Synthesis of Pyrido[3,4-*b*]pyrano[3,4-*b*]indoles

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The synthesis of some pyrido[3,4-*b*]pyrano[3,4-*b*]indoles (**3**) from 3-hydroxy-4-(3-indolyl)piperidines (**6**) is reported.

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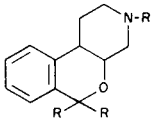
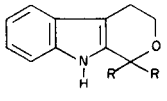
Benzopyranopyridines with different anellations of the three rings have been described; a more recent example is the [2]benzopyrano[3,4-*c*]pyridine (**1**) (1). Derivatives with suitable substitution are claimed to be active in cardiovascular or central nervous system tests. On the other hand, pyranoindoles like **2** are pharmacologically interesting, in particular as potential anti-inflammatory (2) or antidepressive (3) agents. Consequently, we considered it worthwhile to develop the pyrido[3,4-*b*]pyrano[3,4-*b*]indole system **3**.



1



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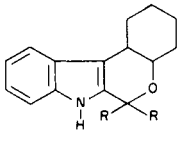


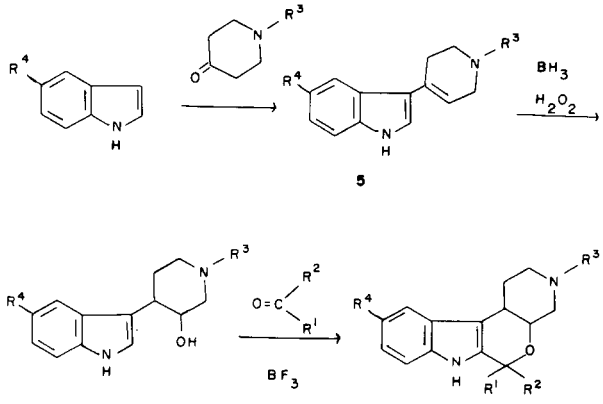
4

The sequence leading smoothly to the benzopyranoindoles (**4**) (4) could not be employed here, since hydroxypiperidones are not easily accessible. We were able, however, to apply the cycloalkenylation reaction described earlier (5) to 2,3-unsubstituted indoles and 4-piperidones.

Some of the resulting 4-(3-indolyl)tetrahydropyridines (**5**) are also accessible by different routes (6,7).

Hydroboration-oxidation (8a) of **5** yielded the 3-hydroxy-4-(3-indolyl)piperidines (**6**). Condensation with aldehydes or ketones, under the same conditions as used for the formation of **4**, gave the novel ring system **3**. The reaction could be carried out with **6a, b** or **c**, but we found that the yields were better when the nitrogen was not basic. We preferred therefore the detour *via* the tosyl derivatives. After removal of the protecting group with sodium in butanol, the alkyl or acyl derivatives **3e** to **k** could be obtained in the usual manner.

As expected, the hydroxy group is introduced by the hydroboration-oxidation reaction in *trans* position (8b).



5

6

3

5, 6

a	$R^3 = CH_3$,	$R^4 = H$
b	R^3 = Tosyl,	$R^4 = H$
c	$R^3 = CH_3$,	$R^4 = OCH_3$

3	R^1	R^2	R^3	R^4
a	CH_3	CH_3	CH_3	H
b	CH_3	CH_3	Tosyl	H
c	CH_3	CH_3	H	H
d	CH_3	CH_3	CH_3	OCH_3
e	CH_3	CH_3	CH_3CO	H
f	CH_3	CH_3	$COCH_2N(C_2H_5)_2$	H
g	CH_3	CH_3	$(CH_2)_2N(C_2H_5)_2$	H
h	CH_3	CH_3	$CH_2-C_6H_5$	H
i	CH_3	CH_3	$(CH_2)_2-C_6H_5$	H
j	CH_3	CH_3	$(CH_2)_3-C_6H_5$	H
k	CH_3	CH_3	$(CH_2)_2OC_6H_5$	H
l	H	C_6H_5	CH_3	H

The pmr spectrum shows the characteristic triplet of doublets for the neighboring proton.

Only compounds **3a, 3i, 3j** and **3l** lowered the blood pressure of hypertensive rats in higher doses.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were performed by Dr. A. B. Gigly, Toronto. The pmr spectra were taken on a Varian T60 instrument, except for a 250 MHz spectrum of **3g** taken on a Bruker WM-250 instrument.

1-Methyl-3-hydroxy-4-(3-indolyl)piperidine (**6a**).

A suspension of 1-methyl-4-(3-indolyl)-1,2,5,6-tetrahydropyridine (**5a**)

(5) (2.1 g, 0.01 mole) in 30 ml of tetrahydrofuran was stirred under dry nitrogen at 20° to 25° bath temperature. Borane-methyl sulfide complex (1.7 g, 22 mmoles) was added slowly, subsequently the mixture was heated to reflux for 2 hours. After cooling to 0°, 2*N* sodium hydroxide (4,4 ml) was added, followed by hydrogen peroxide (30%, 4.4 ml) during 5 to 10 minutes. The mixture was stirred one night at room temperature and heated to reflux for 5 hours. It was poured on ice/water/2*N* hydrochloric acid; the resulting mixture was washed with ethyl acetate, and the aqueous layer made alkaline with sodium hydroxide. The white precipitate was collected and recrystallized from ethanol to give 1.3 g (56%), mp 224-226°; nmr (DMSO-d_6): δ 10.7 (s, 1H) 7.7-6.8 (m, 5H), 4.4 (d, J = 3 Hz, 1H exchangeable), 3.8 (t, d, J = 3 and 9 Hz, 1H), 3.4-1.5 (m, 7H), 2.2 (s, 3H).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.09; H, 7.83; N, 12.21.

1-Tosyl-4-(3-indolyl)-1,2,5,6-tetrahydropyridine (**5b**).

A mixture of indole (6 g, 51 mmoles), 1-tosyl-4-piperidone (25 g, 0.1 mole), ammonium acetate (23 g, 0.3 moles), acetic acid (100 ml) and tetrahydrofuran (100 ml) was stirred at room temperature for 3 days. The white precipitate was collected and recrystallized from glacial acetic acid, yield 9.0 g (55%), mp 224°.

Anal. Calcd. for $C_{20}H_{20}N_2O_2S$: C, 68.18; H, 5.71; N, 7.94. Found: C, 67.88; H, 6.06; N, 7.81.

1-Tosyl-3-hydroxy-4-(3-indolyl)piperidine (**6b**).

The compound was obtained analogously to **6a** by hydroboration-oxidation from **5b** in 75% yield, mp 169-171°; nmr (DMSO-d_6): δ 10.7 (s, 1H), 7.8-6.7 (m, 9H), 4.8 (d, J = 5 Hz, 1H exchangeable) 4.0-3.5 (m, 3H), 2.8-1.6 (m, 5H), 2.4 (s, 3H).

Anal. Calcd. for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.98; N, 7.56. Found: C, 64.86; H, 5.97; N, 7.43.

3,6,6-Trimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]pyrano[3,4-*b*]indole (**3a**).

A mixture of **6a** (2.3 g, 10 mmoles), acetone (1.3 g, 22 mmoles), boron trifluoride ether complex (2.8 g, 20 mmoles) and tetrahydrofuran (25 ml) was heated to reflux for 48 hours. It was poured on ice/ammonia and extracted with ethyl acetate. After washing drying and evaporation a residue remained, which crystallized from petroleum ether, yield 1.6 g (59%), mp 206-208°; nmr (deuteriochloroform): δ 7.9 (s, 1H), 7.7-6.9 (m, 4H), 3.7 (t, J = 9 Hz, of d, J = 4 Hz, 1H), 3.4-1.7 (m, 7H), 2.4 (s, 3H), 1.55 (s, 3H), 1.50 (s, 3H).

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.34; H, 8.26; N, 10.32.

3-Tosyl-6,6-dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]pyrano-[3,4-*b*]indole (**3b**).

A mixture of **6b** (24.0 g, 65 mmoles), acetone (12.0 g, 0.2 moles), boron trifluoride ether complex (18.4 g, 0.13 moles) and dioxane (200 ml) was heated to reflux for 3 hours. The mixture was poured on crushed ice and ammonia, and stirred for one hour; then the white precipitate was filtered and washed with water, yield 23.6 g (89%). The product was sufficiently pure for saponification to **3c**. A sample was recrystallized from acetic acid, mp 275-280°.

Anal. Calcd. for $C_{23}H_{26}N_2O_3S$: C, 67.28; H, 6.38; N, 6.82. Found: C, 66.79; H, 6.19; N, 7.01.

6,6-Dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]pyrano[3,4-*b*]indole (**3c**).

Sodium (25.3 g, 1.1 moles) was added carefully under nitrogen to a suspension of **3b** (15.1 g, 0.037 mole) in 1-butanol (400 ml). The mixture was heated to reflux for 2 hours, cooled and poured into water. The product was extracted with ethyl acetate, and crystallized after addition of ether to the concentrated solution, yield 9.1 g (96%), mp 290-294°; nmr (DMSO-d_6): δ 10.8 (s, 1H), 7.7-6.7 (m, 4H), 3.7-2.1 (m, 9H), 1.51 (s, 3H), 1.48 (s, 3H).

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.51; H, 8.46; N, 10.64.

10-Methoxy-3,6,6-trimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]-pyrano[3,4-*b*]indole (**3d**).

Hydroboration-oxidation of 4-(5-methoxy-3-indolyl)-1-methyl-1,2,5,6-tetrahydropyridine (**5c**) (5), analog to the preparation of **6a**, gave 3-hydroxy-4-(5-methoxy-3-indolyl)-1-methylpiperidine (**6c**) in 73% yield, mp 173-176°.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$; C, 69.24; H, 7.74; N, 10.76. Found: C, 69.36; H, 7.75; N, 10.71.

Condensation with acetone, as described for **3a**, gave **3d** in 31% yield, mp 145-147° from ethanol; the nmr is identical to **3a** except for the CH_3O signal δ = 3.8 and for the aromatic region in accordance with the structure.

Anal. Calcd. for $C_{18}H_{24}N_2O_2$; C, 71.97; H, 8.05; N, 9.33. Found: C, 71.96; H, 7.85; N, 9.18.

3-Acetyl-6,6-dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]pyrano-[3,4-*b*]indole (**3e**).

A solution of **3c** (2 g, 7.5 mmoles) and acetyl chloride (0.6 g, 7.5 mmoles) in dry pyridine (35 ml) was kept at room temperature for 16 hours. It was poured on ice/hydrochloric acid and the product was extracted with ethyl acetate and isolated in the usual way, yield 1.8 g (80%), mp 283°.

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.51; H, 7.30; N, 9.11.

3-Diethylaminoacetyl)-6,6-dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido-[3,4-*b*]pyrano[3,4-*b*]indole (**3f**).

A mixture of **3c** (13 g, 0.05 mole) and chloroacetyl chloride (100 ml) was heated to reflux for 1 hour and then decomposed with ice/ammonia. The white precipitate (14.9 g, 89% yield) was filtered, washed with water and used as such for the next step, mp 224-229°. This chloroacetamide (8.3 g, 25 mmoles), diethylamine (4.6 g, 62 mmoles), sodium bicarbonate (2.6 g, 31 mmoles) and ethanol (200 ml) were heated to reflux under stirring for 4 hours. The solvent was evaporated, water was added, and the precipitate was collected and crystallized from ethanol, to yield 8.2 g (88%), mp 209-212°; nmr (pyridine-d_5): δ 11.7 (s, 1H), 8.0-7.0 (m, 4H), 5.4-2.3 (m, 14H), 1.7 (s, 6H), 1.0 (t, J = 7 Hz, 6H).

Anal. Calcd. for $C_{22}H_{31}N_3O_2$: C, 71.51; H, 8.46; N, 11.37. Found: C, 71.46; H, 8.51; N, 11.11.

3-(Diethylaminoethyl)-6,6-dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]pyrano[3,4-*b*]indole (**3g**).

The amide **3f** (3.7 g, 10 mmoles) was dissolved in 40 ml of tetrahydrofuran. Lithium aluminum hydride (0.76 g, 20 mmoles) was carefully added under stirring in an atmosphere of nitrogen; the reaction was completed by refluxing for 1 hour. After the usual work-up (dilution with ether, dropwise addition of water, filtration, evaporation) the residue was crystallized as dihydrochloride in 51% yield (2.2 g), mp 205-218°; 250 MHz nmr (DMSO-d_6): δ 11.7 (s, 1H, exchangeable), 11.2 (s, 1H, exchangeable), 10.9 (s, 1H, exchangeable), 7.6 (d, J = 8 Hz, 1H), 7.3 (d, J = 8 Hz, 1H), 7.0 (m, 2H), 4.0 (m, 1H), 3.7-2.9 (m, 14H), 1.8 (m, 1H), 1.53 (s, 3H), 1.52 (s, 3H), 1.3 (t, J = 7 Hz, 6H).

Anal. Calcd. for $C_{22}H_{33}N_3O \cdot 2HCl$: C, 61.67; H, 8,23; N, 9.80; Cl, 16.55. Found: C, 61.90; H, 8.03; N, 9.35; Cl, 16.18.

3-Methyl-6-phenyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]pyrano-[3,4-*b*]indole (**3l**).

A mixture of **6a** (2.3 g, 10 mmoles), benzaldehyde (2.4 g, 22 mmoles), boron trifluoride ether complex (1.6 g, 11 mmoles) and dioxane (30 ml) was heated to reflux for five days. The reaction was worked-up as before and the product purified and isolated by silica column chromatography with chloroform/methanol (97/3); yield 0.4 g (13%), mp 89-92°; nmr (deuteriochloroform): δ 8.0-7.0 (m, 10H), 5.9 (d, J = 3 Hz, 1H), 3.8 (t, J = 9 Hz, of d, J = 4 Hz, 1H), 3.4-1.0 (m, 7H), 2.4 (s, 3H).

Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 78.97; H, 7.03; N, 8.78.

General Procedure for the Preparation of 3-Alkyl-6,6-dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]pyrano[3,4-*b*]indoles, (**3h,i,j,k**).

A mixture of **3c** (2.6 g, 10 mmoles), sodium bicarbonate (0.9 g, 11 mmoles), the appropriate halide (11 mmoles), dimethylformamide (20 ml) and tetrahydrofuran (20 ml) was heated to reflux until tlc showed the reaction to be completed. After the usual work-up, the compounds were crystallized as hydrochlorides.

3-Benzyl-6,6-dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]pyrano-[3,4-*b*]indole Hydrochloride (**3h**).

This compound was obtained in a yield of 84%, mp 312-314°.

Anal. Calcd. for $C_{23}H_{26}N_2O \cdot HCl$: C, 72.13; H, 7.10; N, 7.31. Found: C, 72.33; H, 7.30; N, 6.95.

3-Phenethyl-6,6-dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido[3,4-*b*]-pyrano[3,4-*b*]indole Hydrochloride (**3i**).

This compound was obtained in a yield of 52%, mp 306-308°.

Anal. Calcd. for $C_{24}H_{28}N_2O \cdot HCl$: C, 72.61; H, 7.36; N, 7.05. Found: C, 72.53; H, 7.34; N, 6.71.

3-(3-Phenylpropyl)-6,6-dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrano-[3,4-*b*[pyrano[3,4-*b*]indole Hydrochloride (**3j**).

This compound was obtained in a yield of 86%, mp 288-291°.

Anal. Calcd. for $C_{25}H_{30}N_2O \cdot HCl$: C, 73.06; H, 7.60; N, 6.81. Found; C, 73.53; H, 7.74; N, 6.68.

3-(2-Phenoxyethyl)-6,6-dimethyl-1,2,3,4,4a,6,7,11c-octahydropyrido-[3,4-*b*]pyrano[3,4-*b*]indole Hydrochloride (**3k**).

This compound was obtained in a yield of 92%, mp 300-302°.

Anal. Calcd. for $C_{24}H_{28}N_2O_2 \cdot HCl$: C, 69.80; H, 7.07; N, 6.78. Found: C, 69.72; H, 7.30; N, 6.80.

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