Substituted 1,2,3,4-tetrahydro-β-carbolines

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A series of 6-substituted 3- or 4-methyl- and 4,4-dimethyl-1,2,3,4-tetrahydro-β-carbolines was prepared by reduction of the appropriate 1,2,3,4-tetrahydro-1-oxo-β-carbolines. Lithium aluminium hydride was employed for all but the 3-methyl compounds, which required either sodium–butanol or diborane to effect the reduction. A simple preparation is also described for 5-halo-β-methyl- and 5-halo-β,β-dimethyl-tryptamines.

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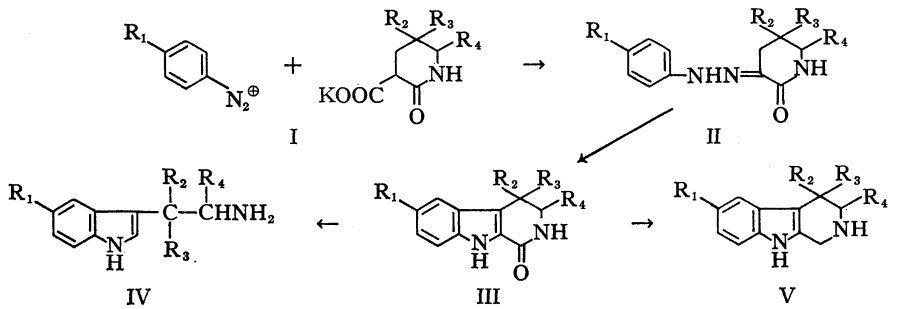
The preparation of 1,2,3,4-tetrahydro-β-carbolines by the reduction of 1,2,3,4-tetrahydro-1-oxo-β-carbolines with sodium and 1-butanol has been reported by Ashley and Robinson (1) and Abramovitch and Shapiro (2). The latter authors also found that lithium aluminium hydride in ether failed to reduce 6-methoxy-1,2,3,4-tetrahydro-1-oxo-β-carboline. By similar means we have prepared a series of 6-substituted 1,2,3,4-tetrahydro-β-carbolines, most of which contain methyl substituents on the 3 or 4 carbon atom.

Lithium aluminium hydride in hot tetrahydrofuran smoothly effected the reduction of all but the 3-methyl-1-oxo-tetrahydro-β-carbolines. These 3-methyl substituted oxocarbolines could be reduced by sodium – 1-butanol. However, when halogen was present at the 6 position, it was totally removed by the reduction in the case of bromine and partially if it were chlorine or fluorine. The use of diborane in tetrahydrofuran was found to be ideal for these latter reductions, and doubtless would have served equally well for all the oxocarbolines.

Cyclization of the *p*-substituted phenylhydrazones (II) in hot hydrogen chloride – acetic acid mixtures gave the oxocarbolines (III). The hydrazones were obtained by the Japp–Klingemann reaction of the appropriate diazotized anilines with the potassium salts of 5-methyl- (3) and 5,5-dimethyl-2-piperidone-3-carboxylic acids (4).

Prolonged acid hydrolysis of the 6-halo oxocarbolines (III*a*–III*f*) yielded the 5-halo-β-methyl- and 5-halo-β,β-dimethyltryptamines (IV*a*–IV*f*). The usual procedure (2–6) has been to hydrolyze the lactams with alkali first, followed by acid-catalyzed decarboxylation of the intermediate 3-aminoalkylindole-2-carboxylic acids. In the case of 6-methylthio-4,4-dimethyl-1,2,3,4-tetrahydro-1-oxo-β-carboline (4) and also the 6-methoxy analogue (III*h*), it was observed that vigorous alkaline hydrolysis would not open the lactam ring. Acid treatment of III*h* served to cleave the methoxy group and gave the 6-hydroxy compound (III*i*) as the only product isolated.



R_1 = F, Cl, Br, OCH_3, or SCH_3; R_2, R_3, and R_4 = H or CH_3

TABLE I

2,3-Piperidione-*p*-substituted phenylhydrazones (II)

II	R_1	R_2	R_3	R_4	Yield* (%)	Melting point (°C)	Formula	Calculated (%) C	H	N	Found (%) C	H	N
a	F	CH_3	H	H	75	220–222	$C_{12}H_{14}FN_3O$	61.3	5.99	17.9	61.2	5.97	18.1
b	F	CH_3	CH_3	H	75	230–231	$C_{13}H_{16}FN_3O$	62.6	6.46	16.9	62.5	6.55	17.0
c	Cl	CH_3	H	H	81	224–226	$C_{12}H_{14}ClN_3O$	57.3	5.60	16.7	57.1	5.54	16.7
d	Cl	CH_3	CH_3	H	77	234–236	$C_{13}H_{16}ClN_3O$	58.8	6.06	15.8	59.0	6.12	16.2
e	Br	CH_3	H	H	91	234–236	$C_{12}H_{14}BrN_3O$	48.7	4.76	14.2	48.3	4.68	14.2
f	Br	CH_3	CH_3	H	69	249–251	$C_{13}H_{16}BrN_3O$	50.3	5.19	13.5	50.2	5.11	13.7
g	OCH_3	CH_3	H	H	51	211–214	$C_{13}H_{17}N_3O_2$	63.1	6.93	17.0	63.0	6.97	17.1
h	OCH_3	CH_3	CH_3	H	64	215–216	$C_{14}H_{19}N_3O_2$	64.3	7.33	16.1	64.4	7.37	16.1

*All recrystallizations were from ethanol.

TABLE II

1,2,3,4-Tetrahydro-1-oxo-*β*-carbolines (III)

III	R_1	R_2	R_3	R_4	Yield (%)	Melting point (°C)	Formula	Calculated (%) C	H	N	Found (%) C	H	N
a	F	CH_3	H	H	66*	214–215	$C_{12}H_{11}FN_2O$	66.0	5.09	12.8	65.5	5.24	12.8
b	F	CH_3	CH_3	H	38†,‡	180–181¶	$C_{13}H_{13}FN_2O$	67.2	5.64	12.1	67.6	5.67	12.0
c	Cl	CH_3	H	H	67§	192–193	$C_{12}H_{11}ClN_2O$	61.4	4.73	11.9	60.8	4.71	12.2
d	Cl	CH_3	CH_3	H	22†	225–226	$C_{13}H_{13}ClN_2O$	62.8	5.27	11.3	62.3	5.18	11.3
e	Br	CH_3	H	H	67§	110–113	$C_{12}H_{11}BrN_2O$	51.6	3.98	10.0	51.5	4.30	10.0
f	Br	CH_3	CH_3	H	24†,§	235–237	$C_{13}H_{13}BrN_2O$	53.3	4.47	9.55	52.9	4.68	9.44
g	OCH_3	CH_3	H	H	76*	235–237	$C_{13}H_{14}N_2O_2$	67.8	6.13	12.2	67.6	6.24	11.9
h	OCH_3	CH_3	CH_3	H	33§	224–226	$C_{14}H_{16}N_2O_2$	68.8	6.60	11.5	68.3	6.57	11.4
i	OH	CH_3	CH_3	H	42‖	219–221	$C_{13}H_{14}N_2O_2$	67.8	6.13	12.2	67.3	6.32	12.2

*Recrystallized from ethanol.
†Chromatographed on silica gel.
‡Recrystallized from benzene.
§Recrystallized from isopropanol.
‖From acid hydrolysis of III*h*; recrystallized from 5% acetic acid.
¶Melting point 180–181°, resolidified and remelted at 196–197°.

TABLE III

5-Halo, methyl-substituted tryptamines (IV)

IV	R_1	R_2	R_3	R_4	Yield (%)	Melting point (°C)	Formula	Calculated (%)			Found (%)		
								C	H	N	C	H	N
a	F	CH_3	H	H	75*	224–227	$C_{17}H_{16}FN_5O_7$	48.5	3.82	16.6	48.6	3.75	16.9
b	F	CH_3	CH_3	H	45†	109–109.5	$C_{12}H_{15}FN_2$	69.9	7.32	13.6	69.2	7.26	13.6
c	Cl	CH_3	H	H	43†	99–100	$C_{11}H_{13}ClN_2$	63.3	6.28	13.4	63.4	6.27	13.3
d	Cl	CH_3	CH_3	H	33†	107–108	$C_{12}H_{15}ClN_2$	64.7	6.78	12.6	64.5	6.79	12.8
e	Br	CH_3	H	H	20*	206–211	$C_{17}H_{16}BrN_5O_7$	42.3	3.34	14.5	42.6	3.18	14.5
f	Br	CH_3	CH_3	H	13*	222–226	$C_{18}H_{18}BrN_5O_7$	43.6	3.65	14.1	43.9	3.56	14.0

*Picrate, crystallized from ethanol.
†Recrystallization from cyclohexane.

TABLE IV

1,2,3,4-Tetrahydro-β-carbolines (V)

V	R_1	R_2	R_3	R_4	Method	Yield (%)	Melting point (°C)	Formula	Calculated (%)			Found (%)		
									C	H	N	C	H	N
a	F	H	H	CH_3	C	15	235–237	$C_{12}H_{13}FN_2$	70.6	6.41	13.7	70.5	6.67	13.9
b	F	CH_3	H	H	A	57*	164–166	$C_{12}H_{13}FN_2$	70.6	6.41	13.7	70.8	6.29	14.0
c	F	CH_3	CH_3	H	A	36*	199–201	$C_{13}H_{15}FN_2$	71.5	6.92	12.8	71.4	7.21	12.7
d	Cl	H	H	CH_3	C	33	239–240	$C_{12}H_{13}ClN_2$	65.3	5.93	12.7	65.1	6.11	12.9
e	Cl	CH_3	H	H	A	45*	205–208	$C_{12}H_{13}ClN_2$	65.3	5.93	12.7	65.3	6.44	12.9
f	Cl	CH_3	CH_3	H	A	49*	228–231	$C_{13}H_{15}ClN_2$	66.5	6.44	11.9	66.9	6.28	12.0
g	Br	H	H	CH_3	C	19	241–243	$C_{12}H_{13}BrN_2$	54.4	4.94	10.6	54.6	4.96	10.7
h	Br	CH_3	H	H	A	58	219–222	$C_{12}H_{13}BrN_2$	54.4	4.94	10.6	54.8	5.15	10.9
i	Br	CH_3	CH_3	H	A	37	243–246	$C_{13}H_{15}BrN_2$	55.9	5.41	10.0	56.2	5.48	9.82
j	CH_3O	H	H	CH_3	B	33	224–227	$C_{13}H_{16}N_2O$	72.2	7.46	13.0	72.2	7.56	13.0
k	CH_3O	CH_3	H	H	A	33	192–193	$C_{13}H_{16}N_2O$	72.2	7.46	13.0	71.8	7.40	12.8
l	CH_3O	CH_3	CH_3	H	A	37	218–221	$C_{14}H_{18}N_2O$	73.0	7.88	12.2	72.9	7.85	12.3
m	CH_3S	H	H	H	A	12	162–164	$C_{12}H_{14}N_2S$	66.0	6.47	12.8	66.1	6.95	12.9
n	CH_3S	H	H	CH_3	B	35	226–230	$C_{13}H_{16}N_2S$	67.2	6.94	12.1	66.9	7.09	12.0
o	CH_3S	CH_3	H	H	A	46	202–203	$C_{13}H_{16}N_2S$	67.2	6.94	12.1	67.3	6.96	12.2
p	CH_3S	CH_3	CH_3	H	A	21	216–218	$C_{14}H_{18}N_2S$	68.3	7.37	11.4	68.1	7.39	11.4

*Recrystallization from benzene; all others were recrystallized from ethyl acetate.

EXPERIMENTAL

2,3-Piperidione Phenylhydrazones (II)

The new phenylhydrazones synthesized are listed in Table I. They were prepared by a previously described general procedure (4), which involved the Japp–Klingemann coupling of appropriate diazotized *p*-substituted anilines with methyl-substituted 3-carboxy-2-piperidones after the method pioneered by Abramovitch and Shapiro (2).

1,2,3,4-Tetrahydro-1-oxo-β-carbolines (III)

6-Methoxy-3-methyl-1,2,3,4-tetrahydro-1-oxo-β-carboline was prepared by the method of Terzyan *et al.* (5). The 6-fluoro-, 6-chloro-, and 6-bromo-3-methyl-1-oxo-β-carbolines were obtained by the method of Suvorov *et al.* (6). The 5-methylthio oxocarbolines were prepared by our previously reported procedure (4). The remaining new oxocarbolines listed in Table II were obtained by the cyclization of the appropriate hydrazones (II) with hydrogen chloride in glacial acetic acid, essentially as described in ref. 4. The *p*-methoxyphenylhydrazones (II*g* and II*h*) were refluxed for 20–30 min, II*a*, II*c*, and II*e* for 3–4 h, and II*b*, II*d*, and II*f* for 20 h, followed by chromatography on silica gel (elution with ethyl acetate).

5-Halo, Methyl-Substituted Tryptamines (IV)

The tryptamines listed in Table III were all prepared by hydrolysis of the oxocarbolines (III*a*–III*f*) with a concentrated hydrochloric acid – acetic acid (1:1) mixture. The reflux time for the 4-methyl oxocarbolines was 2 days, whereas the time for the 4,4-dimethyl-1-oxocarbolines was 5 days. The latter were quite resistant to hydrolysis, and in each case about half of the lactam was recovered unchanged. Treatment of the 6-methoxy-4,4-dimethyl-1-oxocarboline (III*h*) with acetic acid – concentrated hydrochloric acid (1:4) at reflux for 3 h yielded only the 6-hydroxy lactam (III*i*) rather than 5-methoxy-β,β-dimethyltryptamine. The material was soluble at pH 11–12.

1,2,3,4-Tetrahydro-β-carbolines (V)

The following representative procedures were used for preparation of the tetrahydro-β-carbolines listed in Table IV.

Method A

A mixture of 0.20 g of lithium aluminium hydride, 0.40 g of 6-chloro-4-methyl-1,2,3,4-tetrahydro-1-oxo-β-carboline (III*c*), and 15 ml of tetrahydrofuran was stirred at reflux for 15 h. After decomposition of the excess hydride by ethanol and a little water, the solvent was removed *in vacuo*. The residue was suspended in 25 ml of ether, and water was added slowly until a white, pasty aqueous phase formed. The ether was decanted and the residue was similarly extracted with another 20 ml of ether. The ether extracts were dried over magnesium sulfate and evaporated to leave 0.28 g of white crystals. Recrystallization from 12 ml of benzene gave 0.17 g (45%) of white crystals, m.p. 205–208°.

Method B

To a hot (130°) suspension of 0.60 g of 6-methoxy-3-methyl-1,2,3,4-tetrahydro-1-oxo-β-carboline (5) in 15 ml of 1-butanol was rapidly added 1.5 g of sodium (small pellets), with vigorous stirring. After 45 min the sodium was consumed and the mixture was cooled in ice. Water (30 ml) was added, followed by warming until two clear phases were present. The layers were separated and the aqueous layer was extracted with 20 ml of ether. The combined organic extracts were washed twice with 10 ml portions of water and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* yielded 0.50 g of crystals. Two recrystallizations from ethyl acetate gave 0.13 g (33%), m.p. 224–227°.

Method C

To 9 ml (9 mmoles) of 1 *M* borane in tetrahydrofuran (7) at 0–5° was slowly added 0.65 g (3 mmoles) of 6-fluoro-3-methyl-1,2,3,4-tetrahydro-1-oxo-β-carboline (6). After the initial foaming subsided, the mixture was heated under reflux for 2 h. Water (1 ml) was added, followed by 1 ml of 6 *N* hydrochloric acid. The solvent was removed *in vacuo* and the residue was suspended in 400 ml of water. After the addition of 3 ml of 6 *N* sulfuric acid, the mixture was heated to 90° and filtered while hot. The cooled filtrate was made strongly alkaline with 10% sodium hydroxide. After several hours the white, crystalline precipitate was collected, washed with water, and dried to leave 0.21 g of white crystals. Recrystallization from 10 ml of ethyl acetate gave 0.09 g (15%) of white crystals, m.p. 235–237°.

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