[CONTRIBUTION FROM THE RESEARCH DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

Tetrahydroisoquinolines. I. 1-Alkyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines[1]

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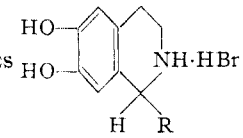
Eleven 1-alkyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines have been prepared by the Bischler–Napieralski ring closure of amides of 3,4-dimethoxyphenylethylamine, catalytic reduction of the dihydroisoquinolines and demethylation of the resulting tetrahydroisoquinolines with hydrobromic acid. The 1-isopropyl analog was found to be the most active bronchodilator agent of the series. Preliminary pharmacological data are given.

1-Methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline[1a,1b] was first prepared by Schöpf and Bayerle using "physiological conditions." This compound is closely related to the naturally occurring alkaloids salsoline and salsolidine which have been isolated from a species of cactus.[2a] No other 1-alkyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines have been reported, although several 1-alkyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines have been reported.[2b]

In the course of an extensive investigation of

TABLE I

1-ALKYL-6,7-DIHYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROBROMIDES

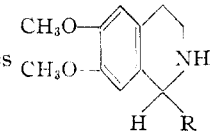


R =	Recrystn. solvent	M.p., °C.	Yield, %	Empirical formula	Analytical data[a] Calculated C	H	Br	Found C	H	Br	Bronchodilator activity[b] Anti-histamine i.p.	Anti-histamine oral	Anti-furmethide[c] i.p.	Anti-furmethide[c] oral
CH_3–	Methanol–ether	186–187[d]	75	.....	...	..	...	...	..	...	50	....	....	....
C_2H_5–	Ethanol–isopropanol	210–211	81	$C_{11}H_{16}O_2NBr$	48.19	5.88	29.15	48.10	5.72	29.27	25	....	....	....
n-C_3H_7–	Acetone	221.5–223	50	$C_{12}H_{18}O_2NBr$	50.01	6.30	27.73	50.05	6.46	27.54	10	15	5	>15
i-C_3H_7–	Acetone–isopropanol	214–215	90	$C_{12}H_{18}O_2HBr$	50.01	6.30	27.73	49.96	6.27	27.90	1	5	1	5
n-C_4H_9–	Ethanol–acetone	196–197	77	$C_{13}H_{20}O_2NBr$	51.66	6.67	26.44	51.53	6.61	26.59	10	>50	>10	....
i-C_4H_9–	Ethanol–acetone	220–222	37	$C_{13}H_{20}O_2NBr$	51.66	6.67	26.44	51.70	6.79	25.92	10	50	5	....
s-C_4H_9–[e]	Ethanol–ether	168.5–170	18	$C_{13}H_{20}O_2NBr$	51.66	6.67	26.44	51.58	6.31	26.89	200	....	....	....
t-C_4H_9–	Acetone–ether	255–258	65	$C_{13}H_{20}O_2NBr$	51.66	6.67	26.44	51.50	6.75	26.44	>100	....	....	....
n-C_5H_{11}–	Ethanol–ethyl acetate	148–149	57	$C_{14}H_{22}O_2NBr$	53.17	7.01	25.27	53.09	6.90	25.38	20	....	....	....
$(C_2H_5)_2$–CH–	Ethanol–ether	207–208.5	62	$C_{14}H_{22}O_2NBr$	53.17	7.01	25.27	53.22	7.20	25.48	40	....	....	....
Cyclopentyl–	Methanol–ether	235–237	86	$C_{14}H_{20}O_2NBr$	53.58	6.42	25.43	53.63	6.50	25.73	20	>50	....	....
	Isopropyl arterenol (Isuprel)										0.1	3.0	0.5	5.0

[a] Analyses performed by the Misses Ruth Savacool, Rita Fox and Frances McCarron. [b] Bronchodilator activity expressed as the lowest dose (mg./kg.) which protected small guinea pigs from lethal doses of aerosolized histamine or "Furmethide." [c] Trade mark reg. U. S. Pat. Off. [d] Reported 184–186° (ref. 1). [e] This compound contains two different asymmetric carbon atoms and should exist in two racemic modifications. The first material obtained melted at 86–100°, and on the recrystallizations required for purification, only the one form reported was obtained analytically pure.

TABLE II

1-ALKYL-6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINES



R =	B.p. °C.	Mm.	M.p.,[a] °C.	Yield, %	Empirical formula	Analytical data Calcd. C	H	Cl	Found C	H	Cl
C_2H_5–	.....	...	214–215[b]	90							
n-C_3H_7–	.....	...	220–221	95	$C_{14}H_{22}O_2NCl$	61.87	8.16	13.05	61.89	7.97	13.16
i-C_3H_7–	152–154	3	242–243	95	$C_{14}H_{22}O_2NCl$	61.87	8.16	13.05	62.11	7.63	13.13
n-C_4H_9–	156	1	206–207	90	$C_{15}H_{24}O_2NCl$	CH_3O, 21.72		12.41	CH_3O, 21.63		12.25
i-C_4H_9–	148–149	1.3	215–219	89	$C_{15}H_{24}O_2NCl$	CH_3O, 21.72		12.41	CH_3O, 21.56		12.26
s-C_4H_9–	145–147	0.8	208–209	87	$C_{15}H_{24}O_2NCl$	CH_3O, 21.72		12.41	CH_3O, 21.60		12.20
t-C_4H_9–	140–142	0.8	270–272	92	$C_{15}H_{24}O_2NCl$	CH_3O, 21.72		12.41	CH_3O, 21.74		12.21
n-C_5H_{11}–	154–156	0.8	185–187.5	91	$C_{16}H_{26}O_2NCl$	64.09	8.74	11.83	63.65	8.35	12.09
$(C_2H_5)_2$CH–	133–138	0.3	240	85	$C_{16}H_{26}O_2NCl$	64.09	8.74	11.83	63.99	8.53	11.92
Cyclopentyl–	.....	...	220–221	43	$C_{16}H_{24}O_2NCl$	64.52	8.12	11.91	64.45	8.17	11.80

[a] Hydrochloride.

(1) Presented at the XIIth International Congress of Pure and Applied Chemistry, Sept. 11, 1951.

(1a) C. Schöpf and H. Bayerle, *Ann.*, **513**, 190 (1934).

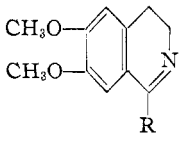
(1b) A. M. Hjort, E. J. DeBeer, J. S. Buck and L. O. Randall, *J. Pharm. Expll. Therap.*, **76**, 263 (1942).

(2a) T. A. Henry, "The Plant Alkaloids," (IV Ed.), The Blakiston Co., Phila., Penna., 1949, pp. 159–160.

(2b) E. Späth and F. Dengel, *Ber.*, **71B**, 114 (1938); see Tables II and III, and references 5 and 6.

TABLE III

1-ALKYL-6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINES



R =	B.p., °C.	Mm.	Yield, %
C_2H_5–[5,6]	127–130	0.3	87
n-C_3H_7–[6]	150–170	2–3	75
i-C_3H_7–	126–129	0.5	90
n-C_4H_9–	148–154	0.8	68
i-C_4H_9–	138–140	0.7	93
s-C_4H_9–	138	0.7	93
t-C_4H_9–	132–138	0.5	83
n-C_5H_{11}–	153–155	0.6	88
$(C_2H_5)_2$–CH–	142–145	0.8	84
Cyclopentyl–	160–168	0.6	81

effects are shown by isopropylarterenol. A complete report of the pharmacology of the 1-isopropyl compound will be published elsewhere.

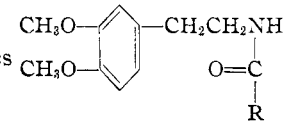
Experimental

The 1-alkyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines (Table I) were prepared by demethylation of the corresponding 6,7-dimethoxy compounds (Table II). These in turn were prepared by catalytic reduction of the corresponding 3,4-dihydroisoquinolines (Table III) which resulted from the application of the Bischler–Napieralski ring closure[4] on the appropriately substituted β-phenethylamides (Table III). The use of benzene and phosphorus oxychloride was found to be the most convenient method for the ring closure.

The reduction of the 3,4-dihydroisoquinolines was readily accomplished at three atmospheres of hydrogen with either platinum oxide or palladium–charcoal catalyst. The free bases of the dihydroisoquinolines were reduced within an hour when ethanol was used as a solvent; whereas aqueous or alcoholic solutions of the hydrochlorides of 3,4-dihydroisoquinolines required from four to six hours for complete

TABLE IV

3,4-DIMETHOXYPHENYLETHYL AMIDES



R =	B.p. °C.	Mm.	M.p., °C	Yield, %	Method of prepn.[a]	Empirical formula	Analytical data — Calcd. C	Calcd. H	Found C	Found H
C_2H_5–	225–230	10	57.5–59[5,6]	95	A	.....	...	..	...	..
n-C_3H_7–	180–185	0.5	51–53[6]	92	A	.....	...	..	...	..
i-C_3H_7–	204–206	3	100–101	90	B	$C_{14}H_{21}O_3N$	66.90	8.42	66.78	8.32
n-C_4H_9–	198–202	1.3	49–50	72	B	$C_{15}H_{23}O_3N$	67.89	8.74	67.87	8.60
i-C_4H_9–	188–193	1.0	62–63	80	B	$C_{15}H_{23}O_3N$	67.89	8.74	67.93	8.75
s-C_4H_9–	190	1.0	82–83	75	B	$C_{15}H_{23}O_3N$	67.89	8.74	68.00	8.75
t-C_4H_9–	168–178	0.6	78–80	58	B	$C_{15}H_{23}O_3N$	67.89	8.74	67.75	8.45
n-C_5H_{11}–	194–198	0.8	59–62	92	B	$C_{16}H_{25}O_3N$	68.78	9.02	68.69	8.76
$(C_2H_5)_2$CH–	.....	..	94–95	88	B	$C_{16}H_{25}O_3N$	68.78	9.02	68.94	8.86
Cyclopentyl–	.....	..	95	95	B	$C_{16}H_{23}O_3N$	69.28	8.36	69.34	8.13

[a] A, acid anhydride; B, acid chloride.

possible bronchodilators, the series of 1-alkyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines listed in Table I was prepared after pharmacological tests on the first two members showed that intensified bronchodilator activity occurred with an increase in size of the 1-alkyl group.

Maximum activity was demonstrated by the 1-isopropyl analog on both oral and intraperitoneal administration to guinea pigs. Preliminary pharmacological data are reported in Table I.

The sympathomimetic amines commonly used as bronchodilators (epinephrine and isopropylarterenol) have intense cardiac activity at low concentrations.[3] Preliminary tests indicate that depressor activity and tachycardia are shown by 1-isopropyl - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline hydrobromide at concentrations about 1000 times the concentrations at which similar

(3) H. Konzett, *Arch. Exptl. Path. Pharmakol.*, **194**, 41 (1940).

reduction. The dihydroisoquinolines were not characterized, but were converted to the tetrahydroisoquinolines immediately after distillation.

The demethylation can be carried out with either the free bases or the hydrochlorides of the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines. A 10% excess of 48% hydrobromic acid (redistilled over a trace of 50% hypophosphorous acid) was mixed with 50% hypophosphorous acid (1 g. for each 100 g. of 48% hydrobromic acid) and the dimethoxy compound was heated with this mixture. After removal of the aqueous forerun, the liquid temperature reached 126°. The time required for demethylation varied from one to three hours, and the reaction was completed when the evolution of methyl bromide ceased. The excess hydrobromic acid was removed under reduced pressure, and the resulting product was recrystallized from the appropriate solvent indicated in Table I. All melting points recorded were taken in open capillaries and are corrected.

PHILADELPHIA, PENNA. RECEIVED SEPTEMBER 7, 1951

(4) A. Bischler and E. Napieralski, *Ber.*, **26**, 1903 (1893).

(5) B. Dey and T. Govindachari, *Arch. Pharm.*, **277**, 177 (1939), report 218°.

(6) E. Späth and N. Polgar, *Monatsh.*, **51**, 190 (1929).