iae, Penicillium notatum, or *Sporobolomyces salmoncolor*, when tested in a paper disk–agar diffusion assay. Compounds **12**, **13**, **19**, **20**, **26**, **27**, **37**–**39**, **40**, and **41** failed to significantly prolong the survival time of mice infected with lethal inocula of *Schistosoma mansoni* cercariae.[22]

Experimental Section

Most of the compounds prepared in this work have been analyzed by pmr using a Varian A-60A or HR-100 spectrometer. Typical uv spectra are given in the representative preparations below.

5,5-Bis(4-chlorophenyl)pentadienoic Acid (14).—A mixture of 20 g (0.08 mole) of 4,4'-dichlorobenzophenone and 5.9 g (0.09 mole) of activated 40-mesh Zn in 100 ml of C_6H_6 and 60 ml of Et_2O was refluxed under N_2. A portion of a solution of 14.3 g (0.08 mole) of methyl 4-bromocrotonate in 35 ml of C_6H_6 was added, and the reaction was initiated with the aid of a few drops of MeMgBr solution. The remainder of the RBr solution was then added. Reflux was maintained for 3 hr. The cooled mixture was treated with 60 ml of 2 *N* HOAc and stirred to yield a clear organic phase. The organic layer was washed (H_2O, twice with 5% $NaHCO_3$, and twice with H_2O) and then dried ($NaSO_4$). The solvent was removed *in vacuo*. The residue was heated on the steam bath for 35 min with 40 ml of 90% HCO_2H. The HCO_2H was removed *in vacuo*. The residue was taken up in 100 ml of boiling MeOH and treated with 4 g of KOH in a little MeOH–H_2O. The solution was refluxed for 1.5 hr while H_2O was gradually added (total 40 ml) to the cloud point. After 16 hr, water was added until no more solid precipitated. Filtration and recrystallization of the residue gave 8.8 g of starting ketone. The filtrate was acidified with concentrated H_2SO_4, and the collected solid was recrystallized from MeOH–H_2O to yield 13.6 g (53%) of the product: uv (EtOH), 243 mμ (ε 15,700), 258 (15,700), 320.5 (28,000).

5,5-Bis(4-chlorophenyl)penta-2,4-dienoic Acid Diethylamide (10).—Acid **14** (3 g, 0.0094 mole) was dissolved in 20 ml of dry THF. Et_3N (0.01 mole) was added at room temperature and the solution was stirred for 20 min. The solution was cooled to 0°, treated dropwise with 0.0103 mole of $ClCO_2Me$, and stirred 15 min more at 0°. Et_2NH (0.0105 mole) was added dropwise to the cold mixture, and the resulting solution was allowed to warm to 20° over 40 min. The resulting mixture was taken up in Et_2O–H_2O, and the Et_2O layer was washed (5% HCl, H_2O, twice with 5% $NaHCO_3$, and twice with H_2O). After drying (Na_2SO_4), the Et_2O was removed *in vacuo* and the solid residue was recrystallized from MeOH–H_2O to yield 2.12 g (60%) of product: uv (95% EtOH) 242 mμ (ε 18,200), 257 (18,700), 325 (35,900). Starting acid (30%) was recovered from the base washes.

4,4'-Dimethoxybenzophenone was prepared in 90% yield either by the reaction of anisic acid with anisol and PPA[20] or by the MeI–K_2CO_3 methylation of bis-4-hydroxybenzophenone.

Bis(4-anisyl)ethynylcarbinol was prepared by the reaction of 4,4'-dimethoxybenzophenone with lithium acetylide–ethylene diamine complex (Foote Mineral Co.) in DMF saturated with C_2H_2. The product was obtained in 90% yield, mp 89–91.5° (lit.[21] mp 93°).

3,3-Bis(4-anisyl)acrolein.—Bis(4-anisyl)ethynylcarbinol (15 g, 0.056 mole) was dissolved in 75 ml of EtOH under N_2. An instantaneous red-purple color developed when the first drops of 20% H_2SO_4 were added. The solution was an opaque dark brown color after a total of 3 ml of acid had been added. The reaction mixture was diluted with 20 ml of EtOH and stirred for 2 hr at room temperature. A copious black oil had precipitated at this time. The reaction mixture was taken up in Et_2O–H_2O. The Et_2O layer was washed (H_2O, 5% Na_2CO_3, H_2O). The Et_2O solution was dried and the Et_2O was removed *in vacuo* to yield the product as 15.4 g of a black oil: ir spectrum, λ_{max}^{neat} 6.01 μ (C=O); tlc, silica gel ($CHCl_3$), R_f 0.35.

Several additional experiments gave poor yields and/or less pure product when less acid was used or the reaction period was shortened or the reactant concentration was decreased.

5,5-Bis(4-anisyl)penta-2,4-dienoic Acid.—To a 500-ml flask containing 100 ml of dry C_6H_6 and 7.27 g (0.0257 mole) of carbomethoxymethylenetriphenylphosphorane was added 5.0 g (0.0187 mole) of 3,3-bis(4-anisyl)acrolein in 30 ml of C_6H_6. The mixture was refluxed for 16 hr and the C_6H_6 was removed *in vacuo*. The resulting solid was dissolved in 30 ml of MeOH and treated with a mixture of 1.8 g of KOH in 20 ml of H_2O. The mixture was refluxed for 2 hr and cooled. A solid, neutral by-product was filtered off and the basic filtrate was acidified with 40% H_2SO_4. The resulting solid was filtered off and recrystallized from MeOH to yield 1.41 g (25%) of the desired acid, mp 186–189°.

(22) This test was performed under the auspices of the Walter Reed Army Institute of Research. We are grateful to Colonel William E. Rothe for providing this information.

(23) P. Cadiot, *Ann. Chim.* (Paris), **13**, 214 (1956).

Synthesis and Pharmacology of Some α-Oxy- and α-Hydroxy-1-benzyltetrahydroisoquinolines

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A series of α-oxy- and α-hydroxyl-1-benzyltetrahydroisoquinolines has been prepared and subjected to several pharmacological screening procedures. These include dose-range studies in mice and analgetic and antipyretic testing. A biological profile of these compounds derived from the results obtained is discussed.

The naturally occurring 1-benzyl and phthalideisoquinoline alkaloids exemplified by laudanosine (I) and narcotine (II) have often been the subject of chemical and pharmacological investigations.[1-3] More recently, synthetic 1-phenethyltetrahydroisoquinoline types such as III–V have undergone extensive chemical study[4] because of their interesting analgetic properties.[5]

In spite of the intense and continuing activity in this area, both the α-oxo- (VI) and α-hydroxy-1-benzyltetrahydroisoquinoline (VII) alkaloid types have not yet been thoroughly examined chemically or, more important, been adequately screened pharmacologically. Occasionally the former have been isolated as by-products in synthetic sequences;[6-8] there also are two

(1) A. Burger, *Alkaloids*, **4**, 29 (1954).

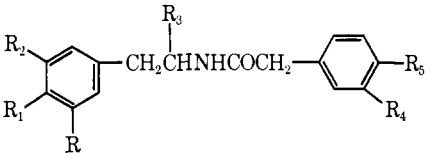
(2) J. Staněk, *ibid.*, **7**, 433 (1960), and references cited therein.

(3) H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961.

(4) A. Brossi, H. Besendorf, L. A. Pirk, and A. Rheiner, Jr., in "Analgetics," G. deStevens, Ed., Academic Press Inc., New York, N. Y., 1965, p 281.

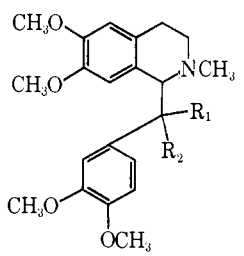
(5) A. Brossi, H. Besendorf, B. Pellmont, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **43**, 1459 (1960).

TABLE I[a]

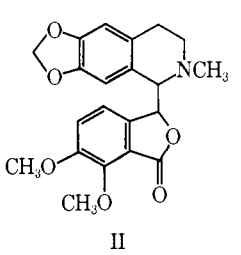


No.	R	R_1	R_2	R_3	R_4	R_5	Mp, °C	Formula[c]
1	H	OCH_2O		CH_3	H	H	100–102	$C_{18}H_{19}NO_3$
2	H	OCH_2O		CH_3	H	Cl	114–115	$C_{18}H_{18}ClNO_3$
3	H	OCH_2O		CH_3	H	OCH_3	110–112	$C_{19}H_{21}NO_4$
4	H	OCH_2O		CH_3	OCH_3	H	114–115	$C_{19}H_{21}NO_4$
5	H	OCH_2O		CH_3	OCH_3	OCH_3	124–125	$C_{20}H_{23}NO_5$
6	H	OCH_2O		H	H	H	96–97.5	$C_{17}H_{17}NO_3$
7	H	OCH_2O		H	H	Cl	139–141	$C_{17}H_{16}ClNO_3$
8	H	OCH_2O		H	H	OCH_3	91–92	$C_{18}H_{19}NO_4$
9	H	OCH_2O		H	OCH_3	H	*b*	
10	H	OCH_2O		H	OCH_3	OCH_3	133–136	$C_{19}H_2NO_5$
11	H	OCH_3	OCH_3	CH_3	H	H	119–120	$C_{19}H_{23}NO_3$
12	H	OCH_3	OCH_3	CH_3	H	Cl	144–145	$C_{19}H_{22}ClNO_3$
13	H	OCH_3	OCH_3	CH_3	H	OCH_3	118–120	$C_{20}H_{25}NO_4$
14	H	OCH_3	OCH_3	CH_3	OCH_3	H	115–116	$C_{20}H_{25}NO_4$
15	H	OCH_3	OCH_3	CH_3	OCH_3	OCH_3	123–125	$C_{21}H_{27}NO_5$
16	H	H	OCH_3	H	H	H	*b*	
17	H	H	OCH_3	H	H	Cl	*b*	
18	H	H	OCH_3	H	H	OCH_3	*b*	
19	H	H	OCH_3	H	OCH_3	H	*b*	
20	H	H	OCH_3	H	OCH_3	OCH_3	*b*	
21	H	OCH_3	OCH_3	H	H	H	107–108	$C_{18}H_{21}NO_3$
22	H	OCH_3	OCH_3	H	H	Cl	124–126	$C_{18}H_{20}ClNO_3$
23	H	OCH_3	OCH_3	H	H	OCH_3	126–127	$C_{19}H_{23}NO_4$
24	H	OCH_3	OCH_3	H	OCH_3	OCH_3	120–122	$C_{20}H_{25}NO_5$
25	OCH_3	OCH_3	OCH_3	CH_3	H	Cl	148–149	$C_{20}H_{24}ClNO_4$
26	OCH_3	OCH_3	OCH_3	CH_3	H	OCH_3	118–120	$C_{21}H_{27}NO_5$
27	OCH_3	OCH_3	OCH_3	CH_3	OCH_3	OCH_3	125–126	$C_{22}H_{29}NO_6$
28	H	H	OCH_3	CH_3	H	H	*b*	
29	H	H	OCH_3	CH_3	H	Cl	101–104	$C_{19}H_{20}ClNO_2$
30	H	H	OCH_3	CH_3	H	OCH_3	*b*	
31	H	H	OCH	CH_3	OCH_3	H	*b*	
32	H	H	OCH_3	CH_3	OCH_3	OCH_3	*b*	

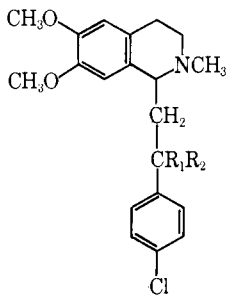
[a] Typically, yields were in the range of 80–100%. [b] Viscous oil which was characterized by means of ir spectroscopy. [c] All compounds except the oils (footnote *b*) were analyzed for C, H, N.



I, $R_1 = R_2 = H$
VI, $R_1R_2 = O$
VII, $R_1 = H$; $R_2 = OH$



II



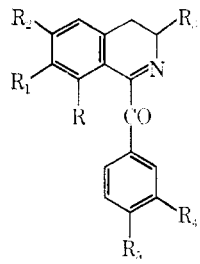
III, $R_1 = R_2 = H$
IV, $R_1R_2 = O$
V, $R_1 = H$; $R_2 = OH$

published descriptions of syntheses specifically directed toward oxolaudanosine (VI) itself.[9,10] We now describe a chemical and pharmacological investigation of a number of compounds of the general types VI and VII (Tables I–VI).

A variety of substituted phenethylamines and phenylacetyl acid chlorides, exemplified by VIII and IX, respectively, were converted to the corresponding amides X by the usual techniques[11] (Scheme I). These were cyclized to the isoquinoline moiety *via* the Bischler–Napieralski reaction employing $POCl_3$ in refluxing toluene as dehydrating agent. Separation and removal of excess reagent was effected by dilution of the cooled reaction mixture with large volumes of petroleum ether, whereupon a dihydroisoquinolium salt usually separated in a semicrystalline state. The latter was not characterized but rather directly converted to the 1-benzyl-3,4-dihydroisoquinoline (XI). Often, particularly with chloro-substituted variants of XI, these

(6) H. Yamaguchi, *J. Pharm. Soc. Japan*, **78**, 733 (1958).
(7) M. Tomita and J. Niimi, *ibid.*, **78**, 1229 (1958).
(8) T. Kametani and K. Fukumoto, *ibid.*, **83**, 1031 (1963).
(9) E. Schlittler and A. Lindenmann, *Helv. Chim. Acta*, **32**, 1880 (1949).
(10) K. W. Bentley and A. W. Murray, *J. Chem. Soc.*, 2487 (1963).
(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p 200.

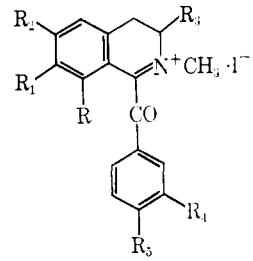
TABLE II[a]



No.	R	R_1	R_2	R_3	R_4	R_5	Mp, °C	Formula[c]
33	H	OCH_2O		CH_3	H	H	90–91	$C_{18}H_{15}NO_3$
34	H	OCH_2O		CH_3	H	Cl	124–127	$C_{18}H_{14}ClNO_3$
35	H	OCH_2O		CH_3	H	OCH_3	122–124	$C_{19}H_{17}NO_4$
36	H	OCH_2O		CH_3	OCH_3	H	99–101	$C_{19}H_{17}NO_4$
37	H	OCH_2O		CH_3	OCH_3	OCH_3	147–149	$C_{20}H_{19}NO_5$
38	H	OCH_2O		H	H	H	106–169 dec[b]	$C_{17}H_{14}ClNO_4$
39	H	OCH_2O		H	H	Cl	132–133	$C_{17}H_{12}ClNO_3$
40	H	OCH_2O		H	H	OCH_3	141–142	$C_{18}H_{15}NO_4$
41	H	OCH_2O		H	OCH_3	H	184–187 dec[b]	$C_{18}H_{16}ClNO_4$
42	H	OCH_2O		H	OCH_3	OCH_3	153–154	$C_{19}H_{17}NO_5$
43	H	OCH_3	OCH_3	CH_3	H	H	117–118	$C_{19}H_{19}NO_3$
44	H	OCH_3	OCH_3	CH_3	H	Cl	136–138	$C_{19}H_{18}ClNO_3$
45	H	OCH_3	OCH_3	CH_3	H	OCH_3	108–109	$C_{20}H_{21}NO_4$
46	H	OCH_3	OCH_3	CH_3	OCH_3	H	126–128	$C_{20}H_{21}NO_4$
47	H	OCH_3	OCH_3	CH_3	OCH_3	OCH_3	119–122	$C_{21}H_{23}NO_5$
48	H	H	OCH_3	H	H	H	98–100	$C_{17}H_{15}NO_2$
49	H	H	OCH_3	H	H	Cl	192–195[b]	$C_{17}H_{15}Cl_2NO_2$
50	H	H	OCH_3	H	H	OCH_3	155–157	$C_{18}H_{17}NO_3$
51	H	H	OCH_3	H	OCH_3	H	157–160[b]	$C_{18}H_{18}ClNO_3$
52	H	H	OCH_3	H	OCH_3	OCH_3	101–103	$C_{19}H_{19}NO_4$
53	H	OCH_3	OCH_3	H	H	H	190–192[b]	$C_{18}H_{18}ClNO_3 \cdot 0.5H_2O$
54	H	OCH_3	OCH_3	H	H	Cl	130–131	$C_{18}H_{16}ClNO_3$
55	H	OCH_3	OCH_3	H	H	OCH_3	105–107	$C_{19}H_{19}NO_4$
56	H	OCH_3	OCH_3	H	OCH_3	OCH_3	192–193	$C_{20}H_{21}NO_5$
57	OCH_3	OCH	OCH_3	CH_3	H	Cl	126–127	$C_{26}H_{20}ClNO_4$
58	OCH_3	OCH_3	OCH_3	CH_3	H	OCH_3	96–98	$C_{21}H_{23}NO_5$
59	OCH_3	OCH_3	OCH_3	CH_3	OCH_3	OCH_3	148–151 dec[b]	$C_{22}H_{26}ClNO_6$
60	H	H	OCH_3	CH_3	H	H	107–109	$C_{18}H_{17}NO_2$
61	H	H	OCH_3	CH_3	H	Cl	228–231 dec[b]	$C_{18}H_{17}Cl_2NO_2$
62	H	H	OCH_3	CH_3	H	OCH_3	180–181 dec[b]	$C_{19}H_{20}ClNO_3 \cdot 0.5CH_3OH$
63	H	H	OCH_3	CH_3	OCH_3	H	185–186 dec[b]	$C_{19}H_{20}ClNO_3$
64	H	H	OCH_3	CH_3	OCH_3	OCH_3	126–128	$C_{20}H_{21}NO_4$

[a] Exact yields were not always computed due to mechanical losses with tarry materials during air oxidation, but were usually in the 25–40% range over-all from amide. [b] Hydrochloride. [c] All compounds were analyzed for C, H, N.

TABLE III



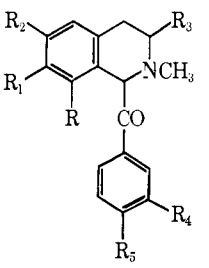
No.	R	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp,[a] °C	Formula[b]
65	H	OCH_2O		CH_3	H	H	81	233–237 dec	$C_{19}H_{18}INO_3$
66	H	OCH_2O		CH_3	H	Cl	92	227–228	$C_{19}H_{17}ClINO_3$
67	H	OCH_2O		CH_3	H	OCH_3	94	248–250	$C_{20}H_{20}INO_4$
68	H	OCH_2O		CH_3	OCH_3	H	98	204–207	$C_{20}H_{20}INO_4$
69	H	OCH_2O		CH_3	OCH_3	OCH_3	97	205–208	$C_{21}H_{22}INO_5$
70	H	OCH_2O		H	H	H	70	229–230	$C_{18}H_{16}INO_3$
71	H	OCH_2O		H	H	Cl	76	241–242	$C_{18}H_{15}ClINO_3$
72	H	OCH_2O		H	H	OCH_3	97	242–243	$C_{19}H_{18}INO_4$
73	H	OCH_2O		H	OCH_3	H	68	220–222	$C_{19}H_{18}INO_4$
74	H	OCH_2O		H	OCH_3	OCH_3	75	230–232	$C_{20}H_{20}INO_5$
75	H	OCH_3	OCH_3	CH_3	H	H	75	191–192	$C_{20}H_{22}INO_3$

TABLE III (*Continued*)

No.	R	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp,[a] °C	Formula[b]
76	H	OCH_3	OCH_3	CH_3	H	Cl	68	175–176	$C_{20}H_{21}ClINO_3$
77	H	OCH_3	OCH_3	CH_3	H	OCH_3	88	179–180	$C_{21}H_{24}INO_4$
78	H	OCH_3	OCH_3	CH_3	OCH_3	H	62	177–179	$C_{21}H_{24}INO_4$
79	H	OCH_3	OCH_3	CH_3	OCH_3	OCH_3	76	202–204	$C_{22}H_{26}INO_5$
80	H	H	OCH	H	H	H	87	198–200	$C_{18}H_{18}INO_2$
81	H	H	OCH_3	H	H	Cl	62	205–207	$C_{18}H_{17}ClINO_2$
82	H	H	OCH_3	H	H	OCH_3	75	193–195	$C_{19}H_{20}INO_3$
83	H	H	OCH_3	H	OCH_3	H	51	192–193	$C_{19}H_{20}INO_3$
84	H	H	OCH_3	H	OCH_3	OCH_3	74	201–202	$C_{20}H_{22}INO_4$
85	H	OCH_3	OCH_3	H	H	H	44	185–186	$C_{19}H_{20}INO_3$
86	H	OCH_3	OCH_3	H	H	Cl	89	172–173	$C_{19}H_{19}ClINO_3 \cdot 0.5CH_3OH$
87	H	OCH_3	OCH_3	H	H	OCH_3	75	157–160	$C_{20}H_{22}INO_4 \cdot CH_3OH$
88	H	OCH_3	OCH_3	H	OCH_3	OCH_3	65	184–185	$C_{21}H_{24}INO_5$
89	OCH_3	OCH_3	OCH_3	CH_3	H	Cl	72	148–150	$C_{21}H_{23}ClINO_4$
90	OCH_3	OCH_3	OCH_3	CH_3	H	OCH_3	67	134–135	$C_{22}H_{26}INO_5 \cdot 0.5CH_3OH$
91	OCH_3	OCH_3	OCH_3	CH_3	OCH_3	OCH_3	57	162–164	$C_{23}H_{28}INO_6$
92	H	H	OCH_3	CH_3	H	H	87	191–193	$C_{19}H_{20}INO_2$
93	H	H	OCH_3	CH_3	H	Cl	81	197–198	$C_{19}H_{19}ClINO_2$
94	H	H	OCH_3	CH_3	H	OCH_3	31	197–198	$C_{20}H_{22}INO_3$
95	H	H	OCH_3	CH	OCH_3	H	47	169–171	$C_{20}H_{22}INO_3$
96	H	H	OCH_3	CH_3	OCH_3	OCH_3	98	204–205	$C_{21}H_{24}INO_4$

[a] In all instances the specimens decomposed rather than melted. [b] See footnote *c*, Table II.

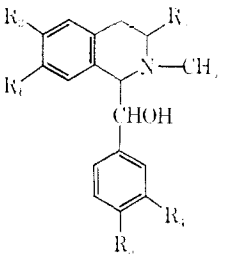
TABLE IV



No.	R	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp, °C	Formula[c]
97	H	OCH_2O		CH_3	H	H	45	141–143	$C_{19}H_{19}NO_3$
98	H	OCH_2O		CH_3	H	Cl	32	135–137	$C_{19}H_{18}ClNO_3$
99	H	OCH_2O		CH_3	H	OCH_3	25	131–132	$C_{20}H_{21}NO_4$
100	H	OCH_2O		CH_3	OCH_3	H	23	209–210[a,b]	$C_{21}H_{26}ClNO_5$
101	H	OCH_2O		CH_3	OCH_3	OCH_3	32	236–239 dec[a]	$C_{21}H_{24}ClNO_5$
102	H	OCH_2O		H	H	H	32	121–122	$C_{18}H_{17}NO_3$
103	H	OCH_2O		H	H	Cl	43	115–117	$C_{18}H_{16}ClNO_3$
104	H	OCH_2O		H	H	OCH_3	49	137–138	$C_{19}H_{19}NO_4$
105	H	OCH_2O		H	OCH_3	H	28	106–108	$C_{19}H_{19}NO_4$
106	H	OCH_2O		H	OCH_3	OCH_3	45	245–246 dec[a]	$C_{20}H_{22}ClNO_5$
107	H	OCH_3	OCH_3	CH_3	H	H	39	105–107	$C_{20}H_{23}NO_3$
108	H	OCH_3	OCH_3	CH_3	H	Cl	31	197–200 dec[a]	$C_{20}H_{23}Cl_2NO_3$
109	H	OCH_3	OCH_3	CH_3	H	OCH_3	35	113–115	$C_{21}H_{25}NO_4$
110	H	OCH_3	OCH_3	CH_3	OCH_3	H	41	100–102	$C_{21}H_{25}NO_4$
111	H	OCH_3	OCH_3	CH_3	OCH_3	OCH_3	34	195–198[a]	$C_{22}H_{28}ClNO_5$
112	H	H	OCH_3	H	H	H	26	108–109	$C_{18}H_{19}NO_2$
113	H	H	OCH_3	H	H	Cl	41	113–114	$C_{18}H_{18}ClNO_2$
114	H	H	OCH_3	H	H	OCH_3	24	104–106	$C_{19}H_{21}NO_3$
115	H	H	OCH_3	H	OCH_3	H	24	167–169 dec[a]	$C_{19}H_{22}ClNO_3$
116	H	H	OCH_3	H	OCH_3	OCH_3	12	190–193 dec[a]	$C_{20}H_{24}ClNO_4$
117	H	OCH_3	OCH_3	H	H	H	23	104–106	$C_{19}H_{21}NO_3$
118	H	OCH_3	OCH_3	H	H	Cl	23	113–115	$C_{19}H_{20}ClNO_3$
119	H	OCH_3	OCH_3	H	H	OCH_3	26	183–185[a]	$C_{20}H_{24}ClNO_4$
120	H	OCH_3	OCH_3	H	OCH_3	OCH_3	29	195–196 dec[a]	$C_{21}H_{26}ClNO_5$
121	OCH_3	OCH_3	OCH_3	CH_3	H	Cl	10	223–225 dec[a]	$C_{21}H_{25}Cl_2NO_4$
122	OCH_3	OCH_3	OCH_3	CH_3	H	OCH_3	19	193–194 dec[a]	$C_{22}H_{28}ClNO_5$
123	OCH_3	OCH_3	OCH_3	CH_3	OCH_3	OCH_3	33	208–209 dec[a]	$C_{23}H_{30}ClNO_6$
124	H	H	OCH_3	CH_3	H	H	38	181–183 dec[a]	$C_{19}H_{22}ClNO_2$
125	H	H	OCH_3	CH_3	H	Cl	21	186–188 dec[a]	$C_{19}H_{21}Cl_2NO_2$
126	H	H	OCH_3	CH_3	H	OCH_3	43	87–89	$C_{20}H_{23}NO_3$
127	H	H	OCH_3	CH_3	OCH_3	H	17	169–171[a]	$C_{20}H_{24}ClNO_3$
128	H	H	OCH_3	CH_3	OCH_3	OCH_3	50	198–200 dec[a]	$C_{21}H_{26}ClNO_4$

[a] Hydrochloride. [b] Methanolate. [c] See Table II, footnote *c*.

TABLE V



No.	R_6	R_7	R_8	R_1	R_5	Yield, %	Mp, °C	Formula[a]
129	OCH_2O		H	H	H	51	248–251 dec[c]	$C_{18}H_{20}ClNO_3$
130	OCH_2O		H	H	Cl	70	218–221 dec[c]	$C_{18}H_{19}Cl_2NO_3$
131	OCH_2O		H	H	OCH_3	43	209–211 dec[c]	$C_{19}H_{22}ClNO_4$
132	OCH_2O		CH_3	H	H	79	274–275 dec[c]	$C_{19}H_{22}ClNO_3$
133	OCH_2O		CH_3	H	Cl	89	231–234 dec[c]	$C_{19}H_{21}Cl_2NO_3$
134	OCH_2O		CH_3	H	OCH_3	84	229–231 dec[c]	$C_{20}H_{24}ClNO_4$
135	OCH_2O		CH_3	OCH_3	OCH_3	38	243–245 dec[c]	$C_{21}H_{26}ClNO_5$
136	OCH_3	OCH_3	CH_3	H	Cl	79	215–217 dec[c]	$C_{20}H_{25}Cl_2NO_3$
137	OCH_3	OCH_3	CH_3	H	OCH_3	94	193–195 dec[c]	$C_{21}H_{28}ClNO_4$
138	OCH_3	OCH_3	CH_3	OCH_3	H	61	204–206 dec[c]	$C_{21}H_{28}ClNO_4$
139	H	OCH_3	H	H	H	56	122–125[c]	$C_{18}H_{22}ClNO_2$[c]
140	H	OCH_3	CH_3	H	Cl	58	270–273 dec[c]	$C_{19}H_{23}Cl_2NO_2$
141	H	OCH_3	CH_3	OCH_3	OCH_3	41	209–211 dec[c]	$C_{21}H_{28}ClNO_4$
142	H	OCH_3	CH_3	OCH_3	H	70	190–193[c]	$C_{20}H_{26}ClNO_4$
143	OCH_3	OCH_3	H	H	H	80	215–217[c]	$C_{19}H_{24}ClNO_4$
144	OCH_3	OCH_3	H	H	Cl	89	197–199[c]	$C_{19}H_{23}Cl_2NO_3$
145	OCH_3	OCH_3	H	H	OCH_3	90	115–116	$C_{20}H_{25}NO_4$
146	OCH_3	OCH_3	H	OCH_3	OCH_3	60	108–110	$C_{21}H_{27}NO_5$

[a] Hydrochloride. [b] See Table II, footnote *c*. [c] C: calcd, 67.60; found, 67.16.

compounds were crystalline as the free base. Usually the compounds were viscous oils. In all instances the total crude reaction product XI was used for oxidation to XII, and thus the reported yields of this compound represent over-all figures for X → XII. Initially oxidation was effected by reaction of XI with $Na_2Cr_2O_7$–HOAc–H_2SO_4 in a vigorously exothermic reaction. The product, first obtained as a black tar, was easily purified by column chromatography, even on a large scale. However, examination of the crystalline material using nmr spectroscopy indicated that it was often a mixture of the dihydro (XII) and fully aromatized 1-benzoylisoquinolines (XIII) and occasionally consisted primarily of the latter product. As attempts to regulate this vigorous exothermic reaction were to no avail, the slow, but mild and specific, air oxidation conditions of Perkin, *et al.*,[12] were applied to XI. Thus, the crude Bischler–Napieralski base was dissolved in excess methanol and stirred in an open tray for periods varying from 1 to 3 weeks. Upon stabilization of the intensity of carbonyl absorption in an ir spectrum of the concentrated reaction mixture, the basic product was isolated in the usual manner and purified by column chromatography and subsequent crystallization. XII was directly reduced to the corresponding 1-α-hydroxybenzyl-1,2,3,4-tetrahydroisoquinoline derivative XIV (stereochemistry unknown) with $NaBH_4$–MeOH.

Treatment of XII with methyl iodide yielded the quaternary salt XV, which was selectively reduced to the 1-benzoyl-N-methyl-1,2,3,4-tetrahydroisoquinoline XVI with Raney nickel and hydrogen at *ca.* atmospheric pressure or alternately to the 1-α-hydroxylbenzyl derivative XVII with $NaBH_4$–MeOH.

(12) J. S. Buck, R. D. Haworth, and W. H. Perkin, Jr., *J. Chem. Soc.*, **125**, 2175 (1924).

Pharmacology.—The series of α-oxo- and α-hydroxy-1-benzyltetrahydroisoquinolines was subjected to several pharmacological screening procedures. Most of these compounds were tested for dose-range studies in the mouse, elevation of pain threshold to pressure, and for antipyretic activity in the rat.

Doses of 300 mg/kg *po* were initially administered to mice which were then observed for gross behavioral changes, pupillary alterations, reaction to thermal pain, lowering of rectal temperature, muscle tonus, and toxicity (Table VII). Presumptive evidence for anti-inflammatory activity was measured by three parameters: pain, skin temperature, and edema. The effect of the compounds on pain threshold was measured by the pressure method of Randall and Selitto[13] (Table VIII) and also by the thermal method of D'Amour and Smith.[14] Skin temperature was measured with a "Banjo" surface probe and telethermometer, while reduction of edema was measured by a modification of the method of Winter, *et al.*[15]

Cardiovascular studies were carried out in the chloralose-anesthetized cat. Mean carotid pressure was recorded by means of a mercury manometer on a smoked kymograph drum. All drugs were administered intravenously *via* the femoral vein. Blood pressure responses to the test compound were recorded as well as the integrity of the peripheral and ganglionic autonomic nervous system. The latter was measured by several specific test agents. These were epinephrine, norepinephrine, DMPP (1,1-dimethyl-4-phenylpiperi-

(13) L. O. Randall and J. J. Selitto, *Arch. Intern. Pharmacodyn.*, **111**, 409 (1957).

(14) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1940).

(15) C. A. Winter, E. A. Risley, and G. W. Nuss, *ibid.*, **141**, 369 (1963).

SCHEME I

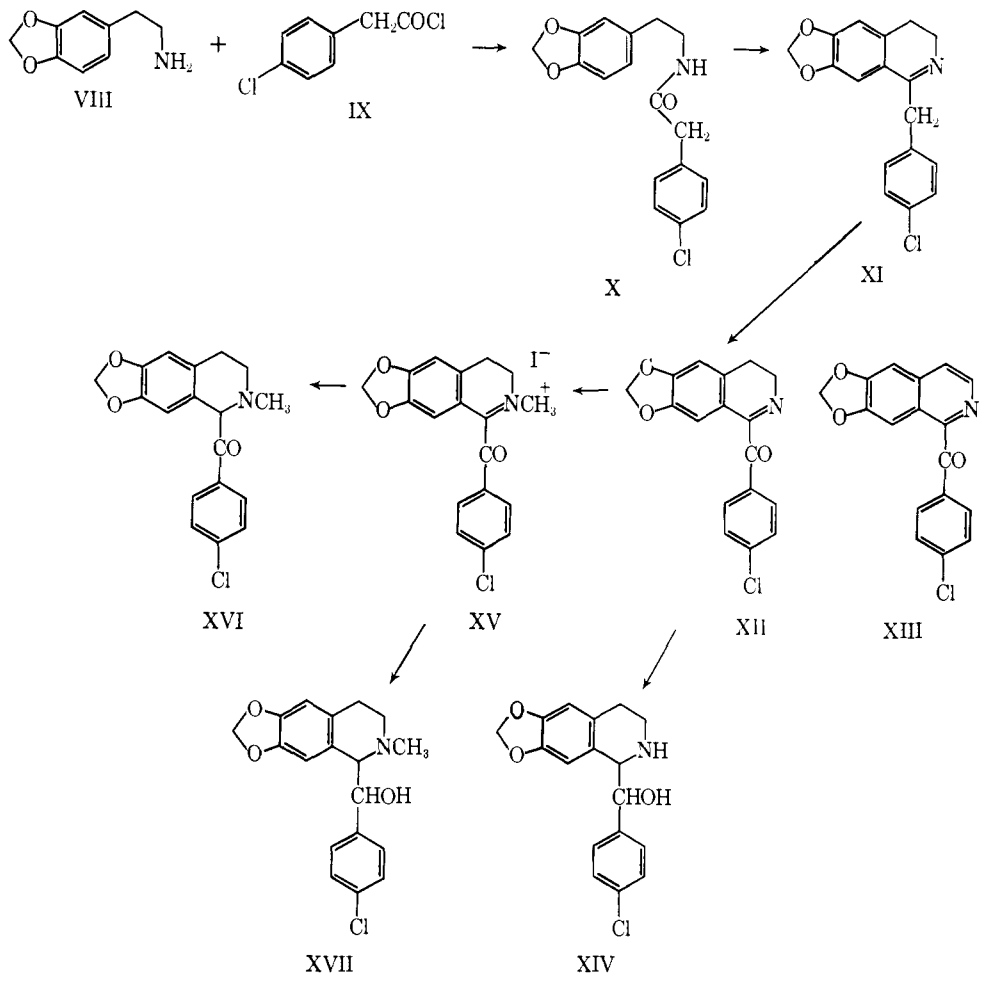
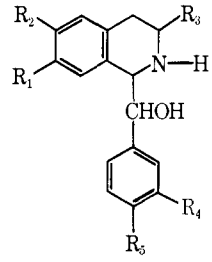


TABLE VI



No.	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp, °C	Formula[b]
147	OCH_3	OCH_3	H	H	OCH_3	67	122–124	$C_{19}H_{23}NO_4$
148	OCH_3	OCH_3	H	H	Cl	53	205–207 dec[a]	$C_{18}H_{21}Cl_2NO_3$
149	OCH_2O		H	H	OCH_3	55	208–209 dec[a]	$C_{18}H_{20}ClNO_4$
150	OCH_2O		H	H	Cl	61	225–227 dec[a]	$C_{17}H_{17}Cl_2NO_3$
151	OCH_3	OCH_3	CH_3	H	H	52	254–256 dec[a]	$C_{19}H_{24}ClNO_3$
152	OCH_3	OCH_3	CH_3	OCH_3	H	50	206–210 dec[a]	$C_{20}H_{26}ClNO_4$
153	OCH_3	OCH_3	CH_3	H	OCH_3	41	244–246 dec[a]	$C_{20}H_{26}ClNO_4$
154	OCH_2O		CH_3	OCH_3	OCH_3	62	225–228 dec[a]	$C_{20}H_{24}ClNO_5$
155	OCH_2O		CH_3	OCH_3	H	50	198–201 dec[a]	$C_{19}H_{22}ClNO_4$

[a] Hydrochloride. [b] See Table II, footnote *c*.

zinium iodide), FTM (furfuryltrimethylammonium iodide), and peripheral vagal stimulation. Antihistaminic activity was determined by blockade of the depressor response to injected histamine, and centrally acting compounds by blocking the pressor effect due to bilateral cartoid occlusion.

Discussion of Results

Table VII shows overt effects produced in mice. One can see that almost all of the compounds which produced effects in the mouse caused a CNS depressant action. This was usually accompanied by one or more of the following effects: decreased spontaneous motor

TABLE VII

SUMMARY OF DOSE RANGE TESTING IN MICE

No.	Dose, mg/kg po	Observations[a]
33	150	NOE
	300	Tachypnea, sl ↓ SMA act.
34–36	300	NOE
37	300	Sl ↓ SMA
38–40	300	NOE
41	300	Sl to marked ↓ SMA
42	300	NOE
43	100	NOE
	200–300	Sl to mod CNS depression, bradypnea, increased pain threshold, low posture
44	300	NOE
45	100–150	Hypothermia
	300	Sl depression, bradypnea, low body posture, increased pain threshold
46	300	Sl ↓ SMA
47	300	Sl ↓ SMA, low posture, bradypnea
48–52	300	NOE
53	150	NOE
	300	Marked depression, low posture, hypotonia, increased pain threshold
54	300	NOE
55	150	NOE
	300	Mod ↓ SMA, low posture, increased pain threshold
56–58	300	NOE
59	300	Sl ↓ SMA
60–61	300	NOE
62	300	Lacrimation
63	300	NOE
64	300	Sl to mod ↓ SMA, dyspnea
97–98	300	NOE
99	300	Tachypnea, dyspnea, mod ↓ SMA, sl mydriasis
100–108	300	NOE
109	300	Increased pain threshold, marked ↓ SMA, sl ptosis, hypotonia, lacrimation, bradypnea, loss pinna reflex
110	300	NOE
111	300	Sl ↓ SMA, bradypnea, mod CNS depression, hypothermia, dyspnea
112–116	300	NOE
117	150	NOE
	300	Dyspnea, low posture, marked decrease SMA, marked CNS depression, lacrimation, bradypnea
118	300	NOE
119	50, 100	Sl ↓ SMA, hypersensitivity, low posture, hyperthermia
	300	Mod ↓ SMA, mod CNS depression, bradypnea, hypersensitivity, hyperthermia, ataxia, dyspnea, mydriasis
120	300	Sl CNS depression, bradypnea, low posture, mydriasis, hypotonia
121–128	300	NOE
129	50	Low posture
	100	Hypothermia, sl CNS depression, dyspnea, mydriasis, convulsions
130	300	Low posture, bradypnea, mod ↓ SMA
131	50	Sl to mod ↓ SMA, hypothermia
	100	Running seizures, convulsions, opisthotonos, acute death
132	100	Sl to mod ↑ SMA, ataxia
	200	Low posture, mod ↑ SMA, ataxia, exophthalmia, mydriasis, hypothermia, lacrimation, sl ptosis
133	300	NOE
134	75	Marked ↑ SMA, high posture
	150	Exophthalmia, straub tail, vocalization, convulsions, mydriasis, ataxia
135	100	Mod stimulation, hypersensitivity
	200	Dyspnea, popcorn convulsions, gasping, salivation, death
136, 137	300	NOE
138	200	Los posture, hypothermia, mod ↓ SMA
	300	Salivation, running seizures, exophthalmos, hypothermia, mod ↓ SMA, mydriasis
139	100	Low posture, hypersensitive to touch, sl ↓ SMA
	200	Straub tail, ataxia, running seizures, convulsions, emprosthotonus, exophthalmos
140	300	NOE
141	200	Sl ↓ SMA, hypothermia
	300	Low body posture, mod depression, tachypnea, seizures, hypothermia, ↓ SMA
142	200	Low posture, ↓ SMA, dyspnea, hypothermia
	300	Mod ↓ SMA, exophthalmos, dyspnea, tremors, hypotonia, cyanosis, acute death
143, 144	300	NOE
145	300	Hypothermia, low posture, ↓ SMA
146	300	Hypothermia, low posture, ↓ SMA
147–149	300	NOE
152	150	Low posture, ↓ SMA
	300	As above, dyspnea, convulsions
153	300	Diarrhea, sl mydriasis
155	75	Sl ↓ SMA, low posture
	150	Ataxia, dyspnea, loss pinna reflex
	300	As above, hypersensitivity to touch, loss righting reflex

[a] SMA = spontaneous motor activity, NOE = no overt side effects.

activity, low posture, hypotonia, respiratory depression, and tremors or convulsions. Of the 89 compounds tested and listed in Table VII only nine produced toxicity in the form of running seizures, tremors, convulsions, or death.

It is interesting to note that in spite of the apparent toxicity of these compounds (**129**, **131**, **134**, **135**, **138**, **139**, **141**, **142**, **152**), only one produced lethality at a dose level as low as 100 mg/kg. Compound **142** caused lethality at 300 mg/kg, while the rest caused only running seizures, tremors, or convulsions. Generally, most of the benzyltetrahydroisoquinolines were relatively nontoxic; however, they were not sufficiently potent as CNS depressants to be considered as tranquilizers, sedatives, or hypnotics, and further neurological investigation was not warranted. Two compounds (**134** and **135**) produced some degree of stimulation in the dose range; however, higher doses caused

TABLE VIII

SUMMARY OF ANALGETIC AND ANTIPYRETIC TESTS (RANDALL AND SELITTO)

No.	Dose, mg/kg *po*	Pain threshold elevation[c]	Antipyresis[c]
33	100	+	−
34–37	100	−	−
38, 39	100	+	−
40, 41	100	−	−
42, 43	100	+	−
44–48	100	−	−
49	100	+	−
50	100	−	−
51	100	++	−
52	100	−	+
55	100	−	++
57	100	−	−
58	100	+	−
59–62	100	−	−
63	100	+	−
64	100	++	−
97[a]	25, 50, 100	−, ++, ++	++, −, ++
98	100	+	−
99	50, 100	−, ++	−, −
100	100	−	+
102	100	++	−
103	100	−	−
104	100	+	+
105	100	−	−
106	100	++	+
108	100	−	+
110	100	+	−
112	100	−	++
115, 120	100	−	−
121	100	+	−
122	100	++	++
127	100	−	−
129	50	++	−
130	100	−	−
131	100	++	++
132, 133	25	−	−
134,[b] 135	100	−	−
136, 137	100	++	−
138	100	++	++
139	100	++	−
140–142	100	−	−
143	100	++	−
144	100	−	+
145, 146	100	−	−
151	100	+++	−
152	100	−	−
153	100	+	−
155	50	−	++

[a] Reduces pleural fluid volume. [b] Reduces carrageenin-induced edema at 25 mg/kg *po* and carrageenin abscess at 100 mg/kg *po*. [c] + = significant, − = not significant.

toxicity. It can be speculated that the increase in spontaneous motor activity observed with these agents was a reflection of toxicity and not a selective stimulating action on the central nervous system.

Table VIII shows a summary of our tests in measuring elevation of pain threshold with the Randall and Selitto procedure. This test is sensitive to agents whose pain threshold properties are at least equivalent to aspirin, phenylbutazone, or acetanilide. It is to be noted that approximately one-third of the 70 compounds screened exhibited some degree of pain threshold elevating properties or analgesia. A number of these were also tested in the D'Amour and Smith tail flick test, which is selective for the more potent analgetic agents, such as codeine or morphine. Only one compound (**97**) had significant pain-elevating effects; nevertheless, it was considerably weaker than codeine in this test procedure. Approximately 20% of the compounds listed in Table VIII showed significant antipyretic activity. Both aspirin and phenylbutazone have such activity in raising pain threshold and lowering temperature of the inflamed foot in the rat and are also effective antiinflammatory agents in man. Compounds having this dual activity in rats are considered candidates for antiinflammatory testing. Compounds **97**, **104**, **106**, **122**, **131**, and **138** produced significant activity in these two parameters; however, they were much less active than phenylbutazone. One compound (**134**) reduced both carrageenin-induced edema and carrageenin-induced abscesses. This agent was also considerably less active than phenylbutazone.

The results indicate that the series of compounds described in this study do not display sufficient biological activity in the aforementioned tests to warrant further testing at this time.

Experimental Section[16]

N-(3,4-Methylenedioxyphenethyl)-4-chlorophenylacetamide (X).—A mixture of *p*-chlorophenylacetic acid (102.0 g, 0.60 mole) and $SOCl_2$ (400 ml) was boiled at reflux for 3 hr. The solution was cooled and evaporated to dryness *in vacuo;* C_6H_6 (100 ml) was added and the concentration was repeated *in vacuo*. The resultant viscous oil was dissolved in C_6H_6 (200 ml) and the solution was added, with cooling and stirring, over a 10-min period to a mixture of 3,4-methylenedioxyphenethylamine (80 g, 0.48 mole), C_6H_6 (200 ml), and 10% NaOH (600 ml). Stirring was continued until crystallization occurred and the mixture was then allowed to remain at 25° for 1 hr. The solid was filtered with suction and washed (H_2O, hexane) to give a white, solid product (134 g, 88%). An analytical specimen, mp 139–141°, was obtained by recrystallization from EtOH–H_2O.

1-(4-Chlorobenzoyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (XII).—A stirred solution of N-(3,4-methylenedioxyphenethyl)-4-chlorophenylacetamide (132.0 g, 0.415 mole) in $POCl_3$ (350 ml) and PhMe (450 ml) was boiled at reflux for 3 hr. The hot solution was cooled to 25° and treated with petroleum ether (2 l., bp 30–60°); a precipitate developed which was separated from the supernatant liquid by decantation. This procedure was repeated with additional petroleum ether (three 1-l. portions) until the liquid phase was essentially colorless. Ice (800 g) was added to the solid and the mixture was made alkaline with NH_4OH and extracted ($CHCl_3$); the organic extract was washed (NaCl solution) and dried (Na_2SO_4). Removal of solvent *in vacuo* yielded a viscous oil which was used in subsequent operations without further purification. It was dissolved in MeOH (4 l.) and placed in an open, well-ventilated tray (28 × 40 cm); periodic additions of MeOH were made in order to keep the solvent at its original level. After 3 weeks the mixture was filtered to yield a solid product (25 g). The filtrate was evaporated to dryness *in vacuo*, and the residual oil was dissolved in $CHCl_3$ which was washed (NH_4OH, NaCl solution) and dried (Na_2SO_4). After concentration *in vacuo* the resultant viscous material was passed over a Florisil column (700 g) in $CHCl_3$ to give additional solid product (15 g, total yield 44%). An analytical sample, mp 132–133°, was obtained by recrystallization from MeOH.

1-(4-Chlorobenzoyl)-2-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolinium Iodide (XV).—A mixture of 1-(4-chloro-

(16) Melting points were taken in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus and are corrected. Microanalyses were carried out by Miss Margaret Carroll and her associates at Smith Kline and French Laboratories. Where analyses are represented by the symbols of the elements, analytical values obtained were within ±0.4% of the theoretical values.

benzoyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (12 g, 0.026 mole) and MeI (80 ml) was heated in a sealed vessel at 100° for 3 hr. The collected precipitate was recrystallized from MeOH–EtOAc to yield a yellow crystalline solid (13.3 g, 76%), mp 241–242° dec.

1-(4-Chlorobenzoyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XVI).—Raney nickel (2 g) was added to a solution of XV (10.0 g, 0.022 mole) in MeOH (1200 ml) and the mixture was hydrogenated at atmospheric pressure; uptake of H_2 essentially ceased after 1 hr with uptake of 1.5 molar equiv. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was treated with 6 *N* HCl to yield a yellow solid which was filtered off and partitioned between $CHCl_3$ and 6 *N* NH_4OH. The organic layer was separated and the aqueous layer was extracted several more times with $CHCl_3$. The combined organic layers were washed (saturated NaCl) and dried (Na_2SO_4). Removal of solvent *in vacuo* yielded an amorphous material which was crystallized from MeOH to give a white crystalline solid (3.1 g, 43%), mp 115–117°.

1-(4-Chlorobenzoyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XIV).—$NaBH_4$ (5.5 g 0.15 mole) was added to a refluxing solution of XII (3.5 g, 0.011 mole) in MeOH (500 ml). Heating was continued for an additional hour; H_2O (200 ml) was added, and the mixture was concentrated to *ca.* 150 ml *in vacuo*. The aqueous solution was extracted with $CHCl_3$, washed (saturated NaCl), and dried (Na_2SO_4). Removal of solvent *in vacuo* yielded a viscous oil which was crystallized as the corresponding hydrochloride (2.4 g, 65%). An analytical sample, mp 225–227°, was obtained by recrystallization from methanol.

1-(4-Chloro-α-hydroxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XVII).—A mixture of XV (3.0 g, 0.0066 mole), $NaBH_4$ (5.0 g, 0.14 mole), and MeOH (400 ml) was boiled at reflux for 90 min. H_2O was added and the mixture was concentrated *in vacuo* to *ca.* 50 ml. The residue was extracted with $CHCl_3$ which was washed with saturated NaCl solution and dried (Na_2SO_4). Removal of solvent *in vacuo* yielded a colorless oil which crystallized (1.29 g, 50%) on treatment with ethereal HCl. An analytical specimen was obtained by recrystallization from MeOH–EtOAc.

Acknowledgment. We wish to thank Miss Susan Danielson for assistance in preparation of this manuscript.

Synthesis and Pharmacology of Some α-Keto-, α-Hydroxy-, and α-Amino-1-benzylisoquinolines

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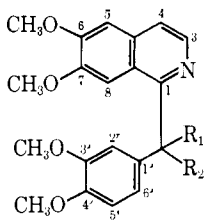
A number of α-keto, α-hydroxy, and α-amino-1-benzylisoquinolines related to papaveraldine and papaverinol have been prepared and examined pharmacologically. Testing covered dose-range studies in mice, examination for cardiovascular activity, and analgetic-antipyretic-antiedema studies. The pharmacological profile of the group, derivable from these data, is discussed.

The α-derivatized 1-benzylisoquinoline derivatives exemplified by papaveraldine (I), papaverinol (II), and papaverinylamine (III) are of general medicinal, chemical, and pharmacological interest because of their direct relationship to the clinically efficacious spasmolytic papaverine (IV). To date, however, there



I, $R_1R_2 = C{=}O$
II, $R_1 = OH$; $R_2 = H$
III, $R_1 = NH_2$; $R_2 = H$
IV, $R_1 = R_2 = H$

are only scattered reports of syntheses and biological testing in this area. Thus, 5'- and 6'-monomethylpapaveraldines,[1,2] as well as a number of variants in which one to four of the methoxyl groups have been replaced by methyl moieties, have been described.[3] In addition, the papaveraldine analogs having the 6,7- or 3',4'-dimethoxy groups replaced by methylenedioxy,[4] the corresponding tetrahydroxy compound,[5] the 3',4',5,6-tetramethoxy isomer,[6] 6-bromopapaveraldine,[7] des(tetramethoxy)papaveraldine (= 1-benzoylisoquinoline),[8] and several substituted 1-(4-pyridoyl)-6,7-dimethoxyisoquinolines[9] have been described. In the papaverinol series, only the 6-bromo[7] and the pyridoyl[9] analogs were prepared, and there is one publication devoted to synthesis of several α-amino compounds.[10]

On the biological side one finds only a few scattered observations in these series. Thus, papaveraldine and papaverinol are apparently in some respects biologically similar to papaverine, *i.e.*, they show activity against barium chloride and acetylcholine-induced spasm,[11] have protective action against histamine-induced bronchospasm,[12] but have little or no analgetic activity after oral administration in rats.[13,14] The corresponding 6'-bromo compounds as well as 6'-bromopapaverine are likewise antispasmodic at similar dosage levels.[7] Some other studies report the absence of any effect of papaveraldine on electrically stimulated laryngeal

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