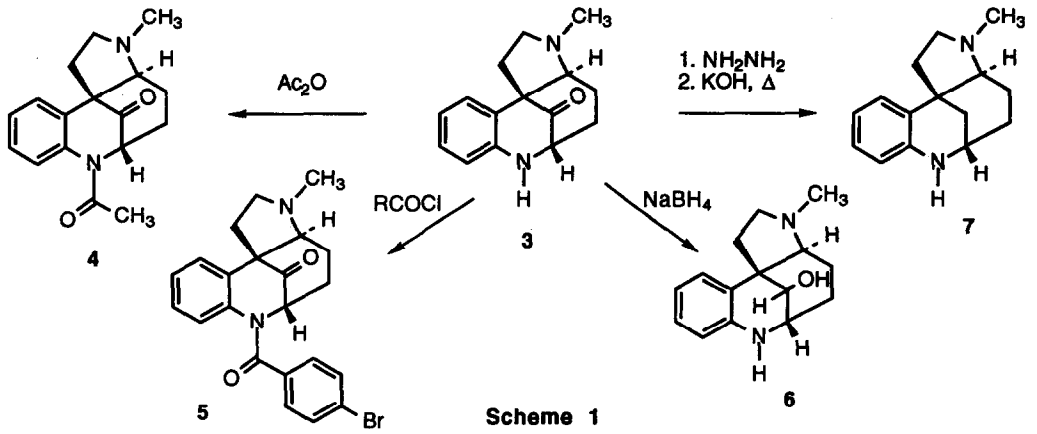
atom n°		^1H[b] (mult, *J* (Hz))	^{13}C[b]	HMBC correlations
C-1	α	2.60 (ddd, 12.5, 9.0, 5.5)	22.5	C12
	β	2.07 (ddd, 12.5, 11.0, 5.0)		C12
C-2	α	2.34 (ddd, 11.0, 9.0, 5.5)	53.5	NCH_3
	β	3.30 (td, 9.0, 5.0)		C3a
C-3a		2.48 (t, 2.0)	80.2	C5, C12
C-4	eq	1.69 (dm, 14.0)	18.2	C6
	ax	1.99 (ddt, 14.5, 13.0, 4.2)		
C-5	eq	1.91 (dm, 14.0)	34.0	C3a
	ax	2.25 (tdd, 13.5, 4.2, 2.5)		
C-6		3.78 (dd, 3.5, 2.5)	58.7	C4, C7a, C8, C12
NH		4.18 (br)		
C-7a			144.7	
C-8		6.53 (dd, 8.2, 1.0)	113.1	C10, C11a
C-9		7.03 (ddd, 7.7, 7.5, 1.0)	128.3	C7a, C11
C-10		6.64 (ddd, 7.7, 7.5, 1.0)	117.3	C8, C11a
C-11		7.07 (dd, 8.2, 1.0)	125.4	C7a, C11b
C-11a			121.0	
C-11b			59.6	
C-12			208.0	
NCH_3		2.18 (s)	39.5	



3

[a] In ppm at 500 MHz for ^1H-NMR and 50 MHz for ^{13}C-NMR. [b] Assignments were aided by HMQC and ^1H-^1H COSY

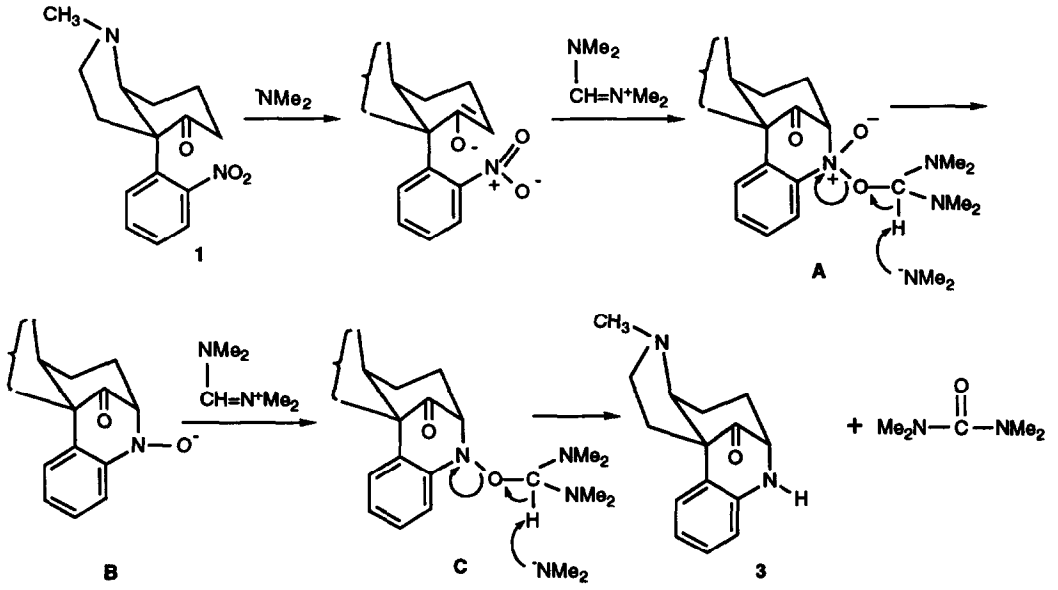
methine proton of the $NHCHCH_2CH_2CHNCH_3$ unit with C-7a of the 1,2-disubstituted aromatic ring, in conjuction with the downfield chemical shift of C-7a (144.7 ppm), linked the aromatic ring with the secondary nitrogen atom of this unit. An HMBC cross peak between the signal for the aromatic proton H-11 and the aliphatic quaternary carbon resonance (C-11b) placed C-11b on the aromatic ring, ortho to H-11 and to the nitrogen (N-7) atom. Linkage of the carbonyl group (C-12) and the new methine carbon (C-6) is supported by the HMBC correlation of H-6 and H-3a with C-12, along with a correlation of H-4 with C-6.



Scheme 1

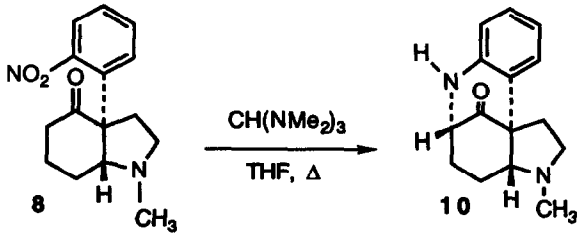
Additionally, compound **3** was transformed by standard procedures (see Scheme 1) into several derivatives such as amides **4** and **5**, alcohol **6**, and diamine **7**, which showed in all cases spectral data (see Table 2) in agreement with the pyrrolobenzazocine framework.[7]

The unprecedented reductive cyclization here described (**1** to **3**) implies that the amidinium cation generated by loss of a dimethylamide anion from $CH(NMe_2)_3$ acts as a reducing instead of a C-formylating agent (tetramethylurea was isolated). Interestingly, the indole synthesis by the Leimgruber-Batcho method[10] implies the formation of enamines of *o*-nitrotoluenes using DMF acetals and related reagents such as tris(dimethylamino)methane,[10b] and, to our knowledge, products of reduction of the nitro group by the amidinium participation have never been reported. This feature suggested to us that the intramolecular nucleophilic attack of the enolate on the nitro group is prior to or simultaneous with the reduction step, generating a hydroxylamine **B** (*via* **A**) in the first instance.[11] A further reduction, through **C** would lead to **3**, as depicted in the following scheme. The crowding upon the enolate due to the α-quaternary center and the spatial proximity of the enolate carbon to the nitro group could be the determining factors of the unexpected course of the reaction of ketone **1** with tris(dimethylamino)methane.



Scheme 2. *Proposed Mechanism for the Transformation of Nitro Ketone 1 into 3*

The scope of this new reaction seems to be quite general as, under the same conditions, nitro ketones **8**[5] and **9**,[2] with the same structural characteristics, provided the bridged tetrahydroquinolines **10** and **11**, respectively.[12]



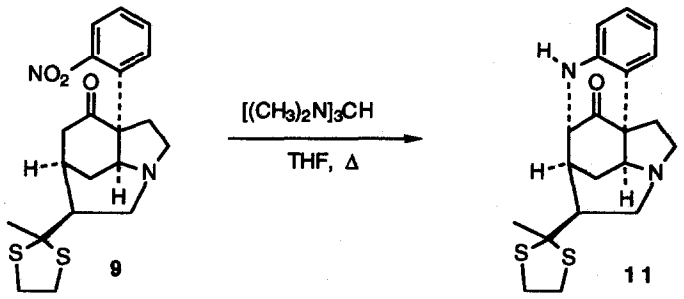


Table 2. ^{13}C NMR Data of Octahydromethanopyrrolo[2,3-*e*][1]benzazocines 3-7 and 10[a]

Comp	C-1	C-2	C-3a	C-4	C-5	C-6	C-7a	C-8	C-9	C-10	C-11	C-11a	C-11b	C-12	NMe
3	22.5	53.5	80.2	18.2	34.0	58.7	144.7	113.1	128.3	117.3	125.4	121.0	59.6	208.0	39.5
4[b]	25.8	54.9	79.6	21.1	27.3	60.0	136.3	123.5	126.5	125.2	127.0	131.8	59.0	203.6	39.4
5[c]	25.7	54.7	79.4	21.2	28.0	61.0	136.9	124.5	126.6	125.3	126.9	130.5	59.5	203.5	39.7
6	31.7	54.4	73.1	18.5	29.5	46.3	145.3	112.7	126.9	115.3	124.2	124.8	42.4	32.1	40.7
7	23.0	55.6	73.4	17.0	27.7	51.3	145.1	112.3	127.4	115.6	124.8	121.8	46.3	71.4	39.0
10	25.7	55.0	78.0	22.4	37.1	58.9	144.1	112.5	129.2	118.1	127.9	122.9	61.3	206.1	40.4

[a] Spectra recorded in $CDCl_3$ at 50MHz (compounds **5**,**6** and **8**), 75 MHz (compound **7**) and 125 MHz (compound **4**) [b] $NCOCH_3$: 169.7; 23.9. [c] $NCOC_6H_5$: 168.8; 134.5; 131.8; 130.2; 125.5

EXPERIMENTAL

General. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50 MHz, respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si, and coupling constants are in hertz. Only noteworthy IR absorptions are listed. TLC was carried out on SiO_2 ($MeOH-CH_2Cl_2$ 7:93) and the spots were located with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2. Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Microanalyses and mass spectra were performed by Centro de Investigación y Desarrollo (C.S.I.C), Barcelona.

(3a*RS*, 6*RS*, 11b*SR*)-3-Methyl-2,3,3a,4,5,6,7,11b-octahydro-1*H*-6,11b-methanopyrrolo[2,3-*e*][1] benzazocin-12-one (3). To a solution of octahydroindole **1**[5] (516 mg, 1.88 mmol) in dry THF (50 ml) was added dropwise under nitrogen tris(dimethylamino)methane (1.63 ml, 1.37 g, 9.4 mmol). After refluxing for 5 h, the solution was evaporated to dryness and the residue was chromatographed (4% MeOH in CH_2Cl_2) affording 364 mg (80%) of tetrahydroquinoline **3**. IR (film) 3396, 1732 cm^{-1}. For ^1H- and ^{13}C-NMR data, see Table 1. Exact mass calcd. for $C_{15}H_{18}N_2O$: 242.1419. Observed: 242.1417.

In some runs **3-Methyl-5-(dimethylaminomethylene)-3a-(*o*-nitrophenyl) octahydroindol-4-one (2)** was also detected (1-7%), eluting with 7-10% MeOH in CH_2Cl_2. IR (KBr) 1644, 1540, 1426, 1355 cm^{-1}; ^1H NMR δ 2.38 (s, NMe), 3.10 (s, NMe_2), 7.48 (s, =CH); ^{13}C-RMN δ 20.8, 22.6, 39.5 (C-6, C-7, C-3), 39.7 (NCH_3), 43.3 (NMe_2), 55.0 (C-2), 59.5 (C-3a), 71.9 (C-7a), 102.0 (C-5), 124.5 (C-3'), 126.8 (C-4'), 130.6 (C-6'), 131.9 (C-5'), 140.6 (C-1'), 149.5 (C-2'); 150.9 (=CH), 197.3 (C-4). Anal Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.68; H, 7.04; N, 12.58.

(3a*RS*, 6*RS*, 11b*SR*)-7-Acetyl-3-methyl-2,3,3a,4,5,6,7,11b-octahydro-1*H*-6,11b-methanopyrrolo[2,3-*e*][1]benzazocin-12-one (4). A solution of **3** (483 mg, 2 mmol) in Ac_2O (4.5 ml) was stirred at room temperature for 4 h. After this time, the reaction mixture was poured into ice-water and stirred for 15 min. The resulting solution was made alkaline with concentrated NH_4OH, and extracted with CH_2Cl_2. The organic layer was dried and evaporated and the residue was chromatographed (3-5% MeOH in CH_2Cl_2) to give acetamide **4** (364 mg, 64%); IR (film) 1736, 1668 cm^{-1}; ^1H NMR δ 1.40 (m, H-4eq), 1.80 (m, H-5eq), 2.05 (m, H-4ax, H-1β), 2.1-2.5 (masked, H-5ax, H-2α), 2.27 (NCH_3), 2.38 ($NCOCH_3$), 2.60 (m, H-3a),2.84 (ddd, *J*=12.5, 9.0, 5.5, H-1α), 3.30 (td, *J*=8.5, 3.0, H-2β), 4.93 (t, *J*=5, H-6), 7.18-7.34 (m, 3H), 7.49 (d, *J*=7.5, H-8).

(3a*RS*, 6*RS*, 11b*SR*)-7-(4-Bromobenzoyl)-3-methyl-2,3,3a,4,5,6,7,11b-octahydro-1*H*-6,11b-methano pyrrolo[2,3-*e*][1]benzazocin-12-one (5). A solution of *p*-bromobenzoyl chloride (492 mg, 2.24 mmol) in methylene chloride (10 ml) was added dropwise under nitrogen to a stirred mixture of amine **4** (190 mg, 0.78 mmol) and triethylamine (86 ml, 0.62 mmol) in methylene chloride (10 ml). After the mixture was stirred at room temperature for 3 days, 5% aqueous NaOH was added, and the resulting mixture was stirred for 5 min. The organic layer was separated and acidified with 1.2 N HCl solution. The organic solution was discarded and the aqueous layer was basified with Na_2CO_3 and extracted with methylene chloride. Evaporation of the dried extracts gave a crude residue which was chromatographed (5% MeOH in CH_2Cl_2) to give amide **6** (147 mg, 45%): IR (KBr) 1734, 1665 cm^{-1}; ^1H NMR δ 1.54 (m, H-4eq), 2.28 (s, NCH_3), 2.35 (m), 2.54 (qd, *J*=9.0, 1.0, H-2α), 2.71 (t, *J*=5.0, H-3a), 2.83 (ddd, *J*=13.0, 9.0, 8.0, H-1α), 3.32 (td, *J*=9.0, 3.2, H-2β), 4.91 (t, *J*=5.0, H-6), 6.90-7.55 (m, 9H). Exact mass calcd for $C_{22}H_{21}BrN_2O_2$: 424.0786. Observed: 424.0781.

(3a*RS*, 6*RS*, 11b*SR*, 12*RS*)-3-Methyl-2,3,3a,4,5,6,7,11b-octahydro-1*H*-6,11b-methanopyrrolo[2,3-*e*][1]benzazocin-12-ol (6). To a solution of ketone **2** (75 mg, 0.31 mmol) in methanol (15 ml) cooled at 0 °C was added sodium borohydride (26 mg, 0.68 mmol). After stirring for 15 min at 0 °C and 5 h at room temperature, water was added and the methanol was evaporated. The resulting mixture was extracted with methylene chloride. The organic layer was dried, evaporated, and the residue chromatographed (6-12% MeOH in CH_2Cl_2) to give 37 mg (51%) of alcohol **6** and 5 mg (7%) of C-12 epimer alcohol. IR (film) 3300, 1606, 1495 cm^{-1}; ^1H-NMR δ 1.41 (dq, H-4), 1.73 (m, 1H), 2.17 (m, 1H), 2.26 (s, NCH_3), 3.43 (m, H-2), 3.68 (dd, H-6), 3.84 (d, H-12), 4.15 (br, NH, OH), 6.50 (d, H-8), 6.61 (t, H-9), 7.02 (t, H-10), 7.17 (d, H-11). Exact mass calcd for $C_{15}H_{20}N_2O$: 244.1576. Observed: 244.1599.

(3a*RS*, 6*RS*, 11b*SR*)-3-Methyl-2,3,3a,4,5,6,7,11b-octahydro-1*H*-6,11b-methanopyrrolo[2,3-*e*][1]benzazocine (7). A solution of ketone **2** (758 mg, 3.13 mmol) and hydrazine monohydrate 99% (2 ml) in ethanol (5 ml) was refluxed for 3 h. Removal of the solvent afforded crude hydrazone as a solid which was used without further purification. A solution of this hydrazone and potassium hydroxide (1.5 g) in triethylene glycol (10 ml) was stirred at 180 °C for 2 h. After cooling, the reaction mixture was poured into brine and extracted with ether. The organic extract was washed with brine, dried, and evaporated to give an oil, which was purified by chromatography (1% diethylamine in ethyl acetate), affording diamine **7** (305 mg, 43%) and alcohol **6** (15 mg, 2%) (see above). Compound **7**: ^1H-NMR (500 MHz, COSY, HMQC) δ 1.42 (m, H-5), 1.48 (m, H-4 and H-12), 1.55 (m, H-1β), 1.58 (m, H-4), 1.76 (tm, H-5), 1.97 (br s, H-3a), 2.14 (dd, *J*=12.0, 2.0, H-12), 2.28 (s, NCH_3), 2.44 (ddd, *J*=12.5, 8, 5, H-2α), 2.48 (td, *J*=12.5, 5, H-1α), 3.39 (ddd, *J*=9, 8, 4.5, H-2β), 3.61 (br s, H-6), 4.17 (br, NH), 6.48 (d, *J*=7.5, H-8), 6.58 (t, *J*=7.5, H-10), 6.98 (t, *J*=7.5, H-9), 7.13 (d, *J*=7,5, H-11). Anal Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.73; H, 8.88; N, 12.20.

(3a*RS*, 6*RS*, 11b*SR*)-3-Methyl-2,3,3a,4,5,6,7,11b-octahydro-1*H*-6,11b-methanopyrrolo[2,3-*e*][1]benzazocin-12-one (10). Following the same procedure as described from ketone **1**, the trans isomer **8**[5] (195 mg, 0.71 mmol) was converted into **10**, which was purified by chromatography (3-10% MeOH in CH_2Cl_2) to afford 46 mg (27%) of pure **10**. IR (film) 1731, 1603, 1495 cm^{-1}. ^1H-NMR δ 1.5 (td, 1H), 2.29 (NCH_3),

2.71 (1H), 3.43 (H-5), 3.70 (br, H-6), 4.20 (br, NH), 6.52 (dd, 8, 1, H-8), 6.75 (td, 8, 1, H-9), 6.98 (dd, 8, 1, H-11), 7.06 (td, 8, 1, H-10).

(3a*RS*,5*RS*,6*RS*,11b*SR*,13*RS*)-13-[2-(2-Methyl-1,3-dithiolanyl)]-2,3,3a,4,5,6,7,11b-octahydro-1*H*-3,5-ethano-6,11b-methanopyrrolo[2,3-*e*][1]benzazocin-12-one (11). In analogy to the reaction of **1**, α-(*o*-nitrophenyl)ketone **9**[2] (50 mg, 0.12 mmol) was converted to tetrahydroquinoline **11** (32 mg, 72%). IR ($CHCl_3$) 3433, 1728 cm^{-1}; ^1H NMR δ 1.81 (s, 3 H), 3.06 (br s, 1 H), 4.15 (t, J = 4, 1 H), 4.37 (br, NH), 6.57 (d, J = 7.5, 1 H), 6.68 (t, J = 7.5, 1 H), 7.05 (m, 2 H); ^{13}C NMR δ 23.5 (C-4), 25.2 C-1), 33.1 (CH_3), 39.2 and 40.4 (SCH_2), 43.2 (C-13), 50.6 (C-14), 51.1 (C-5), 53.6 (C-2), 59.2 (C-6), 61.1 (C-11b) , 68.6 (SCHS), 71.9 (C-3a), 113.8 (C-8), 117.8 (C-10), 122.9 (C-11a), 124.2 (C-11), 128.4 (C-9), 144.6 (C-7a), 213.9 (C-12). Exact mass calcd. for $C_{20}H_{24}N_2OS_2$: 372.1330. Observed: 372.1330.

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