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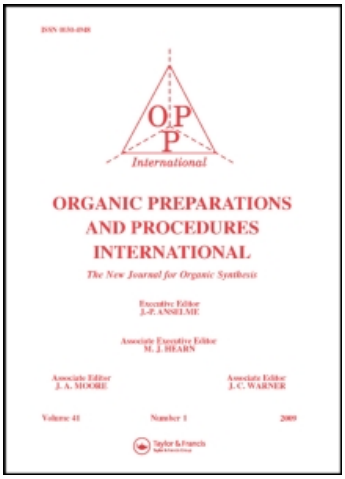

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SYNTHESIS OF PYRAZINO(3,2,1-J,K)CARBAZOLE DERIVATIVES

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SYNTHESIS OF PYRAZINO(3,2,1-J,K)CARBAZOLE DERIVATIVES

Submitted by (04/07/95)

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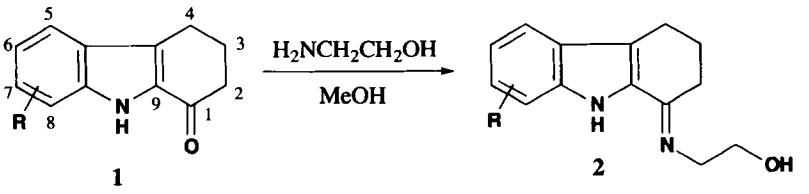
In connection with another project, we required an efficient synthetic route to pharmacologically active pyrazinocarbazoles. The syntheses reported[1] so far suffer from some limitations such as complex procedures, low yield or difficulty assessible starting material. In these procedures, the pyrazino ring was constructed from the 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1**)[2,3] by alkylation followed by cyclization under forcing reaction conditions in low yields. The alkylation of 1-oxo-1,2,3,4-tetrahy-

drocarbazole (**1**) lead to both N- and C-alkylated products since C-2 is an active methylene group.

In our strategy, the nitrogen of pyrazino ring was introduced at the C-1 position by condensation of the carbonyl group of **1** with ethanolamine to afford **2** (~60%). Sodium borohydride reduction of **2** in methanol afforded 1- (2'-hydroxyethylamino)-1,2,3,4-tetrahydrocarbazoles (**3**) which were cyclized to the 3H-pyrazino (3,2,1-j,k)carbazoles (**4**) by treating with ammonium chloride[4] in diphenyl ether. Analytical and spectral data were consistent with the proposed structures **2-4**.



1 **2** **3** **4**

1,2,3 a) R = 8-CH_3 b) R = 7-CH_3 c) R = 6-CH_3 d) R = H

a) R = 10-CH_3 b) R = 8-CH_3 c) R = 9-CH_3 d) R = H

EXPERIMENTAL SECTION

Mps were determined in a Mettler FP_5 apparatus and are uncorrected, IR spectra were recorded in KBr on a Perkin-Elmer 597 IR. NMR spectra were recorded in $CDCl_3$ in a General Electric QE-300 spectrometer. Chemical shifts are reported in ppm downfield from internal TMS. Elemental analyses were performed by Carlo Erba 1106 and Perkin-Elmer model 240 CHN analyzer. Ethanolamine, sodium borohydride, diphenyl ether and ammonium chloride (reagent grade) were obtained from SISCO, India and used as received.

Preparation of 1-(2'-Hydroxyethylimino)-1,2,3,4-tetrahydrocarbazoles (2).- To a solution of the appropriate 1-oxo-1,2,3,4-tetrahydrocarbazole[2] (**1**, 10 mmol) in methanol (40 mL) was added monoethanolamine (4.2 mL, 100 mmol) and the contents were warmed on a water bath for 1 hr. At the end of that time, the precipitated solid was collected and washed with water until the washings were neutral to litmus. The compounds thus obtained were purified by crystallization from methanol (Table).

Preparation of 1- (2'-Hydroxyethylamino)-1,2,3,4-tetrahydrocarbazoles (3).- To a solution of the Schiff base (2, 2 mmol) in methanol (20 mL), cooled to 10° was added in portions sodium borohydride (0.12 g, 3mmol) with stirring. The contents were stirred at room temperature for 2 hrs and poured into ice-cold water. The solids formed were collected, washed well with water and crystallized from methanol (Table).

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TABLE. Mps, Yields, Elemental Analyses and Spectral Data **2-4**

Compd	mp (°C)	Yield (%)	IR (cm^{-1})	^1H NMR	Elemental Analyses (Found) C	H	N
2a	206-207	60	3225 1590	2.03 (2H, q), 2.50 (3H, s), 2.59 (2H, t), 2.51(2H, t), 3.56 (2H, t), 3.74 (2H, t), 6.92-6.96 (2H, m), 7.32 (1H, m), 10.50 (1H, br s)	74.35 (74.26)	7.49 (7.40)	11.56 (11.62)
2b	115-116	55	3250 1590	1.50-1.69 (2H, m), 2.00-2.21 (2H, m), 2.40 (3H, s), 2.45-2.63 (2H, m), 3.59 (2H, t), 4.08 (2H, t), 6.90 (1H, d), 7.14 (1H, s), 7.40 (1H, d), 9.00 (1H, br s)	74.35 (74.29)	7.49 (7.52)	11.56 (11.52)
2c	169-170	59	3270 1580	1.90 (2H, q), 2.41 (2H, t), 2.44 (3H, s), 2.71 (2H, t), 3.59 (2H, t), 3.99 (2H, t), 7 .00-7.20 (3H, m), 8.65 (1H, br s)	74.35 (74.52)	7.49 (7.35)	11.56 (11.50)
2d	148-149	61	3225 1620	1.66 (2H, q), 2.10 (2H, t), 2.55 (2H, t) 3.60 (2H, t), 4.10 (2H, t), 7.07 (1H, t), 7.25 (1H, t), 7.36 (1H, d), 7.52 (1H, d), 8.91 (1H, br s)	73.66 (73.57)	7.06 (7.10)	12.27 (12.12)
3a	138-139	92	3275 3250	1.90-1.94 (2H, m), 2.43 (2H, t), 2.46 (3H, s), 2.90 (2H, t), 3.70-3.73 (3H, m), 3.99 (2H, t), 6.96 (1H, t), 7.0l (1H, d), 7.33 (1H, d), 8.80 (1H, s)	73.44 (73.58)	8, 25 (8.14)	11.46 (11.36)
3b	123-124	87	3250 3200	1.90-1.93 (2H, m), 2.33 (2H, t), 2.44 (3H, s), 2 .84 (2H, t), 3.50-3.69 (3H, m), 3.94 (2H, t), 6.90 (1H, d), 7.08 (1H, s), 7.35 (1H, d), 8.39 (1H, br s)	73.44 (73.62)	8.25 (8.18)	11.46 (11.52)
3c	151-152	90	3260 3200	2.20-2.30 (6H, m), 2.43 (3H, s), 3.50-3.70 (3H, m), 3.97 (2H, t), 6.96 (1H, d), 7. 19 (1H, d), 7.26 (1H, s), 8.53 (1H, s)	73.44 (73.36)	8.25 (8.12)	11.46 (11.33)

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TABLE. Continued

Compd	mp (°C)	Yield (%)	IR (cm^{-1})	^1H NMR	Elemental Analyses (Found) C	H	N
3d	138-139	91	3250 3175	1.85-2.00 (4H, m), 2.50-2.85 (2H, m), 3.60-3.74 (3H, m), 4.00 (2H, t), 7.09 (1H, t), 7.16 (1H, t), 7.33 (1H, d), 7.50 (1H, d), 8.70 (1H, br s)	73.00 (73.14)	7.87 (7.90)	12.16 (12.04)
4a	192-193	44	3375	2.58 (3H, s), 7.00-7.19 (3H, m), 7.20-7.45 (3H, m), 7.94 (1H, d), 7.98 (1H, s), 8.07 (1H, d)	81.79 (81.68)	5.49 (5.42)	12.72 (12.74)
4b	263-264	41	3400	2.55 (3H, s), 7.19 (1H, s), 7.22-7.37 (6H, m), 7.99 (1H, br s), 8.09 (1H, d)	81.79 (81.72)	5.49 (5.44)	12.72 (12.62)
4c	198-199	50	3400	2.53 (3H, s), 7.00-7.29 (6H, m), 7.88 (1H, s), 7.95 (1H, br s), 8.04 (1H, d)	81.79 (81.66)	5.49 (5.50)	12.72 (12.69)
4d	243-244	45	3425	7.06-7.24 (4H, m), 7.30-7.42 (3H, m), 7.98-8.10 (3H, m)	81.53 (81.38)	4.89 (4.78)	13.58 (13.40)

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Preparation of Pyrazino (3,2,1-j,k)carbazole (4).- To a mixture of hydroxyethylamino-1,2,3,4-tetrahydrocarbazole (3, 5mmol) and ammonium chloride (0.11g, 2mmol), diphenyl ether (15 mL) was added and the solution boiled under reflux for 2 hrs. Excess diphenyl ether was then removed under reduced pressure, the residue was extracted with ethyl acetate (50mL), dried and the solvent distilled. The residual solid was purified by passing it through a column of silica gel (Acme's 60-120 mesh, 30 cm column) and eluting with petroleum ether-ethyl acetate (2:1). The products were crystallized from petroleum ether (Table).

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AN EFFICIENT SYNTHESIS OF (*S*)-(+)-2-TRIDECANOL ACETATE, AN AGGREGATION PHEROMONE OF *DROSOPHILA MULLERI*

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Submitted by ((04/14/95)

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(*S*)-(+)-2-Tridecanol acetate (**4**), an aggregation pheromone of *Drosophila mulleri*,[1] has been the subject of several synthetic investigations in the past few years. Besides four multistep-approaches,[1-4] an enzymatic resolution[5] of *rac*-**4** giving the pheromone in poor enantiomeric purity has been described. This report describes a novel efficient preparation of **4** starting from readily available compounds.

1,3-Dithiane (**1**) was deprotonated with *n*-butyllithium and then treated with (*S*)-propylene oxide.[6] The resulting alkoxide was further deprotonated at C-2 of the dithiane ring with *n*-butyllithium to give a dianion[7] which yielded **2** on subsequent C-alkylation with nonyl iodide and aqueous workup. The overall yield of this one-pot reaction was 80%. The alcohol **2** then was converted to the acetate **3** with acetic anhydride. Reductive desulfurization of **3** to give the title pheromone **4** was most conveniently performed with tributyltin hydride/AIBN.[8] This reagent was superior to the commonly used *Raney* nickel. The enantiomeric excess (ee) of **4** was determined by GLC after ester hydrolysis (2 M KOH) and derivatization of the resulting (*S*)-2-tridecanol with (*R*)-phenylethyl isocyanate and found to be >98%. This novel synthesis of pheromone **4** in three steps (overall yield of 64%) should be generally applicable to the synthesis of (*S*)- as well as (*R*)-2-alkanols starting from enantiomeric pure propylene oxides.

Work is in progress to apply this methodology to the synthesis of other chiral natural products containing a methylcarbinol moiety.