AN ENTRY TO 5,6,7,8-TETRAHYDRO-4-CINNOLONES FROM 4,5,6,7-TETRAHYDROBENZO-3(2H)-FURANONE DERIVATIVES

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Abstract---- Synthesis of 3-methyl-5,6,7,8-tetrahydro-4-cinnolone and its N-1 and N-2 methylated derivatives, starting from 2-acetoxy- or -2-methoxy-2-methyl-4,5,6,7-tetrahydrobenzo-3(2H)-furanone is described.

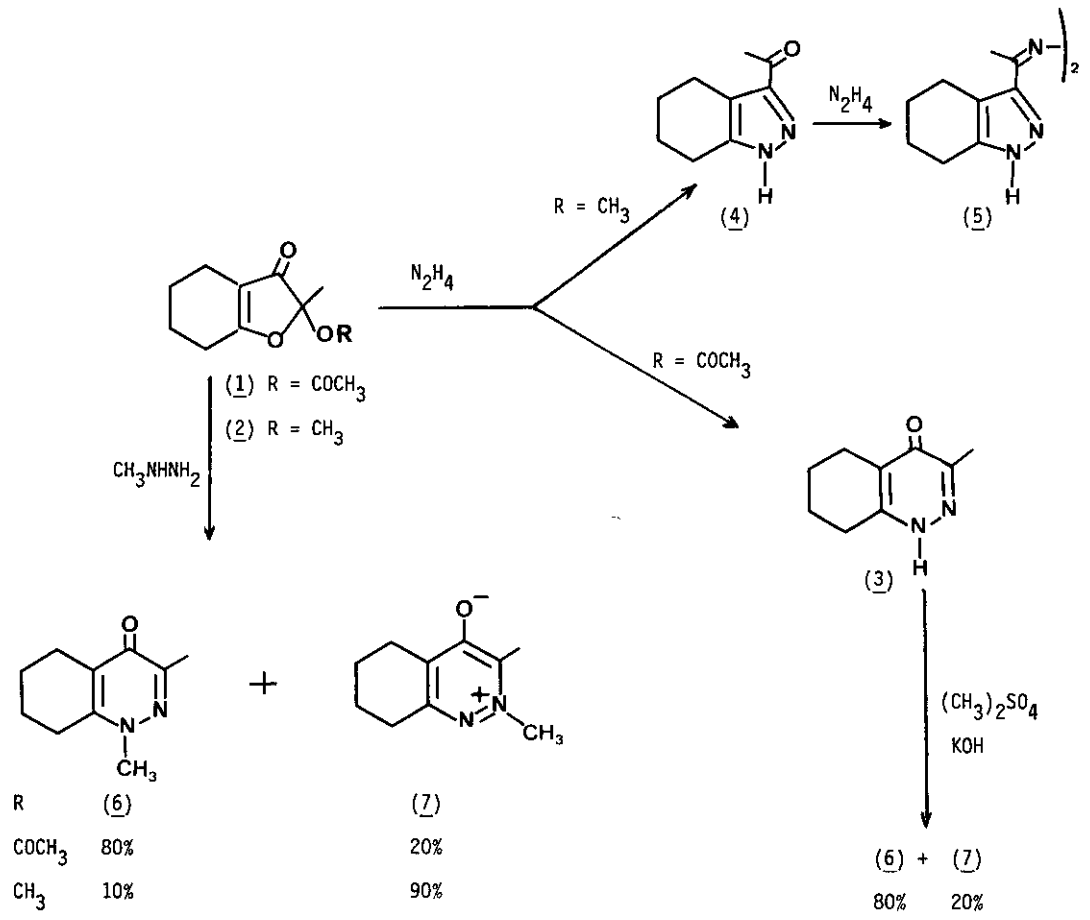
Earlier research from this laboratory revealed several competing nucleophilic ring rearrangements of 2-acetoxy- or -2-methoxy-2,5-substituted 3(2H)-furanones upon reaction with hydrazines[1,2]. The reaction was found to be dependent on the methoxy or acetoxy substituents of these furanones, to afford either a five-membered ring (pyrazole) or a six-membered ring (4-pyridazinone). We have therefore investigated the behavior of tetrahydrobenzo-3(2H)-furanone derivatives, to provide an entry to the 5,6,7,8-tetrahydro-4-cinnolone structure.

When (1) (2-acetoxy) was subjected to treatment with hydrazine hydrate, it was converted to 5,6,7,8-tetrahydro-3-methyl-4-cinnolone (3) in good yield. Treatment of (2) (2-methoxy) yielded only the azine (5), under a variety of conditions. The pyrazole (4) could not be isolated. Compound (5) was also obtained from (4) independently synthetized by the Jones oxidation of known 3-(1-hydroxyethyl)-4,5,6,7-tetrahydroindazole[3].

Compound (3) was methylated, using the procedure described by Ames[4] for the 4-cinnolone derivatives. A mixture of isomers at position N-1 (6 ; 80%) and N-2 (7 ; 20%) was obtained, and (6) and (7) were readily separated using column chromatography. Confirmatory evidence for the structure (6) was provided by its dehydrogenation to known 1,3-dimethyl-4-cinnolone[4].

Treatment of (1) or (2) with methylhydrazine gave an isomeric mixture of (6) and (7). A ring rearrangement into a five-membered ring (tetrahydroindazole) was not observed. The N-1 or the N-2 methyl (betaïne) derivative could be obtained as the major product, simply by varying the 2-acetoxy- or the 2-methoxy substituent (scheme). The N-1 derivative was also furnished, as the main product by alkylation of the N-unsubstituted tetrahydro-4-cinnolone (3). Consequently,

the tetrahydrobenzo-3(2*H*)-furanone derivatives appear convenient starting materials for the synthesis of the 5,6,7,8-tetrahydro-4-cinnolone derivatives, hitherto unknown.



R	(6)	(7)
$COCH_3$	80%	20%
CH_3	10%	90%

EXPERIMENTAL SECTION

All melting points were determined on a Kofler block and are uncorrected. Infrared and ultraviolet spectra were obtained with Beckman Model Acculab 2 and DB spectrometers. NMR spectra were recorded on a Brucker WP 80 spectrometer, with respect to TMS. Elemental analyses were performed by Microanalytical laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

2-Acetoxy-2-methyl-4,5,6,7-tetrahydrobenzo-3(2*H*)-furanone (1)

To a solution of 2-methyl-4,5,6,7-tetrahydrobenzo-3(2*H*)-furanone[3] (7.6 g, 0.05 mol) in dry benzene (50 ml) was added lead (IV) acetate (22.16 g, 0.05 mol) with stirring. The mixture was refluxed for 3h. The resulting slurry was filtered to remove lead (II) acetate, benzene was removed

and the residual product was distilled under reduced pressure ; yield 83%; bp 60°C/0.05 mm; n_D^{26}1.4932; IR ($CHCl_3$) 1720 cm^{-1} ; UV (ethanol): λ nm (ε) 272 (9200); ^{1}H-NMR ($CDCl_3$); δ 1.55 (s,3H); 1.60-1.90 (m,4H); 2.90 (s,3H); 2.10-2.50 (m,4H). Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found; C, 62.86; H, 6.83.

2-Methoxy-2-methyl-4,5,6,7-tetrahydrobenzo-3(2*H*)-furanone (2)

A solution of (1) (2.1 g, 0.01 mol) in 1% methanolic hydrogen chloride (15 ml) was refluxed for 20 min. After elimination of the solvent under reduced pressure, ether (50 ml) was added. The ether extract was washed with water and dried. After elimination of ether, the residue was distilled under reduced pressure; yield 71%; bp 60°C/0.1 mm; n_D^{26}1.4984; IR ($CHCl_3$) 1720 cm^{-1}; UV (ethanol): λ nm (ε) 280 (10300); ^{1}H-NMR (DMSO-d_6): δ 1.44 (s,3H); 1.55-2.00 (m,4H); 2.00-2.55 (m,4H); 3.19 (s,3H). Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.10; H, 7.68.

3-Acetyl-4,5,6,7-tetrahydroindazole azine (5)

To a solution of (2) (0.91 g, 0.005 mol) in ethanol (20 ml) was added hydrazine hydrate (0.5 ml, 0.01 mol). The mixture was allowed to stand overnight. Concentration *in vacuo* afforded the azine as yellow crystals. Yield 72%, mp > 300°C dec; UV (ethanol): λ nm (ε) 256 (10860), 300 (18500); ^{1}H-NMR (DMSO-d_6): δ 1.50-1.95 (m,8H); 2.30 (s,6H); 2.50-2.85 (m,8H); 12.50 (s,2H, broad, exchangeable with D_2O). Anal. Calcd. for $C_{18}H_{24}N_6$: C, 66.64; H, 7.46; N, 25.91. Found: C, 66.02; H, 7.46; N, 25.70.

Action of methylhydrazine upon (1) and (2)

To a solution of (1) or (2) (0.01 mol) in absolute ethanol (20 ml), methylhydrazine (0.56 g, 0.012 mol) was added at 0°C. The mixture was then allowed to stand at room temperature overnight. The crude reaction mixture was analyzed by NMR and pure compounds, identical with those obtained by the methylation of (3), were obtained by chromatography on column, as described above.

1,3-Dimethyl-5,6,7,8-tetrahydro-4-cinnolone (6)

Yield 67% from (1); 6% from (2); mp 143°C (ethyl acetate); IR ($CHCl_3$) 1590 cm^{-1}; UV (ethanol): λ nm (ε): 280 (10500); ^{1}H-NMR ($CDCl_3$): δ 1.60-2.00 (m,4H); 2.29 (s,3H); 2.40-2.80 (m,4H); 3.80 (s,3H). Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.45; H, 8.00; N, 15.72.

Anhydro-4-hydroxy-2,3-dimethyl-5,6,7,8-tetrahydrocinnolinium hydroxide (7)

Yield 15% from (1); 58% from (2); mp 167°C (ethyl acetate); IR ($CHCl_3$) 1580 cm^{-1}; UV (ethanol): λ nm (ε): 265 (3100); 313 (6200); ^{1}H-NMR ($CDCl_3$): δ 1.60-2.00 (m,4H); 2.55 (s,3H); 2.40-2.80 (m,4H); 4.09 (s,3H). Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 66.98; H, 7.96; N, 15.47.

3-Methyl-5,6,7,8-tetrahydro-4-cinnolone (3)

To a solution of (1) (4.2 g, 0.02 mol) in ethanol (20 ml) was added hydrazine hydrate (1.25 ml, 0.025 mol). The mixture was allowed to stand overnight and the solvent was removed under reduced pressure. The precipitate formed after trituration of the residue with ether (10 ml) was collected and recrystallized from ethyl acetate. Yield 85%; mp 220°C; IR ($CHCl_3$) 3420, 3000-2860, 1590 cm^{-1}; UV (ethanol): λ nm (ε) 278 (12200); ^{1}H-NMR (DMSO-d_6): δ 1.55-1.85 (m,4H); 2.12 (s, 3H); 2.55-2.70 (m,4H); 12.60 (s, broad, 1H, exchangeable with D_2O). Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 66.07; H, 7.41; N, 16.87.

Methylation of (3)

Methylation of (3) with dimethyl sulfate and potassium hydroxide, following the same procedure described previously for 3-methyl-4-cinnolone[4], afforded an isomeric mixture in 61% yield, which was chromatographed on silicagel; column elution with ethyl acetate gave the N-1 methyl compound (6) (yield 47%). Further elution with ethyl acetate/methanol 4:1 yielded the betaïne (7) (yield 12%).

1,3-Dimethyl-4-cinnolone

A mixture of (6) (0.89 g, 0.005 mol) and 10% Pd-C catalyst (0.2 g) in decalin (20 ml) was heated under nitrogen at 175°C for 30 h. After filtration and distillation of the major part of the solvent, the product crystallized. Recrystallization from ethyl acetate gave the pure compound, yield 75%; mp 138°C; lit.[4] mp 137-139°C. Its spectral data were identical with the literature data[4].

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